creased by at least two orders of magnitude on substitution by epoxides. Since the pharmacokinetics of parenterally applied lipophilic drugs are very strongly affected by their relative water solubility (21), derivatives 2 and 3 may be useful in modifying the effects of lipophilic drugs.

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Stability of the 6,14-*endo*-Ethanotetrahydrooripavine Analgesics: Acid-Catalyzed Rearrangement of Buprenorphine

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Abstract □ Buprenorphine (I), a member of the 6,14-*endo*-ethanotetrahydrooripavine series of analgesics, undergoes an acid-catalyzed rearrangement reaction when exposed to acid and heat. The product was shown by ^{1}H-NMR and GC–MS to have undergone overall elimination of a molecule of methanol with concurrent formation of a tetrahydrofuran ring at C(6)–C(7) of I. Short-term stability studies across a wide range of pH and temperature conditions indicate that I is stable in aqueous solution at pH > 3 for 24 h at 36–38°C. Under the more extreme conditions of the autoclave, significant loss of I occurred. Long-term stability studies (10 weeks) of I in aqueous solution (pH 1 and pH 5) at 0–4°C and 26–28°C indicate only minor conversion (4%) to the rearrangement product. Eight other 6,14-*endo*-ethanotetrahydrooripavine derivatives were subjected to extremes of acid (pH 0) and temperature (autoclave) to determine if similar rearrangement reactions occur. GC–MS indicated that hydrolysis products were produced whose spectra were consistent with the proposed rearrangement structures.

Keyphrases □ Buprenorphine—6,14-*endo*-ethanotetrahydrooripavine analgesics, stability, acid-catalyzed structural rearrangement □ Analgesics—6,14-*endo*-ethanotetrahydrooripavine series, buprenorphine, stability, acid-catalyzed structural rearrangement □ Stability—buprenorphine and other 6,14-*endo*-ethanotetrahydrooripavine analgesics, acid-catalyzed structural rearrangement

The 6,14-*endo*-ethanotetrahydrooripavine series of analgesics contains numerous potent narcotic agonist and antagonist derivatives including buprenorphine (I), diprenorphine (V), and etorphine (VI). These substances are highly lipophilic (1) and display limited solubility at physiological pH; however, at lower pH values their solubilities increase substantially. Members of the closely related 6,14-*endo*-ethanotetrahydrothebaine series of analgesics have been shown to undergo acid-catalyzed rearrangement under vigorous conditions (2). However, it was not apparent whether a similar rearrangement would be observed for the 6,14-*endo*-ethanotetrahydrooripavine series. Consequently, a study was made of the stability of I under a variety of conditions involving exposure to acid and heat. A rearrangement product of I was identified by mass spectrometry and ^{1}H-NMR. Evidence was obtained by GC–MS for the presence of similar rearrangement products from other 6,14-*endo*-ethanotetrahydrooripavine derivatives following acid hydrolysis.

EXPERIMENTAL

Materials—Compounds I–IX[1] (Table I) were used as received. Their structural identity and purity were confirmed by TLC and GC–MS. Tri-Sil Z[2], obtained in 1-mL sealed glass ampules, was used as supplied. All other chemicals were reagent-grade quality.

Instrumentation—GC was conducted on a gas chromatograph[3] equipped with a flame-ionization detector. The stationary liquid phase, 3% OV-210[4], was coated on 100–120 mesh Gas Chrom Q[5] and packed into a 0.36-m × 2-mm i.d. silanized glass column. The temperatures were:

[1] Reckitt and Coleman, Hull, England.
[2] Pierce, Rockford, Ill.
[3] Model 2700; Varian Associates, Palo Alto, Calif.
[4] Applied Science, State College, Pa.
[5] Supelco Inc., Bellefonte, Pa.

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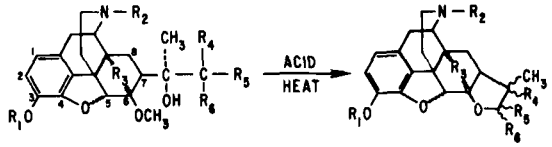
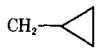
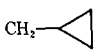
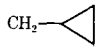
Table I—Structures of the 6,14-*endo*-Ethanotetrahydrooripavine Derivatives and Their Proposed Acid-Catalyzed Rearrangement Product



	Parent Compound	R_1	R_2	R_3	R_4	R_5	R_6
I	Buprenorphine; 21-cyclopropyl-7α-[(*S*)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-*endo*-ethanotetrahydrooripavine	H		CH_2CH_2	CH_3	CH_3	CH_3
II	Norbuprenorphine; 17-Demethyl-7α-[(*S*)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-*endo*-ethanotetrahydrooripavine	H	H	CH_2CH_2	CH_3	CH_3	CH_3
III	17-Demethyl-7α-[(*S*)-1-hydroxy-1,2,2-trimethylpropyl]-17-propyl-6,14-*endo*-ethanotetrahydrooripavine	H	$(CH_2)_2CH_3$	CH_2CH_2	CH_3	CH_3	CH_3
IV	17-Butyl-17-demethyl-7α-[(*S*)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-*endo*-ethanotetrahydrooripavine	H	$(CH_2)_3CH_3$	CH_2CH_2	CH_3	CH_3	CH_3
V	Diprenorphine; 21-cyclopropyl-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethanotetrahydrooripavine	H		CH_2CH_2	H	H	H
VI	Etorphine; 7α-[(*R*)-1-hydroxy-1-methylbutyl]-6,14-*endo*-ethenotetrahydrooripavine	H	CH_3	CH=CH	H	H	CH_2CH_3
VII	7α-[(*R*)-1-Hydroxy-1-methylhexyl]-6,14-*endo*-ethenotetrahydrooripavine	H	CH_3	CH=CH	H	H	$(CH_2)_3CH_3$
VIII	7α-[(*R*)-2-Cyclohexyl-1-hydroxy-1-methylethyl]-6,14-*endo*-ethenotetrahydrooripavine	H	CH_3	CH=CH	H	H	C_6H_{11}
IX	22-Cyclopropyl-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydrothebaine	CH_3		CH=CH	H	H	H

injector, 190°C; detector, 275°C; oven, programmed from 170°C to 260°C at 10°C/min. Nitrogen was the carrier gas at a flow rate of 20 mL/min.

Methane chemical-ionization mass spectral data were obtained on a quadrupole gas chromatograph–mass spectrometer[6]. The GC system was identical to that described. The temperature of the source was 260°C. The electron energy was 70 eV, and the multiplier voltage was 1.4 kV. Methane was used as reagent and carrier gas at a flow rate of 20 mL/min.

^{1}H-NMR[7] spectra were obtained on an NMR spectrometer operating in the Fourier-transform mode. Samples (60 mg) were dissolved in deuterated methanol (2 mL). Chemical shifts (δ) are expressed in ppm relative to tetramethylsilane.

Extraction—Aqueous aliquots (10 mL) of drug standards (5–10 μg/mL) were buffered to pH 9.5 with 2 mL of 3.3 M phosphate buffer. Sodium chloride (1 g) was added and a final adjustment of the pH was made with 2 M NaOH or 2 M HCl. Methylene chloride–isopropyl alcohol (70%, v/v) was added (15 mL) and the contents were shaken for 20 min. Following centrifugation, the aqueous layer was discarded, and 13 mL of the organic layer was transferred. The extract was evaporated to dryness under a stream of nitrogen, and the residue was dissolved in methanol and transferred quantitatively to an acylation tube[8] containing 50 μg of α-isocodeine (internal standard). The contents were evaporated to dryness under a nitrogen stream, and 100 μL of Tri-sil Z was added. The tube was sealed, vortexed, and allowed to remain at room temperature for 1 h. An aliquot (1–2 μL) was removed and analyzed by GC or GC–MS.

Stability Studies—Standard aqueous solutions of I (5–10 μg/mL) were prepared over the pH range of 0–12. The pH of the solutions was maintained constant by the use of saturated phosphate buffers (pH 2–12) or hydrochloric acid and sodium chloride (pH 0–2). Incubation studies were performed under the following conditions: 0–4°C, 24 h; 26–28°C, 24 h; 36–38°C, 24 h; autoclave at 112°C and 75.8 kN/m^2 for 30 min. Following the incubation period, the samples were neutralized and extracted as previously described.

A 10-week incubation study of I at pH 1.0 and 5.0 was performed at 0–4°C and at 26–28°C. Aliquots were removed at weekly intervals and analyzed for the rearrangement product. All samples were analyzed in triplicate, and the mean of the analyses is reported. Controls were included wherever appropriate to ensure that artifacts were not formed during the extraction and analysis procedures.

[6] Model 4021 Automated GC/MS/DS; Finnigan Corp., Sunnyvale, Calif.
[7] Model FT80A; Varian Associates, Palo Alto, Calif.
[8] Regis Chemical Co., Morton Grove, Ill.

RESULTS AND DISCUSSION

Structure of the Acid-Catalyzed Rearrangement Product of Buprenorphine (I)—Preliminary analytical and metabolic studies on the 6,14-*endo*-ethanotetrahydrooripavine derivatives indicated that they were unstable in the presence of acid and heat. When I was subjected to conditions commonly used for the acid-catalyzed cleavage of conjugated opiate metabolites (10% HCl, v/v; autoclave for 30 min at 112°C and 75.8 kN/m^2 steam pressure) (3), conversion was nearly complete to a hydrolysis product. Both I and the acid-hydrolysis product could be extracted from aqueous solution at pH 9.5 with methylene chloride–isopropyl alcohol (70%, v/v) with a 60–90% extraction efficiency. Extracts of I and the acid-hydrolysis product were analyzed by GC as the silyl derivatives. GC tracings are shown in Fig. 1 for standard I and extracts of I following various incubation conditions. The acid-hydrolysis product (R_t = 6.4 min) was not produced during incubation at pH 5 for 24 h (Fig. 1B), but appeared in the same incubation experiment at pH 0 (Fig. 1C). A nearly complete conversion occurred under autoclave conditions (Fig. 1D). Analytical quantities (100 mg) of the acid-hydrolysis product were produced for structural determination *via* the latter conditions and were isolated by precipitation at pH 9. The product was an amorphous white solid which, when converted to the hydrochloride salt, had a melting point range (uncorrected) of 250–268° dec. The methane chemical-ionization spectrum indicated a molecular weight of 435 AMU, representing a loss of 32 AMU from the parent substance. The most abundant ion was observed at *m/z* 436 [$(M + 1)^+$, pseudomolecular ion] and was accompanied by other ions at *m/z* (% relative abundance): 464(15), $(M + 29)^+$ ion; 437(29), isotopic ion; 435(32), M^+ ion; and 434(18), $(M - 1)^+$ ion.

Structural assignment of the acid-hydrolysis product of I was made by ^{1}H-NMR (Fig. 2). The singlets in the spectrum of I for the side-chain methyl groups at δ 1.0 and δ 1.3 ppm as well as the methoxyl group at δ 3.4 ppm are not present in the spectrum of the hydrolysis product. Instead, four new singlets of near equal intensity at δ 1.05, 1.15, 1.20, and 1.25 ppm are present, consistent with the proposed structure in which a new tetrahydrofuran ring is formed at C(6)–C(7). Similar products have been identified for tetrahydrothebaine analgesic derivatives following hydrolysis with formic acid under reflux conditions (2). The formation of the furan ring is speculated to occur following demethylation of the methoxyl group, acid-catalyzed elimination of the tertiary hydroxyl group, and a subsequent 1,2-shift of a substituent group on the C(7) side chain. The overall scheme results in the formation of a new ring with nonequivalent methyl groups on the basic skeleton of I and a net loss of a molecule of CH_3OH (32 AMU).

Stability of I in Aqueous Solution—The stability of I in aqueous

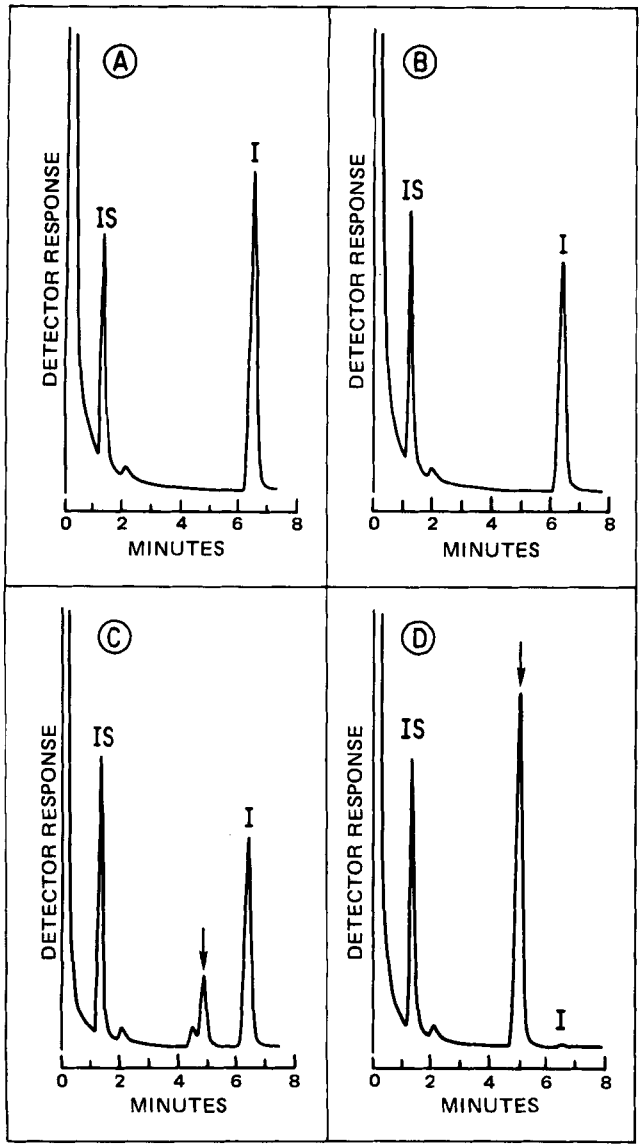


Figure 1—*Gas chromatograms of buprenorphine (I) and extracts following incubation under different conditions. Key: (A) standard I without extraction; (B) extract following incubation of I at pH 5 and 36–38°C for 24 h; (C) extract following incubation of I at pH 0 and 36–38°C for 24 h; (D) extract following incubation of I at pH 0 under autoclave conditions for 30 min; (IS) internal standard. The appearance of the rearrangement product of I is indicated by the arrow.*

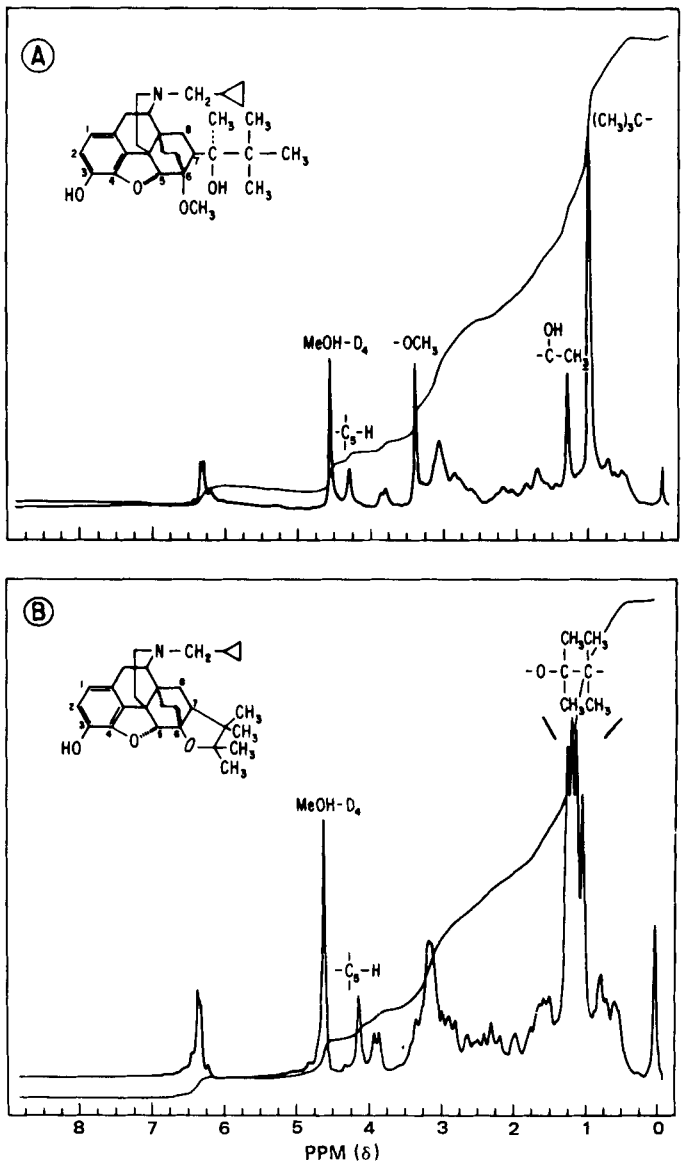


Figure 2—*^{1}H-NMR spectra of buprenorphine (A) and rearrangement product following acid hydrolysis (B).*

solution was studied over pH 0–12 under the following incubation conditions: 0–4°C, 24 h; 26–28°C, 24 h; 36–38°C, 24 h; 30 min, autoclave. Following incubation the samples were extracted and analyzed by GC for I and the rearrangement product. The percent recoveries of I were calculated from peak height ratios of I and the internal standard for extracted samples *versus* unextracted standards. Hence, percent recoveries reflect a combination of extraction efficiency and loss of I through rearrangement and other decomposition pathways. Calculations of percent rearrangement product were based on peak height ratios of rearrangement product to the sum of rearrangement product and parent compound. Therefore, percent rearrangement values are independent of the extraction efficiency of the solvent and reflect only the percentage of I converted to the rearrangement product.

Recoveries of I following incubation were consistently high (60–90%) at pH > 1 for all conditions except the autoclave (Table II). After incubation in the autoclave, recoveries generally fell and reached a low of 17% at pH 7.4, presumably reflecting decomposition *via* hydrolytic pathways other than rearrangement. The nature of these decomposition products is unknown. At pH 0 for all incubation conditions, rearrangement product was detectable, but the amount of rearrangement was clearly related to the temperature of incubation. Only a trace of rearrangement product was present in the 0–4°C samples, whereas a near quantitative conversion occurred under autoclave conditions. Rearrangement product was not detected in any sample at pH > 3.

Long-term incubation studies (10 weeks) were performed with aqueous solutions of I to determine if significant rearrangement occurred during storage at 0–4°C and 26–28°C. Solutions of I (50–100 μg/mL) were prepared for incubation at pH 1 and pH 5. Aliquots were withdrawn at weekly intervals and assayed by GC for I and the rearrangement product. The rearrangement product was first detected in week 2 samples (pH 1, 26–28°C) and represented ~1% of the parent compound. The amount of rearrangement product in these samples increased gradually to ~4% of I at week 10. Rearrangement product was detectable in the remaining solutions (pH 1, 0–4°C; pH 5, 0–4°C; and 26–28°C) only in trace amounts, ~0.1%, at week 10. Buprenorphine (I) was recovered in high yield (60–80%) from all samples throughout the incubation period, and products *via* other decomposition routes were not detected.

Acid-Hydrolysis of 6,14-*endo*-Ethanotetrahydrooripavine Derivatives—Other members of the oripavine series and related derivatives were subjected to autoclave conditions to determine if acid-catalyzed rearrangement occurs similar to that observed for I. The structures of the parent compounds and the potential rearrangement products are illustrated in Table I. Following autoclave incubation, the samples were allowed to cool and were extracted and analyzed by GC and GC–MS. Derivatization of a number of the compounds was found to be necessary for GC analysis. Recoveries of the compounds in Table I from aqueous solution ranged from 65–78% prior to autoclave incubation, but fell to

Table II—Recovery and Rearrangement of Buprenorphine Following Incubation Under Various pH Conditions [a]

pH	0–4°C Incubation [b]		26–28°C Incubation [b]		36–38°C Incubation [b]		Autoclave [c]	
	Recovery, %	Rearrangement, %	Recovery, %	Rearrangement, %	Recovery, %	Rearrangement, %	Recovery, %	Rearrangement, %
0	75.5 ± 6.8	0.7 ± 0.2	57.6 ± 4.5	3.3 ± 0.7	51.2 ± 2.4	18.4 ± 0.8	0.7 ± 0.1	99.3 ± 0.1
1	70.6 ± 5.1	0	63.0 ± 4.4	0	74.0 ± 5.7	0.9 ± 0.1	1.1 ± 0.1	98.7 ± 0.1
2	73.4 ± 1.8	0	72.9 ± 2.6	0	74.0 ± 0.4	0	78.1 ± 2.4	15.3 ± 0.5
2.5	68.6 ± 4.0	0	64.7 ± 2.8	0	76.3 ± 5.4	0	81.8 ± 2.7	4.1 ± 0.4
3	72.1 ± 2.0	0	71.1 ± 1.6	0	74.1 ± 1.4	0	89.4 ± 1.2	1.3 ± 0.3
4	71.9 ± 3.4	0	79.3 ± 5.2	0	73.0 ± 2.1	0	96.3 ± 3.6	0
5	74.9 ± 1.3	0	88.2 ± 2.6	0	71.1 ± 2.3	0	67.9 ± 2.3	0
6	78.3 ± 3.3	0	88.1 ± 5.7	0	70.5 ± 4.0	0	44.8 ± 2.3	0
7	75.4 ± 1.7	0	93.7 ± 4.4	0	73.9 ± 1.6	0	19.0 ± 1.4	0
7.4	71.5 ± 5.1	0	85.9 ± 5.4	0	70.5 ± 3.2	0	17.0 ± 0.3	0
8	91.0 ± 10.1	0	76.1 ± 0	0	76.6 ± 5.0	0	22.5 ± 1.6	0
9	92.5 ± 8.8	0	63.0 ± 3.2	0	76.4 ± 1.1	0	41.4 ± 1.1	0
10	91.2 ± 2.6	0	61.4 ± 6.0	0	77.1 ± 3.6	0	31.1 ± 3.0	0
12	88.9 ± 0.5	0	68.0 ± 4.8	0	80.7 ± 2.3	0	30.6 ± 1.2	0

[a] Decomposition by pathways other than rearrangement account for low recoveries under autoclave conditions and may have contributed to a lesser extent to the variability of recovery under all conditions. [b] For 24 h. [c] For 30 min.

Table III—Methane Chemical Ionization Spectra of 6,14-*endo*-Ethanotetrahydrooripavine Derivatives and Hydrolysis Products [a]

Compound	Standard				Hydrolysis Product		
	Mol. Wt.	$(M + 1)^+$	$(M - 17)^+$	Prominent Ions	Apparent Mol. Wt.	$(M + 1)^+$	Prominent Ions
I–Trimethyl silane	539	540(27)	522(100)	539(14), 538(12), 524(19), 523(39), 508(19), 506(31), 492(29), 490(22), 482(17)	507	508(100)	536(16), 509(39), 507(38), 506(15), 493(21), 492(51)
II–Trimethyl silane	485	486(23)	468(100)	470(19), 469(38), 454(22), 453(17), 452(33), 438(43), 436(34), 428(33), 396(15)	453	454(100)	482(17), 455(34), 453(39), 439(20), 438(58)
III–Trimethyl silane	527	528(21)	510(100)	512(25), 511(43), 496(20), 495(17), 494(34), 480(38), 478(27), 470(25), 438(15)	495	496(100)	524(17), 497(36), 495(37), 494(17), 481(24), 480(63)
IV–Trimethyl silane	541	542(19)	524(100)	541(17), 526(24), 525(43), 510(21), 509(17), 508(34), 498(18), 495(15), 494(38), 492(26), 484(26)	509	510(100)	538(18), 511(38), 509(38) 495(24), 494(62)
V	425	426(26)	408(100)	425(23), 409(31), 394(15), 376(33)	393 [b]	394(84)	448(19), 422(20), 421(25) 420(100), 419(25), 418(25), 395(21), 393(20)
VI	411	412(38)	394(100)	411(29), 410(16), 395(28), 298(18), 216(23)	379	380(100)	408(20), 381(26), 379(17)
VII	439	440(44)	422(100)	439(32), 438(21), 423(28), 298(17), 216(15)	407	408(100)	436(21), 409(26), 407(21), 252(19), 137(41)
VIII	451	452(44)	434(100)	480(18), 451(34), 450(28), 453(17), 435(32), 432(24) 298(40), 216(17), 191(19)	419	420(100)	448(19), 421(29), 419(18), 418(26), 408(20), 216(16), 137(16)
IX–Trimethyl silane	437	438(38)	420(100)	437(21), 421(32), 270(22)	405	406(100)	407(29), 405(17)

[a] *m/z* (percent relative abundance). Only ions ≥15% are reported. [b] Unresolved mixture.

zero following acid-hydrolysis in the autoclave. Compounds I–IV, VI, VII, and IX were converted to single major products, whereas two apparent isomeric products were present for VIII and a complex multicomponent mixture was obtained for V.

Methane chemical-ionization spectra are shown in Table III for I–IX and their major acid-hydrolysis products. The spectra present strong evidence for the formation of rearrangement products similar to that identified for I. The spectra of the parent compounds are characterized by a $(M + 1)^+$ ion (pseudomolecular ion) and a $(M - 17)^+$ ion (loss of —OH), the latter representing the most abundant ion in the spectrum of each compound. With the exception of III, which was a multicomponent mixture, the most abundant ions in the spectra of the acid-hydrolysis products were the $(M + 1)^+$ ions. The pseudomolecular ions were accompanied by corresponding $(M + 15)^+$ and $(M + C_2H_5)^+$ ions, thus supporting the molecular weight assignments of the hydrolysis products. Also, there was a notable lack of $(M - OH)^+$ ions in the spectra of the hydrolysis products. Overall, the mass spectral features of the acid-hydrolysis products of II–IX completely paralleled those observed for the rearrangement product of I and are entirely consistent with the structures of the proposed rearrangement products.

In summary, the acid and heat lability of the *endo*-ethanotetrahydrooripavines must be considered when these compounds are dissolved in aqueous media. Under conditions of high acidity (pH 0–1), heat accelerates an acid-catalyzed rearrangement reaction to yield an hydrolysis product. The structure of the acid-hydrolysis product of I contained a new tetrahydrofuran ring formed at C(6)—C(7) with a net loss of methanol from the parent compound. Evidence for similar acid-hydrolysis products arising from other members of the series (II–IX) was obtained by GC–MS. At higher pH (pH > 1) the rearrangement reaction of I was much slower or nonexistent. After 10 weeks incubation at pH 5 (26–28°C), I was recovered from aqueous solution in high yield with no evidence of decomposition. Significant loss of I *via* other decomposition pathways was apparent following exposure to the extreme conditions of the autoclave.

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