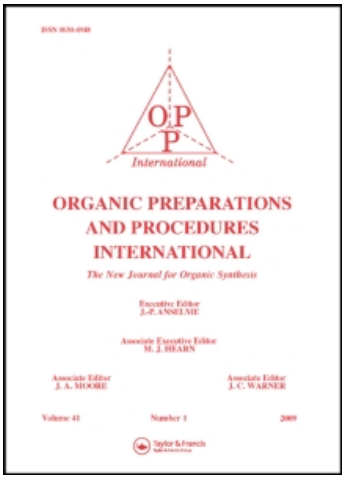

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THE 2- AND 4-NITRO AND 2- AND 4-ACETAMIDO 5,6,7,8,9,10-HEXAHYDRO DERIVATIVES OF CYCLOHEPTA[b]INDOLE

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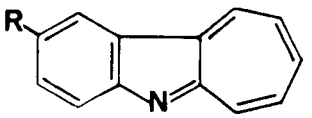
In connection with studies on hetero analogs of azulene,[1] it was desired to determine the position of electrophilic substitution on cyclohepta[b]indole (1-azaben[b]azulene,1a).[1a] Treatment of 1a with a 1:1 mixture of nitric and sulfuric acids gave 76% of the 2-nitro derivative (1b) and the use of an equivalent of potassium nitrate (instead of nitric acid) raised the yield to 82%[2]; no dinitrated products were found. Cyclization of the p-nitrophenylhydrazone of cycloheptanone with 10% sulfuric acid gave a low (20%) yield of 2b, which was also obtained (30%) from the nitration of hexahydrocyclohepta[b]indole (2a). Attempts to convert 2b to 1b by liquid (chloranil) or gas phase (10% Pd/C at 325°) dehydrogenation failed. Catalytic hydrogenation (Pt) of 2b afforded the somewhat unstable amine 2c (90%) which was converted to the amide 2d (94%). The direct conversion of 1b to 2c and then to 2d under the same conditions failed; however, stopping the hydrogenation of 1b after the absorption of three moles of hydrogen gave a 91% yield of 2b. By analogous reactions, the isomeric 4-nitro (2e), 4-amino (2f) and 4-N-acetamido (2g) compounds were prepared from cycloheptanone o-nitrophenylhydrazone in 54%, 100% and 82% yields respectively; they were readily distinguishable (mp and/or ^{1}H NMR and IR spectra) from 2b, 2c and 2d.



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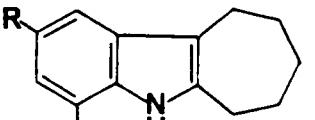
a) R = H b) R = NO_2



2

a) R = R' = H b) R = NO_2, R' = H
c) R = NH_2, R' = H d) R = NHAc, R' =H
e) R = H, R' = NO_2 f) R = H, R' = NH_2
g) R = H, R' = NHAc

EXPERIMENTAL SECTION

Mps. were dertermined on a Fisher-Johns apparatus and are uncorrected. Ultraviolet and visible spectra were taken on a Cary Model 11S Recording Spectrograph. Infrared spectra were obtained on a Perkin Elmer 21 Recording Spectrophotometer with NaCl cells. ^{1}H NMR spectra were recorded on a Varian VXR 300 spectrometer with Me_4Si as an internal standard. Elemental analyses were performed by B. Nist and C. H. Ludwig, University of Washington, Seattle, Washington.

Cyclohepta[b]indole (1a).- The method of Rogers and Corson[3] for the preparation of 5,6,7,8,9,10-hexahydrocyclohepta[b]indole (2a) was followed except that glacial acetic acid was used instead of aqueous alcohol-hydrochloric acid; the yield of 2a, mp. 140-141°, was 81%.[2] To a

boiling, stirred solution of the hexahydroindole (5 g, 0.027 mole), 1-pentanol (130 mL) and xylene (130 mL) was added chloranil (20 g, 0.084 mole) in 2-3 g portions and stirring and heating (under reflux) then continued for 12 hrs. After cooling, the filtered mixture was extracted with 10% NaOH solution until all the tetrachlorohydroquinone was removed (no precipitate formed when the extract was acidified); it was then extracted with four 50 mL portions of 3N hydrochloric acid. The black powder (presumed to be the hydrochloride of 1a) which precipitated from the acid extracts, was separated and heated with 50 mL of 3N hydrochloric acid. The undissolved black powder was separated and heated with a new portion of the acid, and this procedure was repeated again. The combined acid extracts were washed with 50 mL of CH_2Cl_2. The acid solution was basified with aqueous NaOH and then extracted with four 50 mL portions of CH_2Cl_2. The concentrate from the combined extracts was chromatographed (basic Al_2O_3, CH_2Cl_2). The bright red fraction yielded 0.68 g (14%) of 1a, mp. 140-141°,[2] having spectral characteristics (UV, visible, IR) identical to those reported.[2]

2-Nitrocyclohepta[b]indole (1b).- To a solution of 0.30 g (1.68 mmole) of 1a in 10 mL of concentrated sulfuric acid at -5° was added slowly 0.168 g (1.68 mmole) of KNO_3 and the mixture then stirred for 5 min., poured into ice water and the whole basified with 10% NaOH. The solid, orange product was collected, dissolved in the minimum of CH_2Cl_2 and chromatographed on basic Al_2O_3 (CH_2Cl_2). The orange eluate fraction yielded 0.31 g (83%) of orange powder, mp. 239-241° (dec.); UV (EtOH), λ_{max} (D): 242 (0.76), 257 (0.78), 320 (2.14), 332 (2.03), 376 (0.44), 397 nm (0.46); visible (EtOH), λ_{max}: 510 nm. ^1H NMR ($CDCl_3$): δ 7.96 (dt, 1H, $J_{6,7}$ = 8.7 Hz, $J_{7,8}$ = 8.4 Hz, H-7), 8.05 (m, 2H, $J_{7,8}$ = 8.4 Hz, $J_{8,9}$ = 7.2 Hz, $J_{9,10}$ = 9.3 Hz, H-8,9), 8.15 (d, 1H, $J_{3,4}$ = 9.0 Hz, H-4), 8.67 (dd, 1H, $J_{1,3}$ = 2.1 Hz, $J_{3,4}$ = 9.0 Hz, H-3), 8.81 (dd, 1H, $J_{9,10}$ = 9.3 Hz, $J_{8,10}$ = 2.4 Hz, H-10), 9.02 (d, 1H, $J_{7,8}$ = 8.7 Hz, H-7), 9.33 (d, 1H, $J_{1,3}$ = 2.1 Hz, H-1). IR: 1603, 1510 (asym-NO_2), 1453, 1405, 1332 (sym-NO_2), 1292, 1190, 1082 cm^{-1}.

Anal. Calcd. for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.60. Found: C, 69.58; H, 3.88

2-Nitro-5,6,7,8,9,10-hexahydrocyclohepta[b]indole (2b). Method A.- The p-nitrophenylhydrazone of cycloheptanone, mp. 143-144°,[4] (15.0 g, 0.6 mole) was heated under reflux for 6 hrs with 100 mL of 10% sulfuric acid. After cooling, the reaction mixture was extracted with ether (4 x 25 mL) and the solvent was removed from the combined, washed (25 mL of H_2O) extracts. Petroleum ether (30-60°) was added slowly with swirling to a solution of the residue in 20 mL of CH_2Cl_2 until a brown resinous material formed on the walls of the flask. The solution was decanted and the separation of resinous material with petroleum ether repeated. The decantation and addition of petroleum ether was repeated until no resinous material was observed. The addition of excess petroleum ether then precipitated 2b as an orange solid. Recrystallization from methanol gave 2.7 g (20%) of 2b as orange crystals, mp. 167°; UV (EtOH), λ_{max} (D): 278 (1.62), 336 nm (0.70)). ^1H NMR ($CDCl_3$): δ 1.80 (m, 4H, H-7,9), 1.91 (m, 2H, H-8), 2.85 (m, 4H, H-6,10), 7.26 (d, 1H, $J_{3,4}$ = 8.7 Hz, H-4), 8.00 (dd, 1H, $J_{1,3}$ = 2.1 Hz, $J_{3,4}$ = 8.7

Hz, H-3), 8.15 (s, 1H, N-H), 8.44 (d, 1H, $J_{1,3}$ = 2.1 Hz, H-1). IR 3400 (N-H) 2880, 2800, 1630, 1530 (asym-NO_2), 1475, 1330 (sym-NO_2) cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13. Found: C, 67.70; H, 6.39

Method B.- To a solution of 5.0 g (0.027 mole) of 5,6,7,8,9,10-hexahydrocyclohepta[b]indole (2a) (vide supra) in 35 mL of concentrated sulfuric acid at -5° was added slowly with stirring 2.73 g (0.027 mole) of KNO_3. After an additional 5 min. the mixture was poured onto ice. The yellow solid which separated was collected, washed with H_2O and dried to give 6.8 g (100%) of crude product. A hot methanol solution of the material was treated with charcoal, filtered and cooled. Recrystallization from methanol of the orange solid which separated gave 2.1 g (30%) of 2b, mp. 166-167°, identical (mmp. UV, IR) with the product from A.

Method C.- A solution of 0.1094 g (0.488 mmole) of 1b in 35 mL of ethanol was treated with H_2 over Pt catalyst (from the reduction of 0.1 g of PtO_2 in 15 mL of ethanol). The reaction was stopped (22 min) after 34 mL of H_2 had been absorped (calcd. for $3H_2$: 35 mL). Separation of the catalyst by filtration, then removal of the solvent and chromatography of the solid residue over basic Al_2O_3 (CH_2Cl_2-ethanol) gave 0.102 g (91%) of 2b identical (mp, mmp, UV, IR) with the material from A.

2-N-Acetamido-5,6,7,8,9,10-hexahydrocyclohepta[b]indole (2d).- 2-Nitro-5,6,7,8,9,10-hexahydrocyclohepta[b]indole (2b) (1.0 g, 4.34 mmoles) in 50 mL of 95% ethanol was treated with H_2 over Pt catalyst (0.1 g, see Method C above) until 324 mL (theory for 3 H_2: 324 mL at 25°) was taken up. Separation of the catalyst by filtration, treatment of the hot filtrate with charcoal (0.1 g), filtration, removal of the solvent and recrystallization of the solid product from ethanol-H_2O gave 0.79 g (91%) of 2c as colorless crystals, mp. 170-172°, which darkened on standing. A solution of 0.4 g (2.0 mmoles) of this product in 20 mL of benzene containing 1 mL of acetic anhydride was heated (steam bath) for 1 hr. Evaporation of the solvent left a brown residue which was taken up in 25 mL of 95% ethanol. The boiling solution was treated with charcoal (0.5 g) and filtered. Water was added to the hot filtrate until cloudiness appeared. Cooling caused the separation of 0.31 g (64%) of 2d as colorless needles, mp. 216-217°. ^1H NMR ($CDCl_3$): δ 1.79 (m, 4H, H-7,9), 1.83 (m, 2H, H-8), 2.03 (s, 1H, amide N-H), 2.23 (s, 3H, CH_3), 2.81 (m, 2H, $J_{9,10}$ = 5.7 Hz, H-10), 2.86 (m, 2H, $J_{6,7}$ = 6.0 Hz, H-6), 7.12 (dd, 1H, $J_{1,3}$ = 2.1 Hz, $J_{3,4}$ = 8.7 Hz, H-3), 7.22 (d, 1H, $J_{3,4}$ = 8.7 Hz, H-4), 7.27 (s, 1H, ring N-H), 7.67 (d, 1H, $J_{1,3}$ = 2.1 Hz, H-1). IR: 3360 (broad, NH), 2860, 1675 (CO), 1585, 1530 (CO), 1470, 1363, 1322 cm^{-1}.

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49. Found: C, 74.17; H, 7.38

4-Nitro-5,6,7,8,9,10-hexahydrocyclohepta[b]indole (2e).- To a solution of 13.87 g (0.073 mole) of o-nitrophenylhydrazine hydrochloride[5] in 35 mL of hydrochloric acid were added cycloheptanone (8.2 g, 0.073 mole) and 95% ethanol until the mixture was homogeneous. It was heated (steam bath) for 1 hr and then cooled (ice-bath). The orange-red solid which separated was recrystallized from 95% ethanol and gave 6.5 g (36%) of cycloheptanone

o-nitrophenylhydrazone, mp. 93-94°.

Anal. Calcd. for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93. Found: C, 63.11; H, 6.81

A solution of 5.0 g (0.02 mole) of the hydrazone and 100 mL of 20% sulfuric acid was heated under reflux for 5 hrs., then cooled. The precipitate which formed was separated and dissolved in 200 mL of methanol. The hot solution was treated with charcoal (0.2 g), filtered and then cooled (ice) to give 2e as orange plates which, after recrystallization from methanol, amounted to 2.5 g (54%), mp. 163-164°; UV (EtOH), λ_{max} (D): 242 (1.17), 261 (1.17), 370 nm (0.65). ^1H NMR ($CDCl_3$): δ 1.82 (m, 4H, H-7,9), 1.91 (m, 2H, H-8), 2.82 (m, 2H, H-10), 2.92 (m, 2H, H-6), 7.12 (t, 1H, $J_{1,2}$ = 7.8 Hz, $J_{2,3}$ = 8.1 Hz, H-2), 7.77 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 8.03 (d, 1H, $J_{2,3}$ = 8.1 Hz, H-3), 9.48 (s, 1H, NH). IR: 3385 (N-H), 2870, 2800, 1635, 1580, 1515 (asym-NO_2), 1485, 1414, 1375, 1340, 1324 (sym-NO_2), 1292, 1123 cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13. Found: C, 67.82; H, 5.79

4-N-Acetamido-5,6,7,8,9,10-hexahydrocyclohepta[b]indole (2g).- 4-Nitro-5,6,7,8,9,10-hexahydrocyclohepta[b]indole (2e) (0.9 g, 3.91 mmoles) in 50 mL of ethanol was treated with H_2 over 0.1 g of PtO_2[6] until 294 mL (theory for $3H_2$: 285 mL at 22°) was taken up (90 min.). Filtration and removal of the solvent gave 0.78 g (100%) of 2f as colorless crystals, mp. 122-123°, which darkened on standing. The addition of 5 mL of acetic anhydride to a stirred solution of 0.5 g (2.5 mmoles) of 2f in 20 mL of acetic acid caused the near immediate separation of a colorless crystalline solid. Recrystallization from methanol gave 0.49 g (81.5%) of 2g as colorless crystals, mp. 214-216°. ^1H NMR ($CDCl_3$): δ 1.81 (m, 5H, H-7,9; amide N-H), 1.93 (m, 2H, H-8), 2.31 (s, 3H, CH_3), 2.86 (m, 4H, H-6,10), 6.68 (d, 1H, $J_{2,3}$ = 6.9 Hz, H-3), 7.02 (t, 1H, $J_{1,2}$ = 7.8 Hz, $J_{2,3}$ = 6.9 Hz, H-2), 7.36 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 7.53 (s, 1H, ring NH). IR: 3320 (broad, NH), 2860, 1680 (C=O), 1580, 1520 (C=O), 1452, 1363, 1331 cm^{-1}.

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.45. Found: C, 74.22; H, 7.30

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6. Because of the insolubility of the nitroindole in ethanol, the PtO_2 was not reduced in advance.