Two Modes of Reductive Ring Opening in
2,3-Dihydro-6,6-diphenylimidazo[2,1-b]oxazol-5(6H)one

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The bicyclic hydantoin 2,3-dihydro-6,6-diphenylimidazo[2,1-b]oxazol-5(6H)one (I) is the product resulting from the intramolecular alkylation of 3-(2-hydroxyethyl)-5,5-diphenylhydantoin mesylate (1). In an attempt to prepare compound II, the possibility of selectively reducing the C=N bond in I without affecting the amide carbonyl was studied.

While amides and esters are fairly unreactive towards sodium borohydride, esters can be reduced with a large excess of hydride in methanol (2). It was expected that the C=N bond in I might behave as an ester carbonyl and offer the possibility of affecting a selective reduction. Indeed, the compound resisted reduction when an equimolar amount or a slight excess of sodium borohydride was used, with only starting material recovered. A ten-fold excess was required to reduce I in almost quantitative yield to the 4-imidazolidinone (IV). Such a product suggests the intermediacy of the expected perhydroimidazo[2,1-b]oxazole (II) formed after hydride attack in the expected manner. It is postulated that II may then equilibrate with its corresponding ring-opened tautomer III, since ring-chain tautomerism involving hydroxyl and imine functions has been demonstrated (3-5). The imine function in III can then be further reduced to IV. Compound IV had a molecular ion peak at m/e 282, and its ir and nmr characteristics corresponded to those of pre-

of the borohydride reduction took place, it seemed possible that the reduction of the amide function without affecting the rest of the molecule might be possible by the selection of a suitable reducing agent. The reagent of choice was diborane owing to its success in reducing an amide carbonyl selectively and mildly in the presence of a thiolactim ether function (9). However, under similar conditions, the reaction took an unexpected course and the amide function remained unaltered. No trace
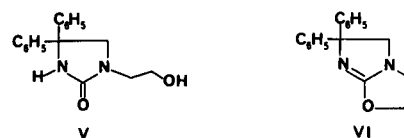
was found of the expected product, VI, which had been previously prepared by a different route in this laboratory (1). Chromatographic separation of the reaction mixture gave the intermediate reduction product 3-ethylhydantoin (VII) and the more completely reduced 3-ethyl-5,5-diphenyl-4-imidazolidinone (VIII).

The observed reduction products suggest that borane attacks the 2-position with IX being the initial intermediate from which compound VII is derived upon hydrolysis. Further reaction with additional borane then reduces IX to give VIII.
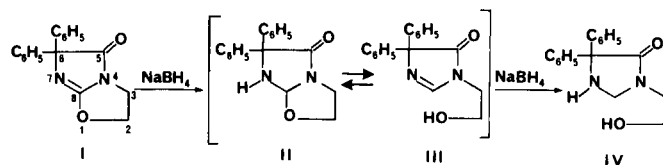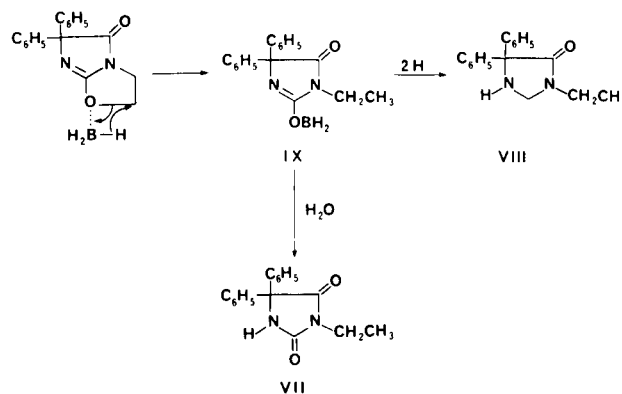

viously reported 4-imidazolidinones (6,7). This ring system has been prepared previously from the Raney-nickel desulfurization of 2-thiohydantoins (6,8). Compound V, an isomer of IV, had been previously prepared by the selective reduction of 3-(2-hydroxyethyl)-5,5-diphenylhydantoin (1).

In view of the stubborness with which the first step

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were measured with Perkin-Elmer 621 and 137 spectrometers. Nmr spectra were recorded on a Varian HA-100D spectrometer and chemical shifts are given in ppm from tetramethylsilane. Nmr spectra were determined as approximately 5% solutions in DMSO-d_6 unless otherwise stated. Elemental analyses were carried out by Dr. W. C. Alford, NIAMD, NIH. Mass spectra were determined by Mr. W. R. Landis, NIAMD, NIH, on a Hitachi/Perkin-Elmer RMU-7 instrument at 70 or 80 ev.

3-(2-Hydroxyethyl)-5,5-diphenyl-4-imidazolidinone (IV).

A suspension of I (0.278 g., 0.001 mole) in 15 ml. of methanol was refluxed in the presence of a ten-fold excess of sodium borohydride (0.540 g.) for 24 hours. After the addition of an excess of 10% hydrochloric acid, the solution was extracted with chloroform. The aqueous layer was then made basic with 10% sodium hydroxide and extracted with ethyl acetate several times. The organic layer was dried (sodium sulfate) and evaporated leaving an oil that solidified on standing overnight. After recrystallization from benzene, 0.25 g. (89%) of IV was obtained, m.p. 127-129°; ir (nujol) 3300, 3100, 1660, 1070, 1030, 960, 865, 755, and 700 cm^{-1}; nmr δ 3.22 (t, 2), 3.54 (t, 2), 4.67 (s, 2), 4.85 (s, 1), 6.54 (s, 1), and 7.30 (m, 10); mass spectrum m/e (rel. intensity) 282 (70) (parent), 252 (42), 239 (40), 205 (100), 194 (30), 165 (54), and 91 (60).

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.31; H, 6.42; N, 9.92. Found: C, 72.19; H, 6.29; N, 10.08.

Diborane Reduction of 2,3-dihydro-6,6-diphenylimidazo[2,1-b]-oxazol-5(6H)one (I).

A diborane-THF solution (14 ml., 0.014 mole) was placed in a 50 ml. 3-neck flask equipped with a magnetic stirrer, thermometer, dropping funnel, and condenser with a drying tube. The system was flushed with dry nitrogen gas and cooled to -8°. To the stirred solution, compound I (0.278 g., 0.001 mole), dissolved in 10 ml. of dry THF, was added slowly over a 15 minute period. The solution was allowed to warm to 5° in 15 minutes, and was then refluxed for 2.5 hours. The solution was cooled and aqueous THF (50%) was added dropwise until the evolution of gas ceased. Treatment with 18% hydrochloric acid (ca. 0.3 ml.) was followed by in vacuo removal of THF. After the solution was made alkaline with 25% sodium hydroxide, it was extracted with chloroform. The chloroform layer was dried (sodium sulfate) and evaporated to yield a clear oil. This oil shows two major and one

minor spots on tlc [alumina, benzene-ethyl acetate (2:1)], R_f 0.54, 0.43, and 0.07 respectively. Separation and isolation of the two major components by column chromatography [basic alumina (40 g.), benzene-ethyl acetate (3:1)] were accomplished. The oil which eluted first (170 mg., 64%), solidified upon scratching and was recrystallized from ether-petroleum ether to give needles, m.p. 88-89°. This compound was identified as 3-ethyl-5,5-diphenyl-4-imidazolidinone (VIII); ir (nujol) 3755, 1685, 1297, 875 and 700 cm^{-1}; nmr δ 1.02 (t, 3), 3.25 (q, 2), 3.82 (s, 1, broad), 4.26 (s, 2), and 7.26 and 7.46 (multiplets, 10); mass spectrum m/e (rel. intensity) 266 (2) (parent), 238 (2), 195 (73), 194 (100), 182 (33), 165 (7) and 104 (12).

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.94; H, 7.12; N, 10.33.

The oil eluted second from the column (65 mg., 23%) solidified upon standing and was recrystallized from benzene-petroleum ether to give fine crystals, m.p. 56-59°. This material was shown to be 3-ethyl-5,5-diphenylhydantoin (VII); ir (nujol) 3160, 3090, 1770, 1720, 1260, 1080, and 855 cm^{-1}; nmr δ 1.10 (t, 3), 3.46 (q, 2), 7.31 (s, 10), and 9.50 (s, 1, broad); mass spectrum m/e (rel. intensity) 280 (70) (parent), 252 (10), 251 (31), 210 (9), 209 (45), 208 (33), 202 (14), 194 (7), 181 (26), 180 (100).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75; N, 10.00. Found: C, 72.72; H, 6.05; N, 9.69.

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