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# The Behavior of 1,4-Benzodiazepine Drugs in Acidic Media. III.[1] Carbon-13 Nuclear Magnetic Resonance Spectra of Flutazolam in Acidic Aqueous Solution[2]

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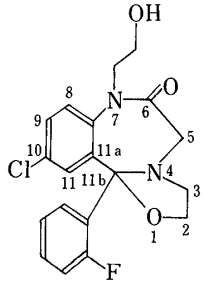
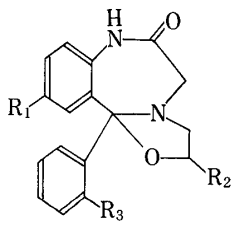
Structural changes of flutazolam in acidic aqueous solution were investigated by using proton and carbon-13 nuclear magnetic resonance spectroscopy. Flutazolam underwent a rapid cleavage of the oxazolidine ring to form an iminium compound, followed by slow hydrolysis of the iminium bond to give a benzophenone compound, like other 1,4-benzodiazepinooxazoles. Neutralization of the flutazolam solution caused recycling, which was not found in the case of other compounds that had no substituent at the nitrogen atom in position 7. The carbon-13 resonances of these compounds and of the corresponding aminobenzophenone derivatives isolated under strongly acidic conditions were assigned.

**Keywords**——flutazolam; benzodiazepine; acidic media; $^{1}$H-NMR; $^{13}$C-NMR

We have reported structural changes in oxazolam, cloxazolam, and haloxazolam in acidic aqueous solution,[3] and have investigated the kinetics and mechanism of the acid–base equilibrium reaction of oxazolam.[1] These three compounds are benzodiazepinooxazoles in the category of 1,4-benzodiazepine drugs with an oxazolidine ring at the 4 and 5 positions of the benzodiazepine ring. In the present work, we investigated the behavior in acidic aqueous solution of those three compounds and of 10-chloro-11b-(2-fluorophenyl)-2,3,5,6,7,11b-hexahydro-7-(2-hydroxyethyl)benzo[6,7]-1,4-diazepino[5,4-*b*]oxazol-6-one, flutazolam (I), which has a 2-hydroxyethyl group attached to the nitrogen atom at position 7.




flutazolam I




benzodiazepinooxazoles

| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| oxazolam | Cl | $CH_3$ | H |
| cloxazolam | Cl | H | Cl |
| haloxazolam | Br | H | F |

Chart 1

Ito *et al.*[4] reported on the decomposition of I in acidic aqueous solution using gas chromatography, but did not discuss the structural changes involved. However, the reaction mechanism is probably the same as for other benzodiazepinooxazoles. Structural changes of I

appear to take place in acidic aqueous solution during dissolution testing and drug administration, and therefore in this work, we have explored the process of the chemical change of I in acidic aqueous solution.

## Experimental

**Material**——Flutazolam (Lot A 424490) was kindly supplied by Mitsui Pharmaceutical Co., Ltd., and was used without further purification.

**Instrument**——Ultraviolet (UV) spectra, infrared (IR) spectra, pH values, and melting points were obtained by using a Hitachi UV 124 spectrophotometer, a JASCO-IRA 2 IR spectrophotometer, a Hitachi-Horiba F-7 pH meter, and a Yanagimoto micro-melting point apparatus (uncorrected), respectively. The $^{1}H$ nuclear magnetic resonance (NMR) spectra were obtained on a JEOL JNM-FX 100 spectrometer at 100 MHz, and $^{13}C$-NMR spectra on a JEOL JNM-FX 100 or GX 400 spectrometer at 25 or 100 MHz.

**Measurement of NMR Spectra**——A solution was prepared by dissolving 30 mg of the sample in 0.4 ml of chloroform-*d* ($CDCl_3$) or dimethylsulfoxide-$d_6$ (DMSO-$d_6$), or by dissolving 20 mg of the sample in 0.4 ml of 0.5 N deuterium chloride (DCl). The conditions of measurement for the $^{13}C$-NMR spectra were as follows: spectral width, 6000 Hz with 8K memory points; repetition time, 2.0 s; pulse width, 6 $\mu$s; number of pulses accumulated, 2000 to 30000. The chemical shift values ($\delta$) were expressed in ppm relative to tetramethylsilane (TMS) used as an internal or external standard, and the coupling constants ($J$) were expressed in Hertz (Hz). The various carbon resonances were assigned on the basis of chemical shift theory, multiplicities generated in single-frequency off-resonance decoupled spectra, and coupling constant values with the fluorine atom.

**Measurement of UV Spectra**——A stock ethanol solution of I ($5.36 \times 10^{-4}$ M) was prepared. Five milliliters of the stock solution was diluted to 100 ml with hydrochloric acid solution. The diluted solution (pH 1.3), which contained 5% (v/v) ethanol and I ($2.68 \times 10^{-5}$ M), was tested after appropriate intervals to measure UV spectral changes.

**Isolation of Hydrolyzates**——*N*-(2-Hydroxyethyl)-*N*-[2-(*o*-fluorobenzoyl)-4-chloro]phenyl-2-(2-hydroxyethyl)-aminoacetamide Hydrochloride (III): A solution of I (500 mg) in 5% (v/v) concentrated hydrochloric acid in ethanol (50 ml) was stirred overnight at room temperature, and concentrated *in vacuo*. The residue was recrystallized from a mixture of ether and ethanol to give 460 mg (80.4%) of III, as colorless columns, mp 176—177 °C (dec.). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3460, 3340 (OH), 2640—2360 ($-\overset{+}{N}H_2-$), 1670 (CO), 1663 (NCO). *Anal.* Calcd for $C_{19}H_{20}ClFN_2O_4 \cdot HCl$: C, 52.91; H, 4.91; N, 6.50. Found: C, 52.93; H, 5.18; N, 6.56.

5-Chloro-2′-fluoro-2-(2-hydroxyethyl)aminobenzophenone (IV): A solution of I (500 mg) in 2 M HCl (10 ml) was stirred for 7 h at 80 °C. The solution was extracted with benzene. The organic layer was washed with $H_2O$, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallized from a mixture of benzene and pet. benzin to give 320 mg (82.2%) of IV, as yellow needles. mp 98.5—101 °C (lit.[5] mp 96—101 °C). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3310 (NH), 3250—3300 (OH), 1620 (CO). $^{1}H$-NMR ($CDCl_3$) $\delta$: 2.24 (1H, br s, OH), 3.46 (2H, t, $J$=6.0 Hz, $NCH_2$), 3.89 (2H, t, $J$=6.0 Hz, $CH_2O$), 6.68—7.64 (7H, m, aromatic protons), 9.04 (1H, br s, NH).

**Identification of Ring Re-closed Product**——A solution of I (100 mg) in 0.5 M HCl (10 ml) was stirred for 5 h at room temperature. The solution was neutralized with 1 M NaOH and extracted with $CHCl_3$. The organic layer was washed with $H_2O$, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallized from benzene to give 88 mg of I, as colorless prisms. mp 150—151 °C. The IR spectrum and melting point of this sample coincided with those of an authentic sample.

## Results and Discussion

### UV Spectral Changes in Acidic Aqueous Solution

The UV spectrum of I in hydrochloric acid, shown in Fig. 1, varied with time. The spectrum at time zero was nearly the same as that of oxazolam, and had absorption maxima at 241 and 282 nm. The changes were quite rapid even at room temperature, and a distinctively different spectrum was obtained three hours later. The spectrum seemed to reflect an apparent one-stage reaction with isosbestic points at about 255 and 270 nm. The final spectrum was similar to the spectra of the hydrolyzates of oxazolam and haloxazolam. These results were suggestive of the process shown in Chart 2, in which compound I takes the form of the oxazolidine ring-cleaved iminium structure II in acidic aqueous solution (as was the case with oxazolam), and then II is converted into the benzophenone structure III as a result of hydrolysis at the iminium site.

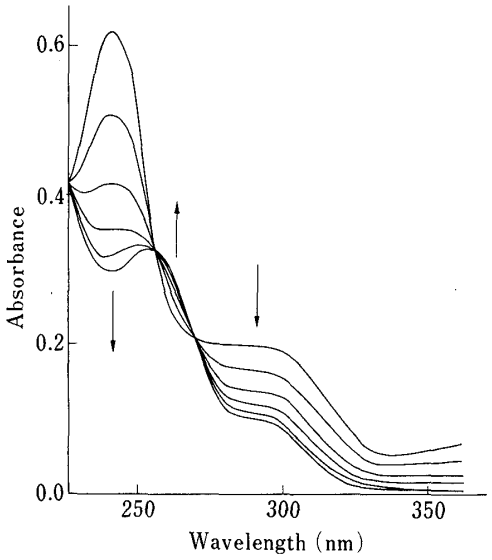



Fig. 1. Typical UV Spectral Changes during the Hydrolysis of $2.68 \times 10^{-5}$ M Flutazolam in Hydrochloric Acid Solution (pH 1.3) at 26 °C

The absorbance at 241 nm decreased with time (0, 10, 30, 60, 100 and 180 ($\infty$) min, from the top).

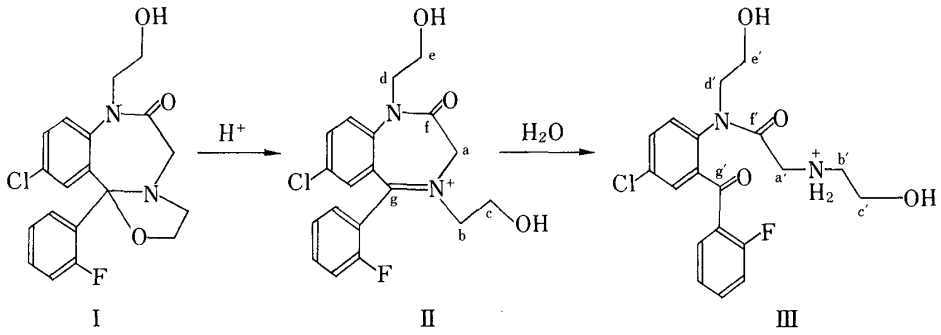



Chart 2

## $^1$H- and $^{13}$C-NMR Spectra in 0.5 N DCl Solution

The NMR spectra were examined in order to establish the structural changes anticipated from the UV spectral change. Figure 2, (A) and (B) show the $^1$H-NMR spectrum observed immediately after and three hours after preparation of a solution of I, respectively. Assignment of signals was difficult because of the complexity, in spite of the variation over time.

The $^{13}$C-NMR spectrum in Fig. 3A was taken after the $^1$H-NMR spectrum had ceased to change. The $^{13}$C-NMR data are listed in Table I. The adjoining two signals at $\delta$ 194.4 and 194.7, which had markedly different intensities, in the lowest field were assigned to the benzophenone carbonyl carbon atom, g′. Two other signals at $\delta$ 168.1 and 168.4, which also had different intensities, were assigned to the amide carbonyl carbon atom, f′. In the high field region, signals at $\delta$ 49.6 and 49.0, at $\delta$ 50.5, and at $\delta$ 57.8 were assigned to the a′, b′, and c′ methylene carbon atoms of III, respectively, by comparing the signals with those of the benzophenone structure formed from haloxazolam in acidic aqueous solution. Other signals at $\delta$ 52.7 and 53.5 were assigned to the d′ methylene carbon atom and that at $\delta$ 59.5 to the e′ methylene carbon atom. The amide carbonyl carbon (f′), benzophenone carbonyl carbon (g′), and a′ and d′ methylene carbon atoms each gave two signals that had different intensities.

As will be described later, compound III was isolated in the form of the hydrochloride salt and had a $^{13}$C-NMR spectrum identical to that of the product from I in 0.5 N DCl solution. The finding that the UV spectrum of III isolated in hydrochloric acid was identical to that of the product after completion of the structural changes suggested that the product was entirely in the form of the benzophenone structure, III, in acidic aqueous solution at room temperature. It also suggested the presence of the product in the form of two isomers

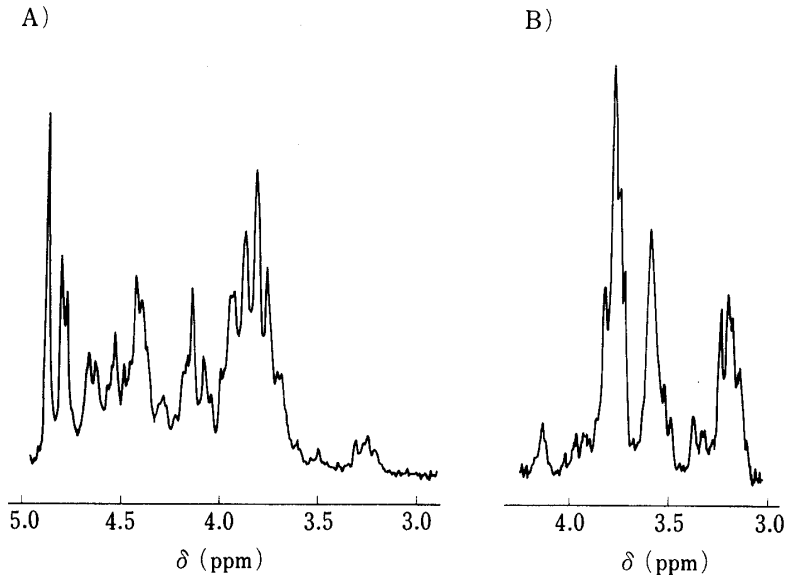



Fig. 2. The Upfield Region of the $^{1}$H-NMR Spectrum of Flutazolam in 0.5 N DCl
A) 0 h at 0 °C, B) 3 h at 23 °C.

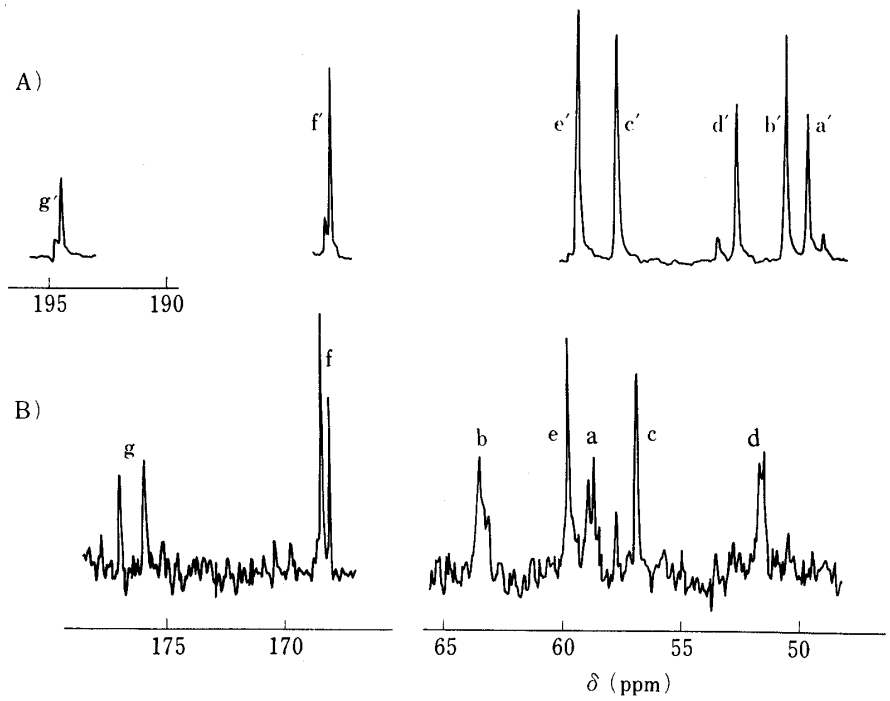



Fig. 3. The Aliphatic and Carbonyl Carbon Region of the $^{13}$C-NMR Spectrum of Flutazolam in 0.5 N DCl
A) 3 h at 23 °C, B) 0 h at 0 °C.

distinguishable by their NMR spectra in this solution.

In view of the UV spectral changes, we think that compound I in acidic aqueous solution was probably present in the form of the iminium structure, II, whose oxazolidine ring was cleaved, as with other benzodiazepinooxazoles. However, the $^{13}$C-NMR spectrum taken immediately after preparation of the sample at room temperature had less intense signals than those of III.

To obtain the spectrum of structure II, we prepared a solution of I in 0.5 N DCl and took the spectrum at 0 °C; the resulting $^{13}$C-NMR spectrum is shown in Fig. 3B. Spectral data are

TABLE I. $^{13}$C-NMR Spectral Data for the Benzophenone (III) and Iminium (II) Structures at 25 MHz

| Solvent | Compound | Carbons | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | a | b | c | d | e | f | g |
| 0.5 N DCl | IIIa | 49.6 | 50.5 | 57.8 | 52.7 | 59.5 | 168.1 | 194.4 |
| | IIIb | 49.0 | | | 53.5 | | 168.4 | 194.7 |
| DMSO-$d_6$[a)] | IIIa | 47.6 | 49.0 | 56.3 | 51.5 | 57.4 | 165.3 | 190.5 |
| | IIIb | 47.1 | 49.1 | 56.1 | 52.0 | 57.8 | 166.3 | 190.3 |
| 0.5 N DCl | II | 58.9 | 63.6 | 56.7 | 51.4 | 59.8 | 168.1 | 176.9 |
| | | 58.6 | 63.2 | | 51.2 | | 167.8 | 175.8 |

*a*) Signals were obtained at 100 MHz.

listed in Table I. This spectrum was clearly different from that of the benzophenone structure, III, and the benzophenone carbonyl signals were absent. Two signals of nearly the same intensity at $\delta$176.9 and 175.8 were assignable to the iminium carbon atom (g) characteristic of the iminium structure II, as also observed in other benzodiazepinooxazoles. Signals at $\delta$ 168.1 and 167.8 were assigned to the amide carbonyl carbon atom (f). The signals in high field at $\delta$ 58.9 and 58.6, at $\delta$ 63.6 and 63.2, and at $\delta$ 56.7 were assigned to the a, b, and c carbon atoms of structure II by comparison of the shift values of the iminium structure of haloxazolam. The remaining signals at $\delta$ 51.4 and 51.2, and at $\delta$ 59.8 were assigned to the d and e carbon atoms, based on the shift values. Based on these assignments, the spectrum in Fig. 3B is consistent with the structure of II.

The iminium and amide carbonyl carbon atoms each gave a pair of signals. The methylene carbon atom in the benzodiazepine ring of II and the b and d carbon atoms near this ring were each observed as two signals. These findings are suggestive of the presence of two isomers related to the iminium structure II. Because the iminium form of haloxazolam has only a single structure, the formation of the isomers might be attributable to the presence of the 2-hydroxyethyl group substituted on the amide nitrogen atom. The existence of the isomers could be explained by assuming that the amide carbonyl group and the 2-hydroxylethyl group attached to the amide nitrogen atom do not lie in the same plane but are twisted relative to each other. However, if rapid rotation occurred around the linking axis of the iminium carbon atom and the 2′-fluorophenyl group, the carbon resonances of the isomers might be euivalent. The two isomers due to a twist at the amide site might be observed because rotation of the 2′-fluorophenyl group is restricted by the 2-hydroxyethyl group substituted on the iminium nitrogen atom, as shown in Chart 3. The single-structure NMR spectrum of haloxazolam may arise because there are no substituents at the amide nitrogen site in the iminium structure of haloxazolam.

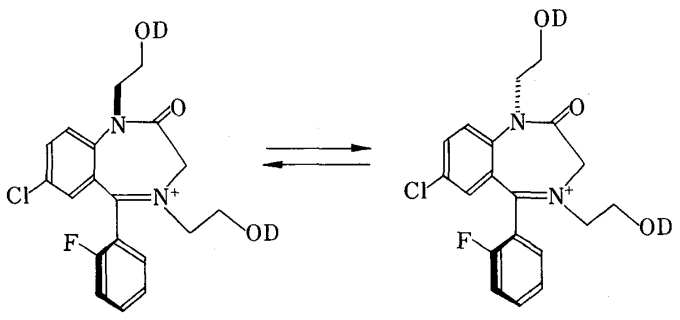



Chart 3

The iminium structure II mentioned here was not stable enough to record its $^{13}$C-NMR spectrum at room temperature. Thus, structure II is more unstable than the iminium structure of haloxazolam, and we did not attempt to investigate it further.

**Isolation of Hydrolyzate**

Compound I was subjected to hydrolysis *via* the process shown in Chart 2, giving the benzophenone structure III. When compound I was dissolved in 0.5 M hydrochloric acid to form III and the solution was neutralized and extracted with chloroform, the resultant substance was identified as the parent drug I, not the desired free base of III. After confirmation by UV spectrometry of the conversion in hydrochloric acid solution of I to III, the solution was brought to pH 9.0 with 1 M sodium hydroxide and then left for several hours at room temperature. Afterwards, the spectrum of the iminium structure II was restored by acidifying the solution again (to pH 1.3) with 1 M hydrochloric acid. The results suggested that there was a reversible ring-closure reaction from III to I, which has properties markedly different from those of oxazolam and haloxazolam, which lack substituents at the amide nitrogen atom.

The following procedure was used to obtain III. Compound I was dissolved in a 5% solution of concentrated hydrochloric acid in ethanol, the solution was concentrated *in vacuo*, and the resultant residue was recrystallized from an ethanol–ether mixture, giving colorless columns, mp 176—177 °C (dec.). The values of elemental analysis were in agreement with the formula $C_{19}H_{20}ClFN_2O_4 \cdot HCl$, and the IR spectrum suggested that hydroxyl, amide carbonyl, and benzophenone carbonyl groups were present. The $^{13}$C-NMR signals (DMSO-$d_6$) were assignable to five methylene (a′, b′, c′, d′, and e′) carbon atoms, and amide carbonyl (f′) and benzophenone carbonyl (g′) carbon atoms (Table I). From the results, we identified the compound as the hydrochloride salt of the benzophenone structure III. The assignment of the

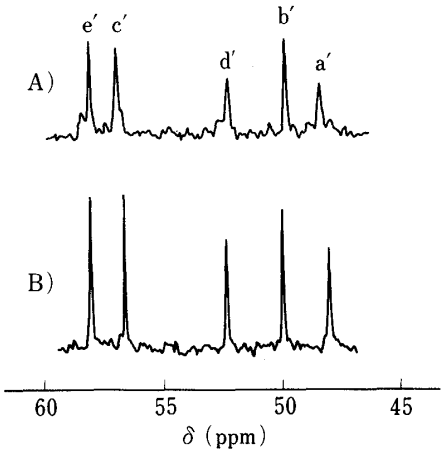
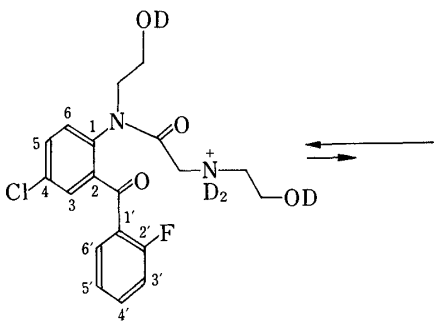
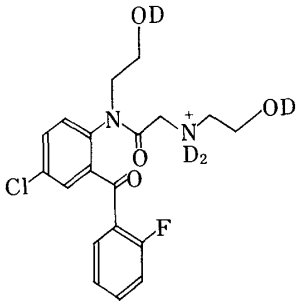



Fig. 4. The Upfield Region of the $^{13}$C-NMR Spectrum of III in DMSO-$d_6$
A) 23 °C, B) 120 °C.

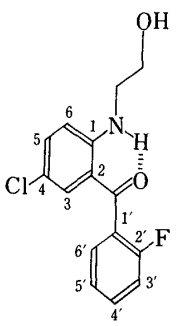


*cis* IIIa



*trans* IIIb

Chart 4



IV

Chart 5

TABLE II. $^{13}$C-NMR Spectral Data for IV and Aromatic Carbons of III[a,b]

| Carbons | Compounds | IV | III | |
|---|---|---|---|---|
| | Solvent | $CDCl_3$ | DMSO-$d_6$ | 0.5 N DCl |
| 1 | | 150.5 | 138.3 | 138.3 |
| 2 | | 119.0[c] | 136.7[d] | 137.1[f] |
| 3 | | 134.0 | 132.8 | 133.6 |
| 4 | | 118.3[e] | 133.5[d] | 136.3[f] |
| 5 | | 135.7 | 133.2 | 135.2 |
| 6 | | 113.4 | 131.7[e] | 133.0[g] |
| 1′ | | 128.0 (16.1) | 124.8 (12.2) | 126.0 (13.3) |
| 2′ | | 158.9 (250.6) | 160.5 (253.3) | 162.1 (254.8) |
| 3′ | | 116.2 (22.0) | 116.8 (21.3) | 118.0 (22.3) |
| 4′ | | 132.1 (7.3) | 135.9 (9.1) | 137.6 (8.8) |
| 5′ | | 124.3 (4.4) | 125.0 | 126.1 |
| 6′ | | 129.6 (2.9) | 129.9[e] | 132.9[g] |
| C=O | | 194.6 | | |
| $NCH_2$ | | 45.0 | | |
| $CH_2OH$ | | 61.1 | | |

*a*) Only the signals of IIIa were assigned. *b*) The CF coupling constants, in Hz, are given in parentheses. *c*—*g*) In each column may be interchangeable.

aromatic carbon atoms of III is described in the section dealing with the isolation of IV.

The $^{13}$C-NMR spectrum of III when DMSO-$d_6$ was used as the solvent has signals that were less intense, as was the case with the spectrum of III prepared from I using 0.5 N DCl. Signals of III in DMSO-$d_6$ had no minor signals at 120 °C (Fig. 4). The results indicated that there was an equilibrium state at the exchange rate at which a pair of signals of different intensity could be distinguished by NMR spectroscopy. The signals were, we think, attributable to an isomer rotating around an amide bond (amide-rotamer)[6] in a tertiary amide (Chart 4). The amide-rotamer of III was in a considerably displaced equilibrium state. Signals of the amide-rotamer having the methylene carbon atom on the same side as the carbonyl oxygen atom were observed at higher field than those of the amide-rotamer having that carbon atom on the opposite side.[7] Therefore, the shift positions suggested that IIIa, with a *cis* configuration with respect to the 2-hydroxyethyl and carbonyl groups, was predominant. As judged from the off-resonance spectrum of III in 0.5 N DCl solution, signals assigned to the d′ methylene carbon atom at $\delta$ 52.7 gave no triplet. This was probably due to the nonequivalence of d′ methylene protons because they had assumed a IIIa strucuture.[8] These results suggest an equilibrium displaced to the IIIa side.

To obtain the final hydrolyzate, a 2 M hydrochloric acid solution of I was heated to give yellow needles with mp 98.5—101 °C. The product had the composition $C_{15}H_{13}ClFNO_2$ and the IR and NMR spectra helped us identify it as 5-chloro-2′-fluoro-2-(2-hydroxyethyl)amino benzophenone (IV)[5] hydrolyzed at the amide site (Chart 5). The $^{13}$C-NMR spectrum of IV was assigned on the basis of the chemical shifts shown in Table II together with the $J_{CF}$ values. The aromatic carbon atoms of III were assigned using the shift values of IV (Table II). Of the compounds belonging to III, only IIIa was assignable. Signals of every carbon atom of III were observed at lower field in 0.5 N DCl solution than in DMSO-$d_6$.

These results demonstrate that compound I, like other benzodiazepinooxazoles, is in the form of an iminium structure produced by rapid cleavage of the oxazolidine ring in acidic aqueous solution. However, the iminium structure is more unstable than that of haloxazolam and the $^{13}$C-NMR spectrum had to be observed at low temperatures. The resultant $^{13}$C-NMR spectrum showed that there were two isomers that we thought were produced by inversion of

the benzodiazepine ring to the iminium structure, in contrast to compounds lacking a substituent at the amide nitrogen atom. Compound II was further hydrolyzed at the iminium site to give the benzophenone structure III.

When we neutralized an acidic solution of III in an attempt to obtain the free base, compound III was ring-closed, unlike other benzodiazepinooxazoles, to yield the parent compound I. The high residual percentages given by Ito *et al.*[4] in reporting on the stability of I in acidic aqueous solution may be easily explained in terms of such ring re-closure caused by neutralization and subsequent extraction. In the case of haloxazolam, a similar compound, the amide linkage of the benzophenone structure produced by hydrolysis is present only in a *trans* conformation with respect to the aniline hydrogen atom and the amide carbonyl group, and is further stabilized by intramolecular hydrogen bonding. Because compound III is present in the equilibrium state of the amide-rotamer in solution, the amine side chain can easily approach the benzophenone carbonyl group, and this may account for the smooth ring-closing reaction. Accordingly, the reversible ring-closing reaction may be caused by the presence of a substituent at the amide nitrogen.

The equilibrium of the amide-rotamer of III was markedly displaced to one side, with IIIa (in a *cis* conformation with respect to the 2-hydroxyethyl and the carbonyl groups) being predominant. These results are different from those on amide-rotamer equilibria observed in *N*-methyldipeptidoamino benzophenone derivatives.[9]

The final hydrolyzate in acidic aqueous solution was amino benzophenone IV, as with other 1,4-benzodiazepine drugs.[10] Compound IV was formed only on heating, the amount produced being practically negligible at room temperature.

The isolated hydrochloride salt of the benzophenone structure III was water-soluble, and attempted generation of the free base of III gave the parent compound, I. These findings suggest that benzodiazepine compounds might be used as water-soluble prodrugs. Compound I as an drug for internal use may produce III under intragastric acidic conditions. When compound III passes to the intestine, it will revert to the parent drug I as a result of the elevation of pH. Accordingly, there should be little loss of drug bioavailability.

Compound III displayed pharmacological effectiveness nearly equal to that of I with regard to anticonvulsion, muscular relaxation, and thiopental hypnosis-potentiating activities.

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