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Synthesis of 3-Deuterated Diazepam and Nordiazepam 4-Oxides and Their Use in the Synthesis of Other 3-Deuterated Derivatives

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SUMMARY

The protons at 3-positions of diazepam 4-oxide and nordiazepam 4-oxide underwent an efficient deuterium exchange via keto-enol tautomerism in deuterated alkaline methanol. The 3-dideuterated 4-oxides were each used as a starting material to synthesize 3-monodeuterated oxazepam and its 3-acetate, 3-monodeuterated temazepam and its 3-acetate, and 3-dideuterated diazepam and nordiazepam.

Key Words: Diazepam, diazepam 4-oxide, nordiazepam, nordiazepam 4-oxide, oxazepam, temazepam.

INTRODUCTION

Diazepam (7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, DZ; Figure 1), oxazepam (7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one, OX) and temazepam (7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, TMZ) are among the most frequently prescribed anxiolytic/hypnotic drugs (1). OX and TMZ are pharmacologically active metabolites of DZ. The goals of this investigation were to prepare 3-dideuterated nordiazepam (7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one, NDZ) and DZ and 3-monodeuterated OX and TMZ containing >95 atom % deuterium. These deuterated compounds may be used as substrates to study isotope effects in oxidative reactions catalyzed by drug-metabolizing enzyme systems.

It was reported (2) that [3-$^2H_2$]diazepam (DZ-d2) containing greater than 95 atom % D could be prepared by two cycles of heating 0.5 g of DZ in 3 ml of D_2O (>99 atom % D) and 7 ml of dimethylformamide in a sealed tube in a 100°C oven for 24 hr. Using the same procedure, an 89% deuterium incorporation into DZ was reported by other investigators (3). By using a slightly modified patented procedure, Forgione et al. (4) reported the synthesis of a partially dideuterated [3-$^2H_2$]NDZ (NDZ-d2, 61 atom % D). A NDZ-d2 with 87 atom % D was synthesized in ~30% yield by refluxing 2-amino-7-chloro-3-hydro-5-phenyl-1,4-benzodiazepine for 30 min in 0.5 ml of 20% DCl in D_2O and

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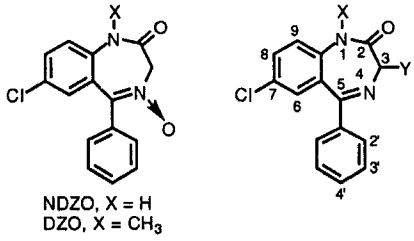
4 ml of CD_3OD (5); the same procedure using NDZ as the starting compound resulted in a NDZ-d2 with 50 atom % D (~40% yield). However, acid-catalyzed deuteration at the C3 position of NDZ (5) was not practical because the procedure resulted in extensive formation of 2-amino-5-chloro-benzophenone. 1,4-Benzodiazepines are known to be readily converted to benzophenones at elevated temperatures in strongly acidic aqueous solutions (6, 7).



NDZO, X = H
DZO, X = CH_3

NDZ, X = Y = H
OXA, X = H, Y = $OCOCH_3$
OX, X = H, Y = OH
DZ, X = CH_3, Y = H
TMZA, X = CH_3, Y = $OCOCH_3$
TMZ, X = CH_3, Y = OH

Fig. 1. Structure and abbreviation of nordiazepam (NDZ), nordiazepam 4-oxide (NDZO), oxazepam 3-acetate (OXA), oxazepam (OX), diazepam (DZ), diazepam 4-oxide (DZO), temazepam 3-acetate (TMZA), and temazepam (TMZ).

[3-^{2}H]OX (OX-d1) may be synthesized via an established 3-step procedure; NDZ-d2 → [3-$^2H_2$]NDZ 4–oxide (NDZO-d2) → [3-^{2}H]OXA (OXA-d1) → OX-d1 (4, 8). However, because of the lack of availability of a highly dideuterated (≥95 atom % D) NDZ, it has not been possible to synthesize highly deuterated NDZO-d2, OXA-d1, and OX-d1 on a large scale. Recently, a one-step procedure to synthesize OX-d1 (~95 atom % D) from OX was described (9). However, decomposition products were formed and, while the method (9) could be used to prepare OX-d1 in a small quantity, it was not suitable for large scale preparations.

There are no reports to the synthesis of [3-^{2}H]TMZ (TMZ-d1) and this may be due to the lack of availability of an appropriate large scale synthesis of DZ-d2. If DZ-d2 was readily available, TMZ-d1 could have been readily synthesized via the established 3-step procedure; DZ-d2 → [3-$^2H_2$]DZ 4–oxide (DZO-d2) → [3-^{2}H]TMZA (TMZA-d1) → TMZ-d1 (8). Under the experimental conditions to prepare OX-d1 from OX (9), the yield of TMZ-d1 was low because TMZ underwent significant base-catalyzed rearrangement (10).

In this report, we describe our findings that the protons at the 3-positions of NDZO and DZO readily underwent an efficient base-catalyzed deuterium exchange via a keto-enol tautomerism similar to those found in the racemization of OXA enantiomers (11) and in the preparation of OX-d1 from OX (9). NDZO-d2 and DZO-d2 could be readily prepared on a reasonably large scale. The 3-dideuterated NDZO-d2 was successfully used to synthesize OXA-d1, OX-d1, and NDZ-d2 similarly acccording to the established methods for the synthesis of nondeuterated compounds (8). Similarly, DZO-d2 was readily prepared from unlabeled DZO and subsequently used to synthesize TMZA-d1, TMZ-d1, and DZ-d2.

EXPERIMENTAL

Materials. The dipotassium salt of 7-chloro-1,3-dihydro-2,2-dihydroxy-5-phenyl-1H-1,4-benzodiazepine-3-carboxylic acid (clorazepate) was purchased from Sigma Chemical Co. (St. Louis, MO). HPLC grade solvents, CH_3OD (MeOD; 99.5+ atom % D), D_2O (99.9 atom % D), D_2SO_4 (98

wt % solution in D_2O, 99.5+ atom % D), DCl (20 wt % solution in D_2O, 99.5 atom % D), and NaOD (40 wt % solution in D_2O, 99.9 atom % D) were obtained from Aldrich Chemical Co. (Milwaukee, WI). NDZ was synthesized from clorazepate by acid hydrolysis (12). DZ was synthesized from NDZ by methylation with dimethyl sulfate (8).

NDZO and DZO were synthesized from NDZ and DZ respectively by a modified procedure of Sternbach and Reeder (13). Briefly, NDZ (or DZ, 10 g) was dissolved in 250 ml of glacial acetic acid and 16 ml of peracetic acid (32 wt % solution in dilute acetic acid). The mixture was left standing at room temperature for 24 hr. Water (2 liters) was added to precipitate the NDZO (or DZO) formed and the solution was neutralized with Na_2CO_3 powder under stirring, then left standing for 2 hr to allow precipitation to complete. The precipitate was filtered, washed with water, dried *in vacuo*. NDZO (colorless needle) was recrystallized from ethanol. DZO (colorless needle) was recrystallized from ethanol:hexane (4:1, v/v). The yields of NDZO and DZO were 80% and 77%, respectively.

Reversed-Phase HPLC. The progress of various reactions described in this report were monitored by reversed-phase HPLC using a Waters Associates (Milford, MA) Model M45 solvent pump and a Kratos (Kratos Analytical Instruments, Ramsey, NJ) Model Spectraflow 757 uv-vis variable wavelength detector set at 232 nm. A Zorbax SB-C18 column (3.5 μ particles, 4.6 mm i.d. x 15 cm; Mac-Mod Analytical Inc., Chadds Ford, PA) was used. The mobile phase was MeCN:0.02 M phosphate buffer pH 7 (1:1, v/v) at a flow rate of 1 ml/min. HPLC analysis was performed at ambient temperature. Samples were injected via a Shimadzu (Shimadzu Corp., Kyoto, Japan) Model SIL-9A automatic sample injector.

Spectral Analysis. Direct exposure electron impact mass spectral analysis was performed on a Finnigan 4500 gas chromatograph-mass spectrometer-data system (Finnigan MAT, San Jose, CA) at 70 eV. The ion source was maintained at 105°C. Diagnostic mass spectral data are listed below for purposes of indicating the extent of deuterium incorporation. Complete mass spectral data for compounds of interest were compiled by Schütz (14). Fourier transform ^{1}H-NMR spectral analysis was performed with a Model GEMINI 300 MHz spectrometer (Varian Associates, Palo Alto, CA). The sample was dissolved in either $CDCl_3$ or $(CD_3)_2SO$ (DMSO-d6) with a trace of tetramethylsilane (TMS). Signals of exchangeable protons were confirmed by the addition of ~0.05 ml of D_2O. Chemical shifts are in ppm relative to TMS.

Synthesis of [3-$^2H_2$]7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide (NDZO-d2)

NDZO (1 g) in MeOD (50 ml) was added with 0.33 ml of 15 M NaOD. The solution was refluxed for 8 hr, neutralized by dropwise addition of 1 M D_2SO_4 (in D_2O), extracted with $CHCl_3$ (50 ml), washed with water (3 x 50 ml). The organic layer was evaporated to dryness *in vacuo*. The procedure was repeated once to ensure complete deuterium exchange. The product [NDZO-d2, 0.92 g; 99±1 (n = 4) atom % D] in the residue was recrystallized from acetone. MS of NDZO: *m/z* 285 (100%), 286 (M^+, 88%), 287 (45%), 288 (29%), 289 (5%), 290 (0.5%). MS of NDZO-d2: *m/z* 285 (0%), 286 (0%), 287 (100%), 288 (M^+, 81%), 289 (43%), 290 (28%), 291 (5%), and 292 (0.7%). ^{1}H-NMR of NDZO (DMSO-d6): δ 4.60 (2H, C3-H_2, broad s), 6.93 (1H, aromatic, d; J = 2.2 Hz), 7.29 (1H, aromatic, d; J = 8.8 Hz), 7.44-7.57 (6H, aromatic, m), and 11.15 (1H, N1-H, s) ppm. ^{1}H-NMR of NDZO-d2 (DMSO-d6): δ 6.92 (1H, aromatic, d; J = 1.1 Hz), 7.29 (1H, aromatic, d; J = 8.8 Hz),

7.45-7.54 (6H, aromatic, m), and 11.15 (1H, N1-H, s) ppm; the signals for protons at C3 were not detected. In the spectra of both NDZO and NDZO-d2, the signals for the protons at N1 disappeared upon the addition of D_2O.

Synthesis of [3-^{2}H]3-acetoxy-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (OXA-d1)

This procedure was similar to that described by Bell and Childress (8). A suspension of NDZO-d2 [1 g, 99±1 (n = 4) atom % D] in acetic anhydride (10 ml) was stirred and heated on a steam bath for 3 hr; a clear solution resulted gradually. Upon cooling, crystals of OXA-d1 [1 g, 98±1 (n = 3) atom % D] was obtained. MS of OXA: *m/z* 43 (42%), 257 (100%), 258 (19 %), 259 (32%), 285 (7%), 286 (79%), and 328 (M^+, 2%). MS of OXA-d1: *m/z* 43 (100%), 257 (50%), 258 (43%), 259 (24%), 285 (0.4%), 286 (9%), 287 (54%), and 329 (M^+, 2.9%). ^{1}H-NMR of OXA ($CDCl_3$): δ 2.35 (3H, CH_3CO, s), 5.99 (1H, C3-H, s), 7.15-7.62 (8H, aromatic, m), and 8.53 (1H, N1-H, s) ppm. ^{1}H-NMR of OXA-d1 ($CDCl_3$): δ 2.35 (3H, CH_3CO, s), 7.15-7.62 (8H, aromatic, m), and 8.53 (1H, N1-H, s) ppm. In the spectra of both OXA and OXA-d1, the signals for the protons at N1 disappeared upon the addition of D_2O.

Synthesis of [3-^{2}H]7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one (OX-d1)

This procedure was modified from that of Bell and Childress (8). OXA-d1 [0.7 g, 98±1 (n = 3) atom % D] in MeOD (16 ml) was added with 4 M NaOD (1.2 ml). The solution was clear following dissolution of OXA-d1 in the first few minutes, but subsequently became cloudy due to the formation of a salt. After standing at room temperature for 30 min, D_2O (16 ml) was added to dissolve the salt. The solution was neutralized by the addition of 1 M D_2SO_4 (in D_2O) under stirring. The product [OX-d1, 0.49 g; 97±2 (n = 5) atom % D] in the residue was recrystallized from C_2H_5OD. MS of OX: *m/z* 77 (100%), 257 (87%), 258 (3%), 259 (35%), 285 (5%), 286 (M^+, 13%), 287 (4%), and 288 (5%). MS of OX-d1: *m/z* 77 (90%), 257 (100%), 258 (30%), 259 (38%), 285 (0%), 286 (8%), 287 (M^+, 22%), 288 (7%), and 289 (8%). ^{1}H-NMR of OX ($CDCl_3$): δ 4.53 (1H, C3-OH, d; J = 8.9 Hz), 5.03 (1H, C3-H, d; J = 8.9 Hz), 7.12-7.60 (8H, aromatic, m), and 8.24 (1H, N1-H, s) ppm. Upon the addition of D_2O, the signal for C3-H became a singlet at 5.02 ppm and the signals for N1-H and C3-OH disappeared. ^{1}H-NMR of OX-d1 ($CDCl_3$): δ 4.52 (1H, C3-OH, s), 7.13-7.60 (8H, aromatic, m), and 8.42 (1H, N1-H, s) ppm; the signal for the proton at C3 was not detectable. Upon the addition of D_2O, the signals for N1-H and C3-OH disappeared.

Synthesis of [3-$^2H_2$]7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (NDZ-d2)

This procedure was modified from that described by Sternbach and Reeder (13) in the synthesis of NDZ from NDZO. NDZO-d2 [1 g, 99±1 (n = 4) atom % D] was dissolved in $CHCl_3$ (80 ml) and PCl_3 (1.7 ml) was subsequently added. Following reflux for 3 hr, the solution was poured into ice-cold D_2O (80 ml) and made alkaline by dropwise addition of 15 M NaOD. The aqueous phase was extracted with chloroform. The organic phases were combined, dehydrated with anhydrous $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The product [NDZ-d2, 0.79 g; 95±3 (n = 5) atom % D by EI-MS analysis] in the residue was recrystallized from acetone. MS of NDZ: *m/z* 235 (16%), 237 (0%), 268 (1%), 269 (75%), 270 (M^+, 100%), 271 (45%), 272 (34%), 273 (7%), and 274 (1%).

MS of NDZ-d2: *m/z* 235 (1%), 237 (14%), 269 (1%), 270 (5%), 271 (71%), 272 (M^+, 100%), 273 (45%), 274 (35%), 275 (7%), and 276 (0.9%). It is of interest to note that, while a sample of NDZ-d2 exhibited no detectable signal of protons at C3 by ^{1}H-NMR analysis (see below), low intensities of mass ions at *m/z* 269 and 270 were detected by solid probe EI-MS analysis. The results indicated that the protons at C3 had undergone some H-D exchanges during EI-MS analysis.

^{1}H-NMR of NDZ ($CDCl_3$): δ 4.33 (2H, C3-H, broad s), 7.13-7.54 (8H, aromatic, m), and 9.61 (1H, N1-H, broad s) ppm. ^{1}H-NMR of NDZ-d2 ($CDCl_3$): δ 7.13-7.55 (8H, aromatic, m) and 9.38 (1H, N1-H, broad s) ppm; the signal for the proton at C3 was not detectable. In the spectra of both NDZ and NDZ-d2, the signals for the protons at N1 disappeared upon the addition of D_2O.

Synthesis of [3-$^2H_2$]7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide (DZO-d2)

DZO (1 g) in MeOD (50 ml) was added with 0.33 ml of 15 M NaOD. The mixture was left standing at room temperature for 4 hr and neutralized with 1 M D_2SO_4 (in D_2O). The solution was extracted with $CHCl_3$ (50 ml) and washed with water (3 x 25 ml). The organic layer was evaporated to dryness *in vacuo*. The procedure was repeated once to ensure complete deuterium exchange. The product [DZO-d2, 0.9 g; 99±1 (n = 3) atom % D] in the residue was crystallized from acetone. MS of DZO: *m/z* 77 (100%), 283 (30%), 284 (8%), 285 (11%), 299 (88%), 300 (M^+, 85%), 301 (42%), and 302 (27%). MS of DZO-d2: *m/z* 77 (45%), 299 (0%), 300 (0%), 301 (100%), and 302 (M^+, 91%).

^{1}H-NMR of DZO (DMSO-d6): δ 3.42 (3H, N1-CH_3, s), 4.34 (C3-H_a, d; J = 12.8 Hz), 4.90 (C3-H_b, d; J = 12.9 Hz), 6.99 (1H, aromatic, apparent s), 7.45-7.46 (3H, aromatic, m), and 7.62-7.64 (4H, aromatic, m) ppm. ^{1}H-NMR of DZO-d2 (DMSO-d6): δ 3.42 (3H, N1-CH_3, s), 6.99 (1H, aromatic, apparent s), 7.44-7.45 (3H, aromatic, m), and 7.46-7.64 (4H, aromatic, m) ppm; the signals for the protons at C3 were not detected.

Synthesis of [3-^{2}H]3-acetoxy-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (TMZA-d1)

This procedure was essentially the same as that described by Bell and Childress (8). DZO-d2 [1 g, 99±1 (n = 3) atom % D] in acetic anhydride (10 ml) was stirred and heated on a steam bath for 3 hr; a clear solution resulted gradually upon heating. Upon cooling, TMZA-d1 [1 g, 97±2 (n = 3) atom % D] was crystallized from the solution. MS of TMZA: *m/z* 43 (100%), 271 (99%), 272 (18%), 273 (34.4%), 300 (35%), 301 (6%), 342 (M^+, 5%), and 343 (1%). MS of TMZA-d1: *m/z* 43 (100%), 271 (20%), 272 (17%), 273 (8%), 300 (1%), 301 (9%), 342 (0%), and 343 (M^+, 5%). ^{1}H-NMR of TMZA ($CDCl_3$): δ 2.34 (3H, C3-OCOCH_3, s), 3.46 (3H, N1-CH_3, s), 5.95 (1H, C3-H, s), and 7.35-7.68 (8H, aromatic, m) ppm. ^{1}H-NMR of TMZA-d1 ($CDCl_3$): δ 2.33 (3H, C3-OCOCH_3, s), 3.46 (3H, N1-CH_3, s), and 7.35-7.68 (8H, aromatic, m) ppm.

Synthesis of [3-^{2}H]7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (TMZ-d1)

This method was modified from that of Bell and Childress (8). TMZA-d1 [0.5 g, 97±2 (n = 3) atom % D] in MeOD (30 ml) and 2.25 ml of 4 M NaOD (in D_2O) was stirred at room temperature for 1 hr. The salt formed was dissolved by the addition of D_2O (30 ml). TMZ-d1 (0.4 g) was precipitated by neutralization with 1 M D_2SO_4 (in D_2O). TMZ-d1 [0.36 g, 96±3 (n = 3) atom % D] was

subsequently recrystallized from ether:petroleum ether (1:1., v/v). MS of TMZ: *m/z* 271 (100%), 272 (10%), 299 (3%), 300 (M^+, 20%), 301 (5%), and 302 (7%). MS of TMZ-d1: *m/z* 271 (100%), 272 (10%), 299 (0%), 300 (4%), 301 (M^+, 30%), and 303 (12%). ^{1}H-NMR of TMZ ($CDCl_3$): δ 3.50 (3H, N1-CH_3, s), 4.74 (1H, C3-OH, d; J = 9.0 Hz), 4.99 (1H, C3-H, d; J = 9.2 Hz), and 7.34-7.65 (8H, aromatic, m) ppm. Upon the addition of D_2O, the signal for the proton at C3 became a singlet at 4.98 ppm and the signal for the hydroxyl group at C3 disappeared. ^{1}H-NMR of TMZ-d1 ($CDCl_3$): δ 3.50 (3H, N1-CH_3, s), 4.73 (1H, C3-OH, s), and 7.34-7.65 (8H, aromatic, m) ppm.

Synthesis of [3-$^2H_2$]7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (DZ-d2)

Method A. This procedure was modified from that described by Sternbach and Reeder (13). DZO-d2 [0.2 g, 99±1 (n = 3) atom % D] was dissolved in $CHCl_3$ (20 ml), followed by the addition of PCl_3 (0.3 ml). The solution was refluxed for 2 hr, then poured into ice-cold D_2O (20 ml). The resulting mixture was made alkaline by the addition of 15 M NaOD. The aqueous phase was further extracted with chloroform (2 x 20 ml). The organic phases were combined, dehydrated with anhydrous $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The product [DZ-d2, 0.15 g; 99±1 (n = 3) atom % D] in the residue was recrystallized from a mixture of ether:petroleum ether (1:1, v/v). MS of DZ: *m/z* 255 (36%), 256 (100%), 257 (52%), 258 (46%), 282 (1%), 283 (76%), 284 (M^+, 85%), 285 (48%), 286 (30%), and 287 (6%). MS of DZ-d2: *m/z* 255 (0%), 256 (100%), 257 (19%), 258 (40%), 282 (0%), 283 (1%), 284 (1%), 285 (51%), 286 (M^+, 55%), 287 (26%), 288 (19%), and 289 (3%). ^{1}H-NMR of DZ ($CDCl_3$): δ 3.39 (3H, N1-CH_3, s), 3.78 (1H, C3-H_a, d; J = 10.8 Hz), 4.84 (1H, C3-H_b, d; J = 10.8 Hz), and 7.26-7.62 (8H, aromatic, m) ppm. ^{1}H-NMR of DZ-d2 ($CDCl_3$): δ 3.39 (3H, N1-CH_3, s) and 7.26-7.62 (8H, aromatic, m) ppm; the signals for the protons at C3 were not detectable.

Method B. NDZ-d2 [100 mg, 99±1 (n = 3) atom % D] was dissolved in acetonitrile (5 ml) under stirring, followed by the addition of 4 M NaOD (0.1 ml). The resulting solution was stirred for 5 min, followed by the addition of dimethyl sulfate (7 x 5 μl). The mixture was stirred for 5 hr at room temperature. The solution was evaporated to dryness *in vacuo* and the residue was extracted with benzene. After benzene was removed by evaporation *in vacuo*, DZ-d2 (75 mg) contained in the residue was recrystallized from a mixture of ether and petroleum ether (1:1, v/v). MS of DZ-d2: *m/z* 255 (0%), 256 (100%), 257 (19%), 258 (40%), 282 (0%), 283 (0.5%), 284 (0.4%), 285 (54%), 286 (M^+, 57%), 287 (27%), 288 (20%), and 289 (3%).

RESULTS AND DISCUSSION

The most important finding of this study was the highly efficient one-step procedure in the preparation of NDZO-d2 and DZO-d2 from the unlabeled NDZO and DZO, respectively. The extent of deuterium incorporation was dependent on the molar ratio of MeOD to NDZO (or DZO). Thus, it is more economical to carry out the deuteration reaction more than once by using a smaller volume of MeOD sufficient to dissolve the reactant (NDZO or DZO). The synthesis of six other C3-deuterated compounds were straightforward via the established NDZO-d2 → OXA-d1 → OX-d1, NDZO-d2 → NDZ-d2, DZO-d2 → TMZA-d1 → TMZ-d1, DZO-d2 → DZ-d2, and NDZ-d2 → DZ-d2 pathways (see Experimental section for literature references).

We propose that a base-catalyzed keto-enol tautomerism (Figure 2) was responsible for the observed deuteration (either NDZO → NDZO-d2 or DZO → DZO-d2). Keto-enol tautomerism played a role in the racemization of OXA enantiomers (11) and was responsible for deuteration at C3 of OX (9) in alkaline media. Additional studies are being carried out to explore the structure-activity relationships of keto-enol tautomerism in 1,4-benzodiazepines in the preparation of various specifically deuterated compounds with high deuterium content. These compounds are valuable for the study of isotope effects in drug metabolism and fragmentation pathways in electron impact mass spectrometry.

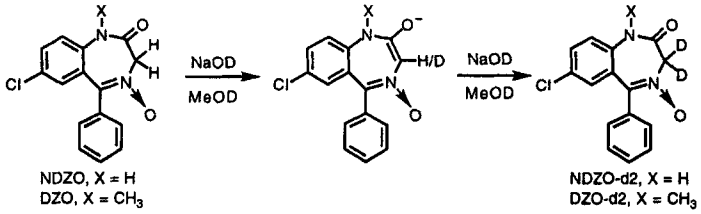


Fig. 2. Proposed keto-enol tautomerism responsible for the observed deuterium exchange of NDZO (X = H) and DZO (X = CH_3) in deuterated alkaline media. See text for discussion.

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