Vibrational and NMR Spectroscopic Study of Aged Flurazepam Mono- and Dihydrochloride Salts for Content Identity

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Abstract □ Archival samples of flurazepam monohydrochloride and "hydrochloride" (i.e., the dihydrochloride) were examined by Fourier transform infrared and Raman spectroscopy to determine evidence of degradation during storage for 13–15 years. No degradation of the three different batches of monohydrochloride salts was detected, but various degrees of degradation of the eight specimens of flurazepam hydrochloride diprotonated salts were indicated by enhanced intensities (IR 1635, 1509, 1226; Raman 1636, 1408, 1149 cm^{-1}) and new features (IR 1742, 943, 755; Raman 1554, 837, 742 cm^{-1}). All of these features, except the 1742 cm^{-1} IR band, were attributed to the presence of the hydrolysis product 5-chloro-2-[[2-(diethylamino)ethyl]amino]-2′-fluorobenzophenone hydrochloride whereas the 1742 cm^{-1} band was attributed to glycine hydrochloride, the other hydrolytic moiety. The flurazepam hydrochloride samples were also examined in deuterated dimethyl sulfoxide solution by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy to verify the presence of the degradation products and to estimate the levels of degradation (~3–36%) of the drug. IR and Raman spectra of the "benzophenone" hydrochloride in the "fingerprint" region are compared with two samples of flurazepam dihydrochloride (slightly and highly degraded) and their features discussed. Vibrational assignments are made and discussed for the observed IR and Raman wavenumbers for the "benzophenone" hydrochloride.

Introduction

The work described in this paper on the characterization of aged samples of flurazepam hydrochloride arose as a practical analytical extension to our previous study[1] of delorazepam, fludiazepam, tetrazepam, and flurazepam, the fourth part of systematic studies[2–4] of the vibrational spectra, infrared (IR) and Raman, of a series of benzodiazepines. Our interest in examining various archival mono- and dihydrochloride salts of flurazepam (**1**) (see Figure 1) by these vibrational spectroscopic techniques was heightened also by an earlier IR study by Ng and Bhattacharyya[5] of flurazepam dihydrochloride recrystallized from different solvents in which spectral differences were attributed to different equilibrium mixtures of flurazepam mono- and dihydrochlorides and/or free base in these solvents (including water). Three years previously, Kuwayama et al.[6] claimed on the basis of a carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectroscopic study of flurazepam in acidic aqueous solution (0.5 N DCl) that flurazepam was present in the form of diprotonated iminium structure (**2**). This entity was said to form immediately after preparation of the solution and subsequently to undergo hydrolysis to give a ring-opened benzophenone structure (**3**) (major portion), which was in equilibrium with the ring-closed iminium structure (minor portion). They also indicated that no end hydrolysates (**4** and **5**) were contained in the solution. Since Ng and Bhattacharyya[5] had made no mention of a possible ring-opened benzophenone degradation product in their study, we considered that our collection of13–15 year old samples of flurazepam hydrochloride salts could offer such an opportunity for identification.

In 1971 de Silva and Strojny[7] had reported a spectrophotofluorometric assay, for the determination of flurazepam and its major benzophenone metabolite (**4**) in blood and in urine. Conditions for the preparation of this degradation product (now available as the USP flurazepam Reference "C" Standard) and the desalkylflurazepam known as 7-chloro-5-(*o*-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (also now available as the USP flurazepam Reference "F" Standard) are described by Rudy and Senkowski.[8] Minagawa et al.[9] recently reported the vapor-phase IR spectrum of 5-chloro-2-[[2-(diethylamino)ethyl]amino]-2′-fluorobenzophenone (**4**) in a GC/FT-IR analytical study of benzophenones formed as hydrolysis products of benzodiazepines. Whereas liquid chromatographic analytical methodology continues to be developed for determination of flurazepam (di)hydrochloride content in pharmaceutical preparations, with[10] or without[11] mention of the USP flurazepam Reference "C" and "F" standards, little or no effort appears to have been directed at seeking evidence for the existence (transient or otherwise) of the (aminoacyl)benzophenone precursor **3**.

Flurazepam (base) (**1**), a white solid known systematically as 7-chloro-1-[2-(diethylamino)ethyl]-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, is marketed under the trade names of Felmane, Noctosom, or Stauroderm.[12] The substance, however, is more commonly encountered as the pale yellow dihydrochloride salt (**2**) (confusingly referred to in the pharmaceutical literature as flurazepam hydrochloride for which a USP compendial monograph[13] exits) under any of the following proprietary names: Ro 56901, Benozil, Dalmadorm, Dalmane, Dalmate, Dormodor, Felison, Insumin, Lunipax, or Somlan.[12] In addition, a white or almost white monohydrochloride salt of flurazepam (**1**) is known, quite properly, as "flurazepam monohydrochloride".[14]

The purpose of this study was to examine three aged samples of flurazepam monohydrochloride and eight aged samples of flurazepam "hydrochloride" (i.e., the dihydrochloride), including a National Formulary (NF) reference specimen in their natural solid state by infrared and Raman spectroscopy to determine any spectral differences as evidence of altered composition due to degradation during storage. In addition, the eight aged samples of flurazepam hydrochloride were examined in deuterated dimethyl sulfoxide (DMSO-d_6) solutions by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy both to verify the presence of the degradation products detected in the solid state by FT-IR and Raman spectroscopy and to estimate the level of these products in each sample.

Experimental Section

Materials—The various flurazepam hydrochloride salts used in this study had been stored in the dark at room

† Deceased.
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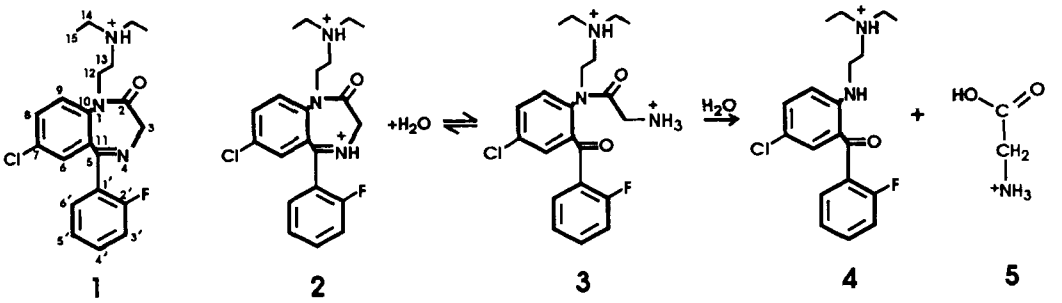

Figure 1—The degradation pathway for monoprotonated flurazepam (**1**) and diprotonated flurazepam (**2**) leading to formation of the ring-opened benzophenone (**3**) and the monoprotonated hydrolysis products, 5-chloro-2-[[2-(diethylamino)ethyl]amino]-2′-fluorobenzophenone (**4**) and glycine (**5**).

temperature for several years as part of our drug archival collection. The samples were contained in glass bottles fitted with tight screw caps; they were freshly opened for this study as needed. The samples consisted of three monohydrochloride (M102, no. 5–1, and no. 7) and two (di)hydrochloride (M101 and no. 56–2) lots obtained from Frank W. Horner Inc. (5485, rue Ferrier, Ville Mont-Royal, P. Q., Canada H4P 1M6) in 1977 and 1979, two lots of the (di)hydrochloride obtained from Hoffmann-LaRoche in 1979 (R8434) and 1981 (R9086), and single lots of the (di)hydrochloride obtained from Industria Chimia Profarmaco (Lot J-559, Batch 140304, 1977), Industria Chimia Profarmaco (no. 160304, 1979), and Apotex (C-G401, 1981). In addition, a National Formulary (NF) Reference Standard (Lot 1076) of flurazepam (di)hydrochloride and its degradation product, 5-chloro-2-[[2-(diethylamino)ethyl]amino]-2′-fluorobenzophenone hydrochloride (**4**) (Lot 578), were available from the same period. The authenticity of the latter substance was verified by gas chromatography–mass spectrometry and by proton (^{1}H-NMR) nuclear magnetic resonance spectroscopy. The newly released USP flurazepam (di)-hydrochloride reference standard (Lot H-2) and a sample of glycine hydrochloride (Aldrich, 10008JY) were also used for comparison purposes.

Equipment and Procedures—Fourier transform infrared (FT-IR) spectra were recorded from 4000 to 400 cm^{-1} with resolution of 2 cm^{-1} using a Nicolet 60 SX spectrometer with a DTGS (deuterated triglycine sulfate) detector. Samples for IR studies were prepared as fused KBr disks (0.3% sample) using spectral-grade potassium bromide.

Samples of FT-Raman spectroscopy were prepared in the form of disks 3 mm in diameter with a KBr backing. The disks were formed in a hand-held minipress. Fourier transform Raman spectra were recorded at the Thornton Research Centre, Shell Research Ltd., Chester, U.K. The experimental arrangement has been described in two earlier publications,[15,16] and details of operation remain as recently reported.[1–4] The nitrogen-cooled germanium detector covers the spectral range 9400–6200 cm^{-1}, which is equivalent to a Raman shift range of 0–3200 cm^{-1}. The 0–400 cm^{-1} region, however, is obscured by the filters needed to remove the intense Rayleigh scattering and any unscattered laser radiation. The detector response is not linear and is very low in the CH stretching region of the Raman spectrum near 3000 cm^{-1}. The NH stretching region near 3300 cm^{-1} and the OH stretching region near 3450 cm^{-1} cannot be observed. The Raman spectra shown in Figure 3 have not been corrected for detector response and are presented here only for qualitative comparisons.

High-resolution ^{1}H-NMR spectra were recorded at 400 MHz using a Bruker AM 400 cryostatic instrument. Spectra of flurazepam hydrochloride (~2 mg) in DMSO-d_6 (~0.5 mL) were recorded (−1.0 to 14 ppm) from 16 scans each (Figure 4). Integrals were determined for all resonance bands.

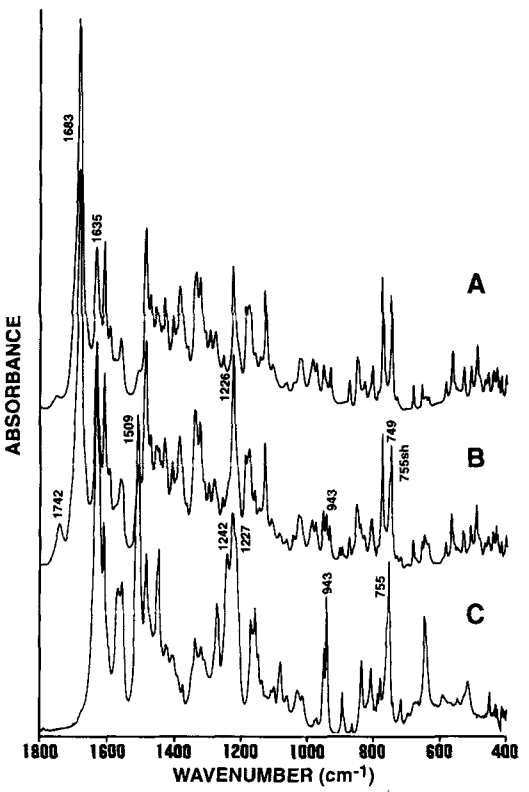

Figure 2—FT-IR spectra (1800–400 cm^{-1}) of (A) flurazepam hydrochloride (National Formulary (NF) Reference Standard, Lot 1076), (B) 14-year old naturally degraded sample of flurazepam hydrochloride (Industria Chimia Profarmaco, no. 160304) (both dihydrochlorides), and (C) 5-chloro-2-[[2-(diethylamino)ethyl]amino]-2′-fluorobenzophenone hydrochloride (NF Reference Standard, Lot 578). For experimental conditions, see the text.

Results and Discussion

No alteration was detected in either the IR or Raman spectra of the aged (white to creamy white) samples of flurazepam monohydrochloride when compared to previously published spectra.[1,17]

Of the eight aged samples of flurazepam dihydrochloride examined, including a National Formulary (NF) Reference (Lot 1076) sample, five of these samples provided identical IR and Raman spectra to the IR and Raman spectra obtained with the NF material (Figures 2 and 3, spectra A), each of which retained a lemon yellow color. In contrast, two of the "hydrochloride" samples (Horner 1979 and Industria Chimia Profarmaco no. 160304) were orange to dark yellow in color and showed augmentation of relative IR band intensities at 1635, 1509, and 1226 cm^{-1}, with additional new bands at 1742, 943, and 755 cm^{-1} (Figure 2, spectrum B). Each of these alterations, except the presence of the 1742 cm^{-1} band, can be accounted for as additions arising from the IR spectral

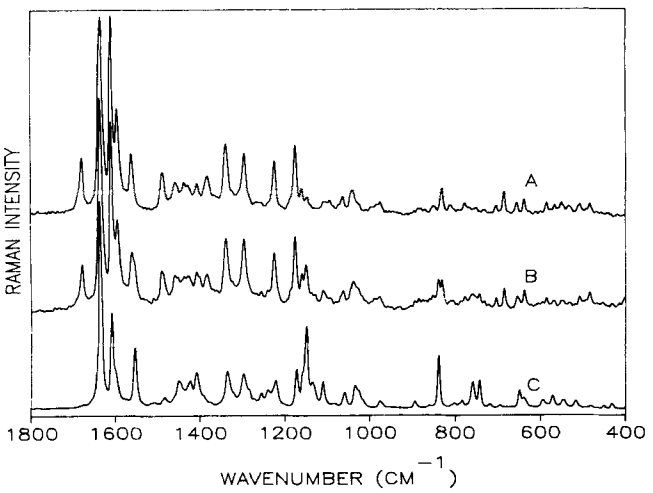

Figure 3—FT-Raman spectra (1800–400 cm^{-1}) of (A) flurazepam hydrochloride (National Formulary (NF) Reference Standard, Lot 1076), (B) 14-year old naturally degraded sample of flurazepam hydrochloride (Industria Chimia Profarmaco, no. 160304) (both dihydrochlorides), and (C) 5-chloro-2-[[2-(diethylamino)ethyl]amino]-2′-fluorobenzophenone hydrochloride (NF Reference Standard, Lot 578). For experimental conditions, see the text.

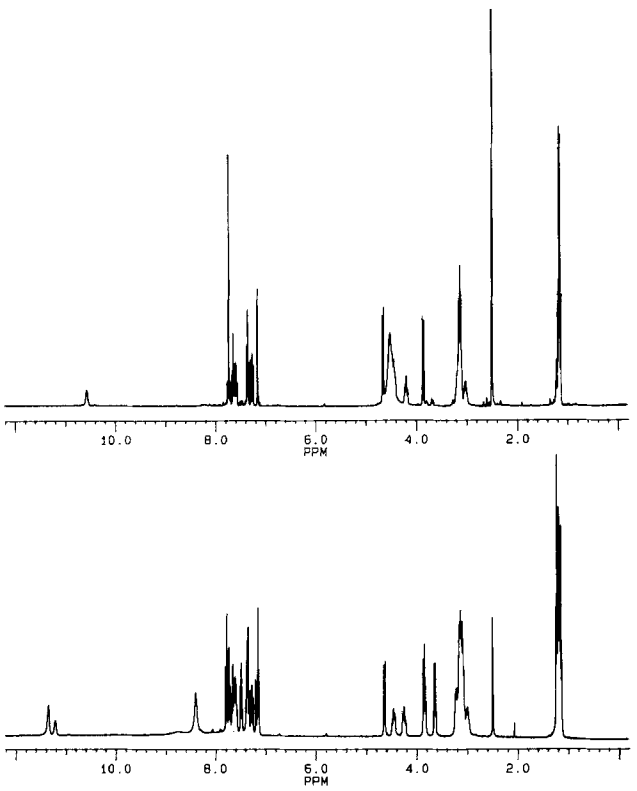

Figure 4—^{1}H-NMR spectra (400 MHz) of flurazepam (di)hydrochloride samples in DMSO-d_6 solution: (top) slightly degraded (~7%) Horner (56–2) product, and (bottom) the Horner (1979) product showing appreciable (~36%) degradation. For experimental conditions, see the text.

character of 5-chloro-2-[[2-(diethylamino)ethyl]amino]-2′-fluorobenzophenone hydrochloride (**4**) (Figure 2, spectrum C), the "benzophenone" hydrochloride degradation product of flurazepam hydrochloride. The 1742 cm^{-1} band, however, can be attributed to the carbonyl stretching frequency ($\nu_{C=O}$) of glycine hydrochloride **5**, the other hydrolysis moiety of entity **3**. An equally intense band at 1226 cm^{-1} in the spectrum of glycine hydrochloride also contributes to the augmentation of the 1226 cm^{-1} band in the degraded flurazepam (di)hydrochloride samples. The merest indication of the 1742 cm^{-1} peak can also be seen in the spectrum of the flurazepam (di)hydrochloride NF reference substance (Figure 2, spectrum A). In an earlier study[18] of the freshly obtained samples, none of the "benzophenone" hydrochloride degradation product (**4**) (limited to a maximum of 0.1% by the USP raw material monograph, as determined by a thin-layer chromatography method) was detected in the two Roche drug raw material samples, which was also confirmed in the present study by FT-IR and Raman techniques. From temperature and humidity stress studies conducted on samples of flurazepam mono- and (di)hydrochloride over a period of one year,[18] the monohydrochloride salt was found to be the more stable at higher temperature and/or humidity.

Similar identification and contribution of the "benzophenone" hydrochloride component can also be seen in the Raman spectra of the two aged flurazepam hydrochloride samples (Figure 3). Although the pure "benzophenone" hydrochloride material (**4**) is a paler lemon yellow color than undegraded flurazepam (di)hydrochloride, the presence of the protonated benzophenone and glycine components in degraded samples apparently results in orange coloration with darker orange coloration being indicative of higher "benzophenone" and glycine hydrochloride content.

Since the IR and Raman spectra of flurazepam base and mono- and (di)hydrochloride salts will be discussed separately in the context of comparative vibrational assignments,[19] only the vibrational characteristics of 5-chloro-2-[[2-(diethylamino)-ethyl]amino]-2′-fluorobenzophenone hydrochloride (**4**) (the "benzophenone" hydrochloride) and glycine hydrochloride and their contribution to the spectra of the aged flurazepam dihydrochloride samples are discussed in this paper. The IR and Raman spectra of the "benzophenone" hydrochloride in the "fingerprint" region are compared with two samples of flurazepam (di)hydrochloride (slightly and highly degraded) in Figures 2 and 3, respectively. The observed wavenumbers for the "benzophenone" hydrochloride together with suggested vibrational assignments are listed in Table 1.

FT-IR Spectra—Ng and Bhattacharyya[5] correctly attributed the sharp band of medium intensity at 1635 cm^{-1} in the IR spectrum of flurazepam (di)hydrochloride to the $C{=}N^+$ stretching vibration, having noted that this band is absent in the spectra of the monohydrochloride and the free base. Whereas the intensity of this band in the reference flurazepam hydrochloride spectrum is of the same relative intensity as the adjacent 1611 cm^{-1} band (Figure 2, spectrum A), the 1635 cm^{-1} band of the sample of degraded flurazepam hydrochloride (Figure 2, spectrum B) shows increased relative intensity attributable to the overlapping contribution of the carbonyl stretching ($\nu_{C=O}$ 1635 cm^{-1}) band from the "benzophenone" hydrochloride degradation product **4**. Similarly, the augmentation of the intensity of the 1509 and 1226 cm^{-1} bands in the "degraded hydrochloride" are seen to arise from the overlapping contribution from the "benzophenone" hydrochloride component vibrations at 1510 and 1227 cm^{-1}, respectively, supplemented by contribution from the 1226 cm^{-1} band of glycine hydrochloride. The two new, weak but definite, band incursions at 943 and 755 cm^{-1} in the "degraded hydrochloride" (Figure 2B) are seen to arise from penetration of the medium intensity 943 and 755 cm^{-1} bands of the "benzophenone" hydrochloride (Figure 2C) to give a triplet-like band character in Figure 2B where only a doublet-like character is seen and a shoulder on the high frequency side of the 749 cm^{-1} band in Figure 2B where none existed in Figure 2A.

FT-Raman Spectra—Figure 3 compares the FT-Raman spectra of a lemon yellow colored reference sample of flurazepam (di)hydrochloride (spectrum A) with a dark yellow to orange colored degraded sample (spectrum B) and a sample of the "benzophenone" hydrochloride degradation product

Table 1—Observed Wavenumbers (cm^{-1})[a] in the FT-Raman and IR Spectra of 5-Chloro-2-[[2-(diethylamino)ethyl]amino]-2′-fluorobenzophenone Hydrochloride

Raman	IR	assignment[b]	Raman	IR	assignment[b]
517 w	519 w	γ arom. ring	1221 m	1227 s	CF str
545 w	548 vw	β CF	1240 w	1242 sh	CH_2 wag
570 w	571 vw	δ arom ring	1256 w	–	C=C str
594 w	592 vw	C–Cl str	–	1272 m	CH_2 wag
–	616 vw	δ arom ring	1298 m	–	C=C str
637 sh	–	γ C=O	–	1322 w	CH_3 sym def
648 m	649 m	δ arom ring	1336 m	1340	CH_3 sym def
718 vw	720 w	γ CH	1409 m	1409 w	C=C str
742 m	743 sh	CH_2 rock	1424 m	1426 w	CH_2 def
758 m	755 m	γ CH	1451 m	1447 m	CH_2 def
783 vw	783 w	γ CH	1483 w	1485 m	CH_3 asym def
802 vw	810 w	γ CH	1508 vvw	1510 vs	NH^+ def
837 s	839 w	C–N–C str	1554 ms	1556 m	C=C str
893 w	896 w	N–C–C str	–	1567 m	C=C str
–	943 m	γ CH	1609 s	1612 sh	NH def
976 w	975 vw	C–C str	1636 vvs	1635 vvs	C=O str
1034 m	1031 vw	β CH	–	2475 s, br	amine–HCl
1059 w	1061 w	β CH	–	2573 s, br	amine–HCl
–	1083 w	β CH	2943 vw	2943 m	aliphatic CH str
1110 m	1110 vw	β CH	2977 vw	2978 m	aliphatic CH str
1135 sh	1138 sh	CH_3 rock	3056 vw	3056 w	arom CH str
1149 ms	1159 m	CH_2 wag	3072 w	3071 vw	arom CH str
1172 m	1172 m	β CH	–	3298 s, br	NH str

[a] v = very, s = strong, m = medium, w = weak, sh = shoulder, br = broad. [b] str = stretch, arom = aromatic, def = deformation, sym = symmetric, asym = antisymmetric, γ = arom out-of-plane def, δ = in-plane def, β = aromatic in-plane bend.

(spectrum C). A careful examination of spectra A and B reveals differences at 1636, 1408, and 1149 cm^{-1} (enhanced intensity), at 1554 cm^{-1} (shoulder), and at 837 and 742 cm^{-1} (new bands). All of these features can be attributed to the presence of the "benzophenone" hydrochloride degradation product.

The relative intensities of the components of the very strong doublet at 1635/1609 cm^{-1} in the Raman spectrum of flurazepam (di)hydrochloride (spectrum A) are changed in the spectrum of the degraded material (spectrum B) because of the contribution of the very strong line at 1636 cm^{-1} in the spectrum of the "benzophenone" hydrochloride (spectrum C). The intensity of the weak band at 1406 cm^{-1} in spectrum A is enhanced relative to its neighbors, and a shoulder appears at 1409 cm^{-1} in spectrum B. These changes also may be attributed to the presence of the "benzophenone" hydrochloride degradation product, which has a band of medium intensity at 1409 cm^{-1} in its Raman spectrum (spectrum C). There is an intensity reversal of the two weak bands at 1159 and 1147 cm^{-1}, which appear as shoulders on the strong peak at 1175 cm^{-1} in the Raman spectrum of the undegraded sample (spectrum A). The intensity of the lower frequency band is enhanced in spectrum B by the underlying band at 1149 cm^{-1} in the spectrum of the "benzophenone" hydrochloride (spectrum C).

The band of medium intensity at 1562 cm^{-1} in spectrum A is seen to have a shoulder in spectrum B. This shoulder is undoubtedly due to the 1554 cm^{-1} band of the "benzophenone" hydrochloride (spectrum C). The band at 829 cm^{-1} in spectrum A becomes a doublet at 837/829 cm^{-1} in spectrum B due to the strong "benzophenone" hydrochloride band at 837 cm^{-1}. A new weak feature appears at 742 cm^{-1} in the spectrum of the degraded material due to a band of medium intensity in the spectrum of the "benzophenone" hydrochloride at 742 cm^{-1}.

Although other medium-intensity bands in both the IR and Raman spectra of the "benzophenone" hydrochloride and glycine hydrochloride undoubtedly contribute to the net spectral features of the "degraded hydrochloride" (Figures 2B and 3B), no effort was made to identify their contribution. The bands highlighted above, however, are salient and serve to indicate the presence of both the "benzophenone" hydrochloride and glycine hydrochloride moieties in degraded flurazepam dihydrochloride.

Because both FT-Raman and IR spectroscopy are able to discern the presence of the benzophenone **4** and glycine hydrochlorides in degraded (aged) flurazepam hydrochloride, either technique affords a quick and convenient means for product quality and identity testing.

^{1}H-NMR Spectra and Product Distribution—A typical ^{1}H-NMR spectrum of aged flurazepam (di)hydrochloride, dissolved in DMSO-d_6, is shown in Figure 4. The complexity of the overall spectral features, particularly the relatively broad lower field resonance clusters seen at δ 10.8–11.5 and δ 8.2–8.9 were resolved by examining glycine hydrochloride and the benzophenone hydrochloride (USP flurazepam related compound C) separately in DMSO-d_6 and then as successively spiked additions of each of these substances to a DMSO-d_6 solution of the new USP flurazepam (di)hydrochloride reference standard (Lot H-2). The ^{1}H-NMR spectrum of the fresh flurazepam reference material appeared on preliminary examination to exist entirely in the open-chain form (**3**) with the ethylamino proton resonating near δ 11.1 and the protonated amino group of **3** resonating as a broad band centered near δ 8.6 and integrating in a 1:3 ratio, respectively. Reexamination of the sample by ^{13}C-NMR spectroscopy, however, clearly showed the drug to be entirely in the ring-closed form (**2**) because of the absence of a signal for the "benzophenone" carbonyl (i.e., not as an equilibrium of forms **2** and **3** as reported by Kuwayama et al.[6] in aqueous solution). The broad resonance at δ 8.6 was found to be variable in chemical shift and peak area in further studies, which also indicated that its appearance was dependent on the water content of the solvent. Also, it was noted that upon adding some glycine hydrochloride to the DMSO-d_6 solution of the fresh flurazepam monohydrochloride, the protonated amino resonance of **5** appeared in the mixed spectrum at δ 8.3 (as it does for glycine hydrochloride alone in DMSO-d_6) whereas the protonated amino resonance of **3** shifts upfield to δ ~5.2 as a somewhat less broad band. The methylene proton resonance of **5**,

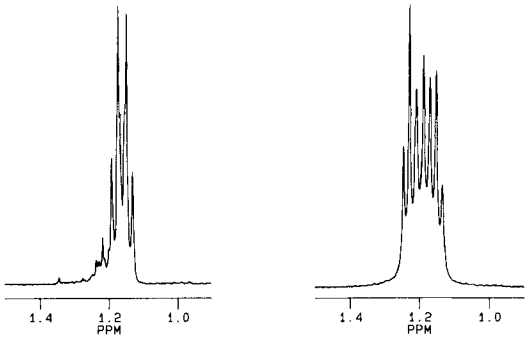

Figure 5—Expanded ^{1}H-NMR spectra (400 MHz) of the methyl proton resonances of flurazepam (di)hydrochloride samples: (left) slightly degraded Horner (56–2) product, and (right) the Horner (1979) product showing the presence of an additional methyl triplet (at ~1.23 ppm) indicative of appreciable sample degradation. For experimental conditions, see the text.

Table 2—Extent of Flurazepam (Di)hydrochloride Decomposition to the Benzophenone 4 in Aged (Archival) Samples As Determined by ^{1}H-NMR Integration of Spectral Regions Discussed

Sample and Lot	% Decomposition to 4	Sample Year
Industria J-559	3	1977
Roche R8434	6	1979
Horner 56-2	7	1977
Roche R9086	7	1981
NF Ref Std 0475-F	8	1981
Apotex C-G401	15	1981
Industria 160304	26	1979
Horner M101	36	1979

observed as a sharp singlet from **5** alone in DMSO-d_6 at δ 3.6, appears centered at the same frequency in the mixed solute as a complex multiplet. Addition of some benzophenone hydrochloride **4** to the mixed solute causes resonances to appear near δ 10.95 and 8.75 for the tertiary and secondary amine protons of **4**, respectively, but not in an exact 1:1 ratio of integrated peaks possibly because of different proton exchange behavior. Further addition of the benzophenone hydrochloride to the mixed solute does not alter the chemical shifts of the resonances of the protonated amino groups of **4**, but it does result in further upfield shifting to δ ~4.5 (with concomitant narrowing) of the resonance for the protonated amino group of **3**. Because of the complexity of nitrogen-proton exchange in the mixed system and the possibility of some minor further decomposition products as indicated by the trace resonance at δ 10.9 and the shoulder on the high-field base side of the glycine amino resonance near δ 8.3, an aromatic proton multiplet centered near δ 7.48, arising from the fluorinated ring **4**, and appearing in a window for the aromatic protons of **2** could possibly be used as an alternative basis to confirm the levels from the protonated amine resonances in estimating the degree of degradation of **2** to **4**. Alternatively, the methyl triplets (Figure 5) could also be used for ratio determination. On these bases, the benzophenone **4** content was found to vary from ~3% to more than 35% of the drug (Table 2). These features will be discussed more fully together with other NMR complexities in a subsequent paper on the stability of flurazepam hydrochloride preparations.[20]

Support for the above assignments is found in the expanded spectrum for the methyl proton resonances of the ethylamino moieties from both the benzophenone and parent substance. The expanded spectrum of this region (Figure 5) shows two methyl triplets of essentially equal intensity centered at δ 1.15 and 1.17, which can be attributed to the diethylamino group of the intact flurazepam (di)hydrochloride because of the steric rigidity its ethyl groups would experience (and thus be magnetically nonequivalent) possibly from intramolecular

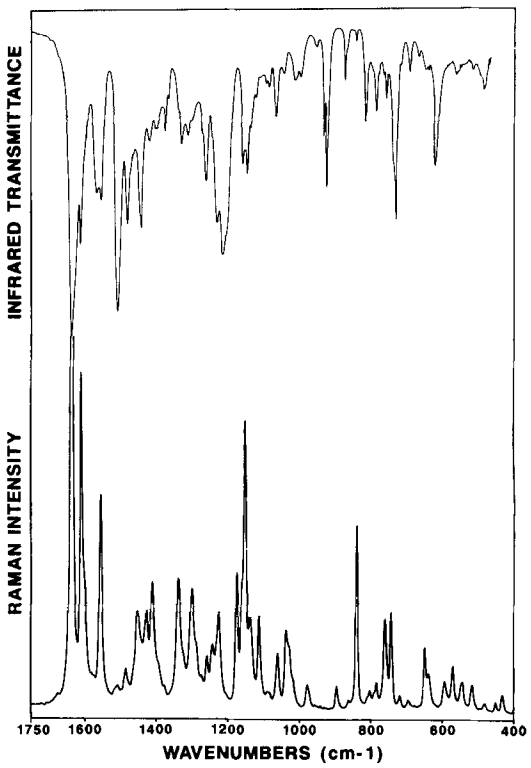

Figure 6—FT-Raman spectrum (lower) and IR (upper) spectrum of the fingerprint region (1750–400 cm^{-1}) of 5-chloro-2-[[2-(diethylamino)ethyl]amino]-2′-fluorobenzophenone hydrochloride (NF Reference Standard, Lot 578) determined in KBr. For experimental conditions, see the text.

hydrogen bonding in **2** but not in **4**. The other component of this methyl proton cluster is seen to consist of virtually a single methyl triplet centered at δ 1.23 and having slightly greater intensity than the other methyl triplets. The triplet centered at δ 1.23, therefore, would be consistent with the diethylamino group of the benzophenone **4** whose opened-ring structure would allow for less hindered rotation of the *N*-ethyl substituents (and apparent magnetic equivalence).

Raman and IR spectra of the "Benzophenone" Hydrochloride—Table 1 lists the wavenumbers (cm^{-1}) of bands observed in the Raman and IR spectra of 5-chloro-2-[[2-(diethylamino)ethyl]amino]-2′-fluorobenzophenone hydrochloride (**4**). It should be noted that many of the assignments suggested in Table 1 are made arbitrarily on the basis of the frequency ranges in which the observed bands occur.[21–24] The Raman and IR spectra of the "benzophenone" hydrochloride are shown together in Figure 6.

There are many similarities between the spectra of flurazepam (either the free base or the hydrochlorides)[19] and the "benzophenone" hydrochloride due to the presence of the two substituted benzene rings and the (diethylamino)ethyl group in each compound. Major differences in the spectra of the "benzophenone" hydrochloride can be attributed to the presence of an NH group (secondary amine) and the carbonyl group, which is now a benzophenone carbonyl group rather than a cyclic amido carbonyl group and the absence of the C=N group and the diazepine ring. A distinctive feature of the IR spectrum of the "benzophenone" hydrochloride is the very strong band at 1635 cm^{-1}. This is assigned to the C=O stretching mode and is in the usual region for substituted benzophenones.[21,22] The presence of the NH group is indicated by the sharp peak at 3298 cm^{-1} in the IR spectrum attributable to the NH stretching vibration. The tertiary amine hydrochloride group gives rise to the very broad feature between 2700 and 2400 cm^{-1}. This feature is very weak in the Raman spectrum.

Two important bands occur at similar frequencies in both Raman and IR spectra of flurazepam and the "benzophenone" hydrochloride near 1635 and 1610 cm^{-1}. The assignments, however, are completely different for each compound. For flurazepam dihydrochloride, the 1635 cm^{-1} frequency is attributed to the $C{=}N^+$ stretching mode of the diazepine ring, whereas in the spectra of the "benzophenone" hydrochloride the bands observed at this frequency are assigned to the C=O stretching mode. For flurazepam (di)hydrochloride the 1610 cm^{-1} frequency is assigned to a C=C stretching mode of a benzene ring, whereas for the "benzophenone" hydrochloride it is assigned to the deformation mode of the NH group attached to the benzene ring.

Several other major features of the "benzophenone" hydrochloride spectra contribute to the overall spectra of the degraded flurazepam (di)hydrochloride samples. In the Raman spectrum, a medium-strong band at 1554 cm^{-1} is assigned to a benzene ring C=C stretching mode; strong bands at 1149 and 837 cm^{-1} are assigned to a CH_2 wag mode and a C–N–C stretching mode, respectively, and two sharp bands of medium intensity at 742 and 758 cm^{-1} are attributed to a CH_2 rock and an out-of-plane CH deformation mode of the benzene ring. In the IR spectrum, a very strong band at 1510 cm^{-1} is assigned to the NH^+ deformation of the protonated (diethylamino)ethyl group. A strong band at 1227 cm^{-1} is assigned to the C–F stretching mode; strong absorptions at 755 and 943 cm^{-1} are attributed to out-of-plane CH deformation modes of the benzene ring, and a medium-strong band at 649 cm^{-1} is assigned to an in-plane deformation of the benzene ring.

References and Notes

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