STEREOSELECTIVE BRIDGING OF TETRAHYDRO-1,5-BENZODIAZEPINES

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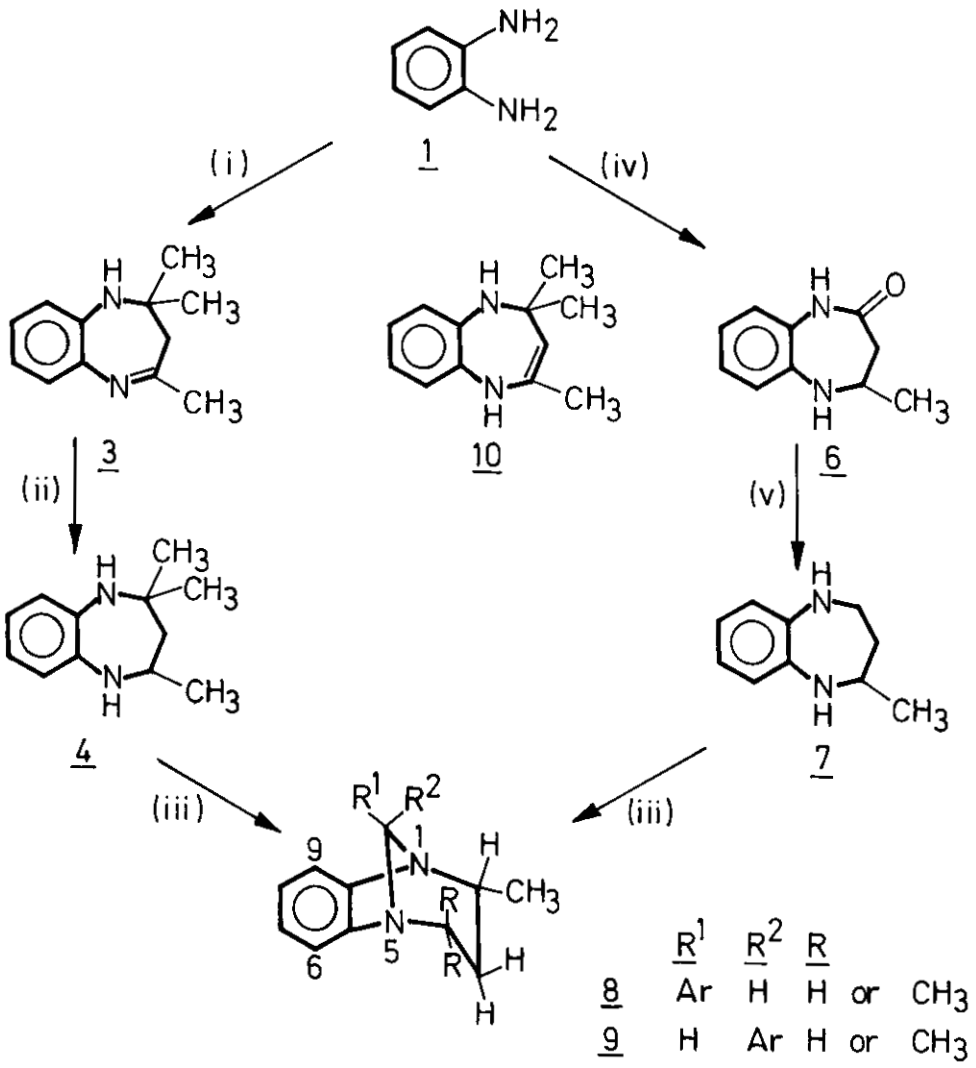
Abstract----A reaction of tetrahydro-1,5-benzodiazepines with aromatic aldehydes which yields the hitherto unknown 1,5-methanotetrahydro-1,5-benzodiazepines as a single stereoisomer is described. The stereochemistry of the products is established using proton nmr spectra.

1,5-Benzodiazepines belong to a pharmacologically important group of heterocycles Clobazam and Lofendazam being two examples possessing 1,5-benzodiazepine skeleton. Several 1,5-benzodiazepine analogs are active in animal models as sedatives, muscle relaxants, and display useful CNS activity.[1] In spite of the voluminous work[1] in the area, the reactions of tetrahydrobenzodiazepines have not been extensively studied. We report herein a reaction of tetrahydro-1,5-benzodiazepines namely, a stereoselective bridging reaction with aromatic aldehydes to give bridged 1,5-benzodiazepines (8).

RESULTS AND DISCUSSION

The synthesis of bridged 1,5-benzodiazepines (8) was accomplished according to the synthetic sequence described in Scheme. The common starting material for the two intermediate tetrahydro-1,5-benzodiazepines (4 and 7) was o-phenylenediamine. Thus o-phenylenediamine was condensed[2] with mesityl oxide (2) to yield the benzodiazepine (3) which was then reduced catalytically with hydrogen to yield the tetrahydro derivative (4). The structure for the condensation product between o-phenylenediamine and mesityl oxide was previously indicated as 10 but ^{1}H nmr spectral evidence clearly argues against the enamino structure 10 and confirms the assignment as 3.

The other tetrahydro-1,5-benzodiazepine (8) was synthesized by the lithium aluminum hydride reduction[3] of the 1,5-benzodiazepinone (6), the latter derived from o-phenylenediamine (1) and crotonic acid (5)[4].



	R^1	R^2	R
8	Ar	H	H or CH_3
9	H	Ar	H or CH_3

Scheme : Synthesis of Bridged 1,5-Benzodiazepines

Reagents : (i) Mesityl oxide (2), 50-60°C (ii) H_2/Ra Ni, 45°C, 45 psi (iii) ArCHO, C_2H_5OH, Δ (iv) Crotonic Acid (5) Δ (v) $LiAlH_4$, THF.

The tetrahydro-1,5-benzodiazepines (4 and 7) underwent smooth condensation with aromatic aldehydes to yield a single isomer of bridged 1,5-benzodiazepine (8 or 9). That only one stereoisomer (8 or 9) was formed in this reaction was suggested by the examination of the crude product by ^{1}H nmr within the limits of detection. The recrystallized samples (all of which had identical ^{1}H nmr with the corresponding crude samples) were analyzed by ^{13}C nmr which indicated exclusively the formation of a single stereoisomer (no duplication of <u>any</u> of the carbon signals). The structure of the isomer is shown to be 8 (and not 9) by the following evidence.

The analysis of the ^{1}H nmr spectra of the bridged 1,5-benzodiazepines gave the crucial evidence for the stereostructure (Table). The seven line signal at δ 3.45 was unequivocally assigned to H^{2a} with coupling constants of 12, 6 and 6 Hz. The intensities of the seven constituent lines were corresponding to 1:4:7:8:7:4:1. The coupling constant J = 12 Hz was then assigned to $J_{2a,3a}$, a diaxial coupling. The other two coupling values of 6 Hz each could be assigned to $J_{2a,3e}$ and $J_{2a,2\text{-}CH_3}$ couplings. Hence, the ^{1}H nmr spectrum clearly points to a distortionless chair form for the the six membered ring defined by N^1-C^2-C^3-C^4-N^5-C^{10} and confirms the stereo structure 8-a and 8-b. This distortionless chair form would be difficult with 9 where the aryl group at C_{10} (R^2 = Ar in 9) would have severe interactions with C_4-axial methyl group. Thus the stereochemistry at C_{10} in the bridged 1,5-benzodiazepines is proved to be as shown in 8.

Similar proton chemical shift values of C_2-methyl hydrogens in 8-a and 8-b point out that in the latter compounds also, the C_2-methyl group is equatorially disposed (Table). Also, the C_{10}-H signals in 8-a and 8-b are at lower field strengths by 0.3 ppm than the corresponding signal in 8-c, 8-d or 8-e. This is attributable to steric deshielding between C_{10}-hydrogen and C_4-axial methyl group protons in 8-a and 8-b. This observation indicates stereochemical identity at C_{10} between 8-a, 8-b series and 8-c, 8-d, 8-e series. In addition strong ^{13}C nmr chemical shift[5] similarities, for example, between 8-a and 8-c, corroborates the above conclusion.

EXPERIMENTAL

The melting points reported are uncorrected. The ^{1}H nmr spectra were run on a Varian EM-360 spectrometer using TMS as the internal standard. Chemical shifts are in δ values.

1H-2,3-Dihydro-2,2,4-trimethyl-1,5-benzodiazepine (3)

Mesityl oxide (2, 9.8 g, 0.93 mol) was added slowly in about 1 h to a warm (50-60° C) solution of o-phenylenediamine (1, 10.8 g, 0.10 mol) in benzene (50 ml). The reaction mixture was refluxed for 7 h. Solvent was removed to get a paste that slowly solidified to a brown solid. The solid was recrystallized from petroleum ether (bp 40-60 °C). Yield: 5.2 g (28 %); mp 125-128 °C. ^{1}H Nmr(CDCl$_3$) 1.35(s, 6H, C$_2$-(CH$_3$)$_2$), 2.23 (s, 2H, C^{3}H$_2$), 2.38(s, 3H, C^4-CH$_3$), 2.93 (br s, 1H, NH), 6.58-7.26(m, 4H, aromatic hydrogens).

1H-2,3,4,5-Tetrahydro-2,2,4-trimethyl-1,5-benzodiazepine(4)

The benzodiazepine (3, 10 g, 0.053 mol) was reduced in ethyl acetate (500 ml) under an atmosphere of hydrogen to the benzodiazepine (4) using Raney nickel (7 g) at 45 °C and 45 psi pressure for 20 h. The reaction mixture was filtered to remove the catalyst. The solvent was removed and the resulting oil solidified slowly. The product was purified by crystallizing from petroleum ether (bp 40-60 °C). Yield 6.6 g (65.5 %); mp 69-71 °C; (lit.,[2] mp 69° C). ^{1}H Nmr (CDCl$_3$, D$_2$O exchanged to remove NH signals) 1.06(s, 3H, C^2-CH$_3$), 1.23(d, J = 6.0 Hz, 3H, C^4-CH$_3$), 1.38(s, 3H, C^2-CH$_3$), 1.60(m, 2H, C^{3}H$_2$), 3.20(m, 1H, C^{2}H), 6.70(br s, 4H, aromatic hydrogens)

1H-2,3,4,5-Tetrahydro-2-methyl-1,5-benzodiazepine(7)

To a warm suspension of lithium aluminum hydride (0.6 g, 15.8 mmol) in dry THF (50 ml), benzodiazepinone (6) (1.5 g, 8.5 mmol) in about 50 ml of dry THF was added slowly in about 1 h. Frothing was observed as soon as the addition started. The reaction mixture was stirred at 40-50 C for 2 h, at room temperature overnight and again at 40-50° C for 1 h. Unreacted lithium aluminum hydride was decomposed by the addition of 2N NaOH solution till frothing ceased. THF was decanted from the white solid formed and the solid was washed well with THF. The combined THF washings were concentrated in vacuo to get a dark brown liquid. It was extracted with ether and the organic extract was washed well with water and dried over anhydrous sodium sulfate. Ether was removed to get an oil which solidified on cooling. The solid was recrystallized from petroleum ether (bp 40-60 °C). Yield 0.5 g (36 %); mp 98-100 °C; (lit.,[3] mp 98-99° C). ^{1}H Nmr (CDCl$_3$) 1.25(d, J = 6.0 Hz, 3H, C^2-CH$_3$), 1.33-2.80(m, 2H, C^{3}H$_2$), 2.40-3.30(m, 5H, C^{2}H and C^{4}H$_2$, N^{1}H and N^{5}H), 6.65(s, 4H, aromatic hydrogens).

General Procedure for the Synthesis of 1,5-Methano-4H-2,3-dihydro-10-aryl-1,5-benzodiazepines (8 a-e)

Benzodiazepine 4 or 7 (0.01 mol) and the aromatic aldehyde (0.01 mol) were mixed in 100 ml of benzene and the water separated was removed in a Dean-Stark apparatus for the length of time indicated in the Table for the

Physical Data on Bridged 1,5-Benzodiazepines(8)

NO.	R^1	R	mp°C (Solvent)	Yield (Rxn hrs.)	^{1}H nmr data on 8	Molecular Formula	C(%) Required	H(%) Required	N(%) Required (Found)
8a	3,4-dichlorophenyl	CH_3	162-165 (ethyl acetate)	36 (5)	0.60-1.35(m, 8H, C^3H_2, C^4-CH_3 at 1.10 (s), C^2-CH_3 at 1.05 (d) with J = 6 Hz); 1.45(s, 3H, C^4-CH_3); 3.45(septet, 1H, J = 12, 6, 6 Hz); 5.45(s, 1H, C^{10}-H); 6.85-7.65(m, 7H, arom. hydr.)	$C_{19}H_{20}N_2Cl_2$	65.50 (65.71)	5.76 (5.80)	8.21 (8.07)
8b	3-nitrophenyl	CH_3	138-140 (pet. ether)	71 (5)	0.60-1.25(m, 8H, C^3H_2, C^4-CH_3 at 1.12 (s), C^2-CH_3 at 1.10 (d) with J = 6 Hz); 1.53(s, 3H, C^4-CH_3); 3.50(septet, 1H, J = 12, 6, 6 Hz, C^2H,); 5.60 (s, 1H, C^{10}H); 6.90-7.40(m, 5H, arom. hydr.); 7.70-8.00(m, 2H, arom. hydr. on nitrophenyl ring); 8.45(s, br, 1H, arom. hydr. on nitrophenyl ring)	$C_{19}H_{21}N_3O_2$	70.87 (70.56)	6.74 (6.55)	13.25 (13.00)
8c	3,4-dichlorophenyl	H	155-157 (ethyl acetate)	33 (5)	0.60-1.40(m, 5H, C^3H_2, C^2-CH_3, the latter at 1.10(d) with J = 6 Hz); 2.90-3.60 (m, 3H, C^2H and C^4H_2); 5.12(s, 1H, C^{10}H); 7.00-7.10(m, 7H, arom. hydr.)	$C_{17}H_{16}N_2Cl_2$	63.88 (63.96)	5.27 (5.05)	9.17 (8.78)
8d	3-nitrophenyl	H	129-132 (pet. ether)	65 (5)	0.60-1.40(m, 5H, C^3H_2, C^2-CH_3, the latter at 1.10(d) with J=6 Hz); 2.90-3.80 (m, 3H, C^2H and C^4H_2); 5.22(s, 1H, C^{10}H); 7.00-7.40(m, 5H, arom. hydr.); 7.60-8.00 (m, 2H, arom. hydr. on nitrophenyl ring); 8.40(s, br, 1H, arom. hydr. on nitrophenyl ring)	$C_{17}H_{17}N_3O_2$	69.11 (69.13)	6.04 (5.90)	13.87 (14.23)
8e	2-hydroxy-3,5-dibromophenyl	H	209-212 (ethyl acetate-pet. ether)	55 (7)	0.65-1.40(m, 5H, C^3H_2, C^2-CH_3, the latter at 1.12(d) with J=6 Hz); 2.90-3.90 (m, 3H, C^2H and C^4H_2); 5.35(s, 1H, C^{10}H); 7.10-7.60(m, 6H, arom. hydr.); 11.00-11.40(br, -OH)	$C_{17}H_{16}N_2OBr_2$	48.38 (48.14)	4.00 (3.90)	6.52 (6.60)

individual compounds. Solvent was then removed in vacuo and ^1H nmr of the crude solid was examined. The product was then purified by recrystallization from a suitable solvent mentioned in the Table for analysis and mp.

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5. The ^{13}C chemical shifts (off-resonance multiplicities indicated by s = singlet, d = doublet, t = triplet and q = quartet) for 8-c are 21.2(q), 25.7(t), 53.5(t), 57.4(d), 91.0(d), 118.9(d), 120.6(d), 125.8(d), 126.7(d), 126.8(d), 129.5(d), 129.7(d), 131.2(s), 132.1(s), 141.2(s), 145.1(s) and 148.3(s). For 8-a 20.6(q), 27.6(q), 30.1(q), 38.0(t), 54.3(d), 55.2(s), 85.3(d), 121.2(d), 122.3(d), 125.4(d), 125.8(d), 126.7(d), 129.5(d), 130.9(s), 131.9(s), 141.9(s), 145.1(s), 147.5(s).

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