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Studies on Benzodiazepinooxazoles. IV.[1] The Formation of Quinolones by the Ring Contraction of a Benzo[6,7]-1,4-diazepino[5,4-*b*]-oxazole Derivative

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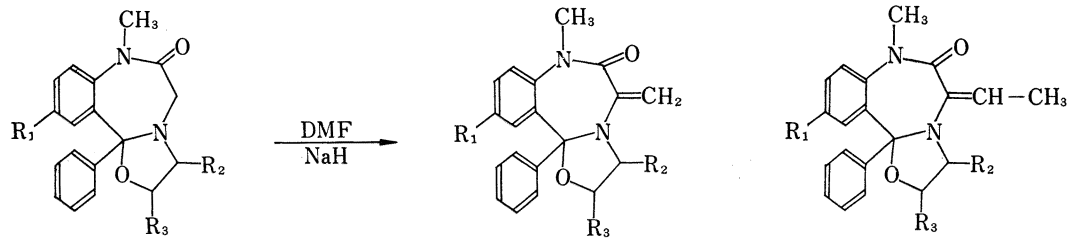
Treatment of 10-chloro-2,3,5,6,7,11b-hexahydro-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]oxazol-6-one (IV) with sodium hydride in dimethyl acetamide gave the two compounds, 6-chloro-3-(2-hydroxyethyl)-1-methyl-4-phenyl-2(1H)-quinolone (V) and 6-chloro-3-hydroxy-1-methyl-4-phenyl-2(1H)-quinolone (VI). A mechanistic assumption for the formation of V was discussed.

In the past few years, it has been reported that 1,4-benzodiazepines undergo rearrangements leading to isoindoles,[1,3] indoles,[4] quinazolines,[5–7] quinoxalines[8] and quinolines.[9]

In the preceding paper, we have reported[1] on the base-catalyzed intramolecular rearrangements of benzo[6,7]-1,4-diazepino[5,4-*b*] oxazoles giving isoindole and acridanone derivatives, and on the reactions of I with N,N-dimethyl formamide (DMF) in the presence of sodium hydride affording exo-methylene compounds as shown in Chart 1. Our interest in the for-



I II III

Chart 1

mation of the exo-methylene compounds prompted us to investigate the reaction of 1,4-benzodiazepinooxazoles with dimethyl acetamide (DMA) instead of DMF expecting the production of ethylidene compounds such as III. Contrary to our expectation, the reaction of 1,4-benzodiazepinooxazoles with sodium hydride in DMA gave no ethylidene compounds, but afforded some interesting rearrangement products with ring contraction.

Treatment of 10-chloro-2,3,5,6,7,11b-hexahydro-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]oxazol-6-one (IV) with sodium hydride in DMA at 110—120° gave two compounds (V and VI) of mp 167° and 248°.

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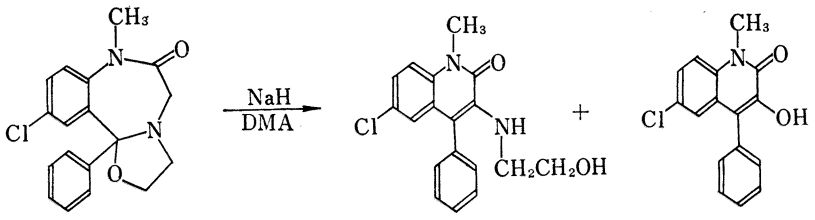


IV V VI

Chart 2

The lower melting point substance (V), obtained in 10% yield, had an empirical formula, $C_{18}H_{17}O_2N_2Cl$, which corresponded to that of the starting material (IV). The infrared (IR) spectrum of V showed a hydroxyl band at 3410 cm^{-1}, an amide band at 1635 cm^{-1} and a strong band at 1610 cm^{-1} for the tetrasubstituted double bond. The ultraviolet (UV) spectrum showed absorption maxima at 238, 261, 303, 314, 338, 352 nm with resembrance to that of 3-aminoquinolone derivative[10] as shown in Fig. 1. Fryer and his co-workers[10] have reported that 3-aminoquinolones show two characteristic absorption maxima in the 330—360 nm region, while 3-dialkylaminoquinolones which can not exist in the imino form exhibit a broad absorption band near 360 nm. It follows that the product (V) should have at least one hydrogen on the 3-amino nitrogen. The nuclear magnetic resonance (NMR) spectrum in d_6-DMSO exhibited a quartet at 2.51 ppm (2H, J=5.5 Hz) due to the methylene protons attached to the amino group, a quartet at 3.30 ppm (2H, J=5.5 Hz) assignable to another methylene protons adjacent to the hydroxyl group, a singlet at 3.79 ppm (3H) for the methyl protons, a triplet at 4.62 ppm (1H, J=5.5 Hz) assigned to the secondary amine proton, a triplet at 3.86 ppm (1H, J=5.5 Hz) due to the hydroxyl proton and an aromatic multiplet centered at 7.12 ppm (8H). The addition of deuterium oxide resulted in the spectral change of the two methylene quartets at 2.51 and 3.30 ppm to the two pairs of triplets at 2.58 and 3.39 ppm (J=5.5 Hz), respectively with disappearance of the amino and hydroxyl proton peaks. These results enabled one to assign V as 6-chloro-3-(2-hydroxyethyl)-1-methyl-4-phenyl-2(1H)-quinolone and the structure was confirmed by the following synthesis of V according to Fryer's method.[10] The ring closure reaction of VII[11] under basic conditions, and subsequent methylation with methyl iodide gave the cyclized compound (V). It should be noted that the alkylation of VIII with methyl iodide gave only the corresponding 1-alkyl derivative.

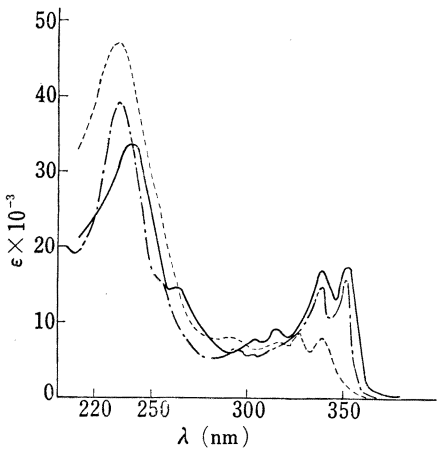
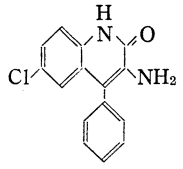


Fig. 1. UV Spectra of V, VI and 3-Amino-6-chloro-4-phenyl-2(1H)-quinolone

———: V
-------: VI
—·—·—:



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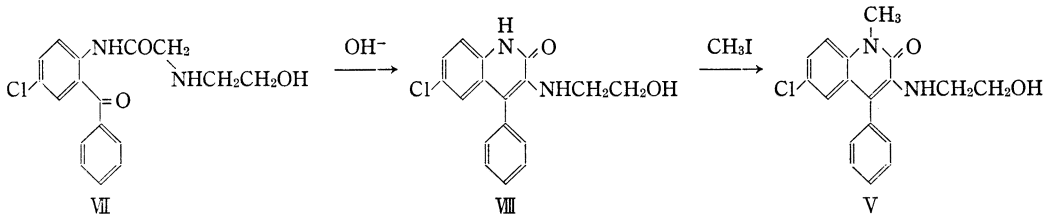

Chart 3

The higher melting point product (VI), obtained in 10% yield, agreeded with an empirical formula, $C_{16}H_{12}O_2NCl$. The IR spectrum showed a hydroxyl band at 3280 cm^{-1} and an amide band at 1640 cm^{-1}. The UV spectrum revealed an absorption characteristic of quinolones as shown in Fig. 1. By analogy with the 3-aminoquinolone derivatives, the two sharp absorption maxima at 327 and 339 nm can be ascribed to the keto form. The NMR spectrum exhibited a singlet at 3.80 ppm (3H) due to the methyl protons and an aromatic multiplet centered at 7.25 ppm (8H). These spectral data was in accord with the structure of 6-chloro-3-hydroxy-1-methyl-4-phenyl-2(1H)-quinolone and the final confirmation was made by comparison with a sample obtained by treatment of IX with ethanolic sodium hydroxide.

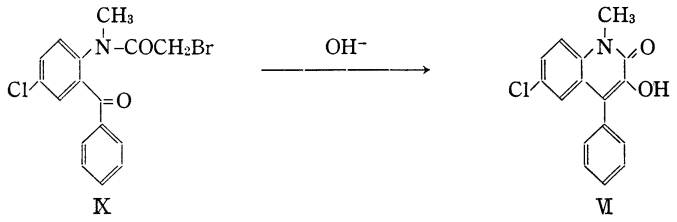

Chart 4

Regarding the reaction mechanism, the compound V, a possible precursor of VI, was treated under the reaction conditions employed for the DMA reaction, but no change was found even at an elevated (refluxing) temperature. The compound V undergoes acid-catalyzed hydrolysis with amide bond cleavage in which the 3-hydroxyl compound (VI) is not formed.[10] Thus, one can exclude the possibility that VI might be derived from V.

A plausible mechanism for the formation of V is shown in Chart 5. The initially formed carbanion (X) could undergo the ring contraction to afford the tricyclic intermediate (XI), followed by aziridine ring opening giving the product (V). On the other hand, a mechanism for the formation of VI is not clear at present and there remains unsolved this interesting rearrangement.

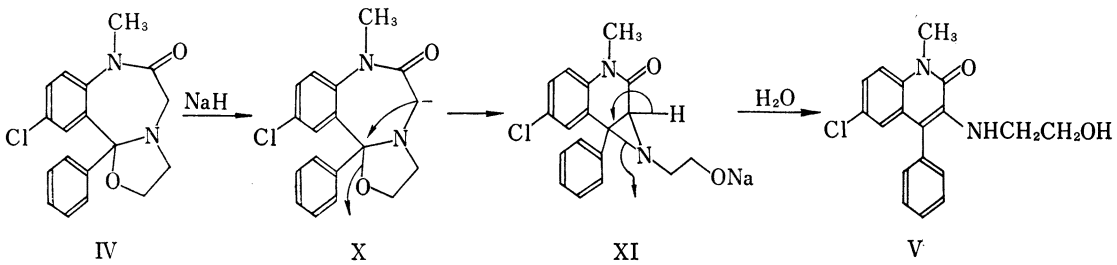

Chart 5

Behavioral differences between the formation of exo-methylene compound (II) in DMF[1] and the ring contraction products (V and VI) in DMA are not elucidated but it can be explained possibly by higher reactivity of DMF.

Experimental[12)]

6-Chloro-3-(2-hydroxyethylamino)-1-methyl-4-phenyl-2(1H)-quinolone (V) and 6-Chloro-3-hydroxy-1-methyl-4-phenyl-2(1H)-quinolone (VI)——A mixture of 10-chloro-2,3,5,6,7,11b-hexahydro-7-methyl-11b-phenylbenzo-[6,7]-1,4-diazepino[5,4-*b*]oxazol-6-one (IV) (3.3 g), DMA (15 ml) and NaH (50% oily mixture, 0.5 g) was heated at 110—120° for 6 hr under N_2 atmosphere. After cooling, the reaction mixture was poured into ice–water. The resulting precipitate was collected by filtration and recrystallized from EtOH to afford VI (0.29 g) as colorless needles, mp 246—248°. IR ν_{max}^{Nujol} cm^{-1}: 3280, 1640. UV λ_{max}^{EtOH} mμ (ε): 232.5 (47400), 292 (8500), 315 (7400), 327 (9800), 339 (8100). NMR (δ in d_6-DMSO): 3.80 (3H, singlet, $-\overset{|}{N}-CH_3$), 7.25 (center, 8H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{16}H_{12}O_2NCl$: C, 67.25; H, 4.23; N, 4.90; Cl, 12.41. Found: C, 67.34; H, 4.27; N, 4.94; Cl, 12.49. The aqueous layer was extracted with $CHCl_3$ and combined extracts were washed with H_2O and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and residual oily substance (2.6 g) was chromatographed on silica gel (100 g) and eluted with C_6H_6–AcOEt (5: 1) to give a solid. Recrystallization from EtOH gave V (0.33 g) as pale yellow needles, mp 165—167°. IR ν_{max}^{Nujol} cm^{-1}: 3410, 1635, 1610. UV λ_{max}^{EtOH} nm (ε): 238 (32800), 261 (14900), 303 (7800), 314 (9300), 338 (16900), 352 (17400). NMR (δ in d_6-DMSO): 2.51 (2H, quartet, J=5.5 Hz $-NH-CH_2-$), 3.30 (2H, quartet, J=5.5 Hz, $-CH_2-OH$), 3.79 (3H, singlet, $-N-CH_3$), 4.62 (1H, triplet, J=5.5 Hz, –NH–), 5.86 (1H, triplet, J=5.5 Hz, –OH), 7.12 (8H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{18}H_{17}O_2N_2Cl$: C, 65.75; H, 5.17; N, 8.52; Cl, 10.80. Found: C, 65.46; H, 5.20; N, 8.41; Cl, 10.84.

6-Chloro-3-(2-hydroxylethylamino)-4-phenyl-2(1H)-quinolone (VIII)——A mixture of NaOEt in EtOH, prepared from Na (0.23 g) and abs. EtOH (50 ml), and 5-chloro-2-(2-hydroxyethylaminoacetamido)-benzophenone (3.33 g) was refluxed for 2 hr. After cooling, 30 ml of H_2O was added to the above mixture. The reaction mixture was refluxed for 2 hr and then poured into ice–water. The resulting precipitate was collected by filtration and recrystallized from $CHCl_3$ to give VIII (0.85 g) as colorless needles, mp 228—230°. IR ν_{max}^{Nujol} cm^{-1}: 3395, 1750. UV λ_{max}^{EtOH} nm (ε): 238 (34400), 260 (14600), 300 (8500), 311 (9600), 337 (17900), 351 (18400). NMR (δ in d_6-DMSO): 2.56 (2H, quartet, J=5.5 Hz, $-NH-CH_2-$), 3.34 (2H, quartet, J=5.5 Hz, $-CH_2-OH$), 4.64 (1H, triplet, J=5.5 Hz, –NH), 5.78 (1H, triplet, J=5.5 Hz, –OH), 6.70—7.70 (8H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{17}H_{15}O_2N_2Cl$: C, 64.86; H, 4.80; N, 8.90; Cl, 11.26. Found: C, 64.42; H, 4.79; N, 8.54; Cl, 11.32.

6-Chloro-3-(2-hydroxyethylamino)-1-methyl-4-phenyl-2(1H)-quinolone (V) from VIII——To a mixture of NaOMe in MeOH, prepared from Na (0.069 g) and abs. MeOH (1 ml), 6-chloro-3-(2-hydroxyethyl)-4-phenyl-2(1H)-quinolone (VIII) (0.8 g) and 5 ml of DMF was added CH_3I (0.512 g) at 10°. The solution was stirred at room temperature for 3 hr and then poured into ice–water. The resulting precipitate was separated by filtration, washed with H_2O, and recrystallized from EtOH to give V (0.8 g) as pale yellow needles, mp 165—167°. The IR spectrum was superimposable on that of V obtained from IV.

6-Chloro-3-hydroxy-1-methyl-4-phenyl-2(1H)-quinolone (VI) from IX——To a solution of 5-chloro-2-(N-methylbromoacetamido)-benzophenone (16.0 g) in 170 ml of EtOH was added 130 ml of 1N NaOH at room temperature. After standing overnight, the reaction mixture was acidified with AcOH. The resulting precipitate was collected by filtration and recrystallized from EtOH to give VI (4.0 g) as colorless needles, mp 246—248°. The IR spectrum was superimposable on that of VI obtained from IV.

Acknowledgement We wish to express our gratitude to Dr. G. Sunagawa, Director of this Laboratories, and to Dr. K. Tanabe, Assistant Director, for their encouragement and discussion. We are also indebted to Miss M. Takemasa for her technical assistance.

12) All melting points are uncorrected. NMR spectra were recorded on a Varian A-60 spectrometer.