NEW SYNTHESIS OF DIHYDRO-AND TETRAHYDRO-1,5-BENZODIAZEPINES BY REDUCTIVE CONDENSATION OF O-PHENYLENEDIAMINE AND KETONES IN THE PRESENCE OF SODIUM BOROHYDRIDE

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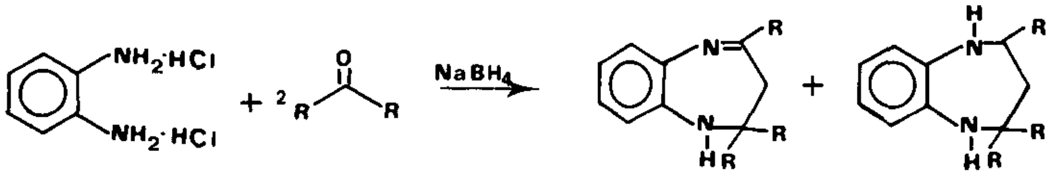
Abstract—Dihydro- and tetrahydro-benzodiazepines have been synthesized from o-phenylenediamine dihydrochloride and aliphatic ketones in the presence of sodium borohydride.

This article describes a new synthesis of 1,5-benzodiazepine derivatives, and represents a useful extension of known preparative routes to these compounds. It has been described previously that $NaBH_4$ can be efficiently used to achieve monoalkylation of primary amines with carbonyl compounds[1]. Herein, we would like to extend our findings to an aromatic diamine. Thus, it was observed that o-phenylenediamine dihydrochloride reacts with two ketone molecules in the presence of sodium borohydride affording the unexpected 1,5-benzodiazepines in good yields (Table I).

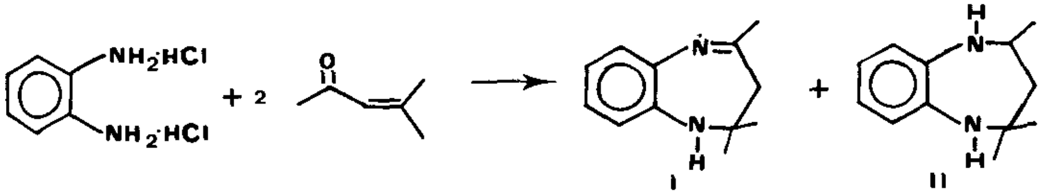
In all cases the products were characterized by spectroscopic methods: IR, MS, and ^1H NMR (Table I); ^{13}C NMR (Table II).



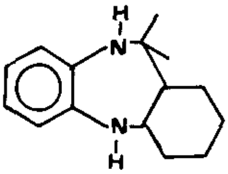
Although many examples of dihydro- and tetrahydro-1,5-benzodiazepines are known,[2-5] their synthesis has been generally carried out by reaction of o-phenylenediamine with either and α,β-unsaturated carbonyl compounds or the corresponding β-halocarbonyl compounds[6].

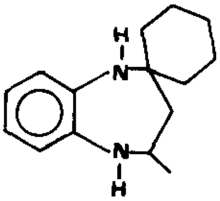
The $NaBH_4$ procedure described here has the advantage of greater simplicity in manipulation, and higher yields.

Compounds I and II were also obtained when o-phenylenediamine hydrochloride was treated with 4-methyl-3-penten-2-one and sodium borohydride. These samples have been prepared by Hunter et al.[7,8] by a different synthetic method and our spectroscopic data are in agreement with those described in their reports.



Compounds III, IV and V are new species and their spectral data are summarized in Tables I and II. Compounds III and IV appeared as a single isomer as can be seen in ^{13}C nmr, assignment of a trans or cis structures have not been investigated. When a mixture of acetone and cyclohexanone was allowed to react with the diamine dihydrochloride, compounds I and II were obtained, instead of other possible condensation products VII and VIII. Similarly an isomeric mixture was obtained when 2-methylcyclohexanone or methyl ethyl ketone was used.


VII


VIII

As expected, the 1,5-benzodiazepines were not obtained when aromatic ketones or aldehydes like acetophenone, acetaldehyde or benzaldehyde were used.

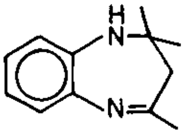
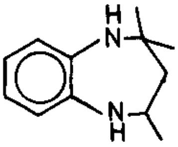
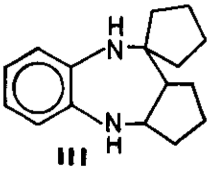
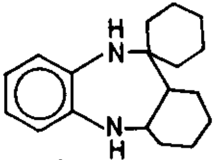
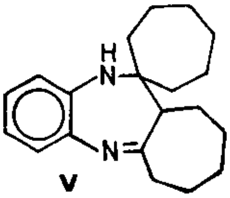
EXPERIMENTAL

The procedure for the preparation of 2,3-dihydro-2,4,4-trimethyl-1H-1,5-benzodiazepine (I) and 2,3,4,5-tetrahydro-2,2,4-trimethyl-1H-1,5-benzodiazepine (II) is representative of all reactions performed.

A 50 ml reaction flask, fitted with a magnetic stirring bar, was charged with 1.0 g (5.5 mmol) of o-phenylenediamine dihydrochloride, 10 ml of 1:1 isopropanol/methanol solution, 1.6 ml (22 mmol) of acetone and 0.42 g (11 mmol) of $NaBH_4$.

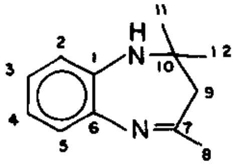
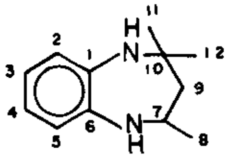
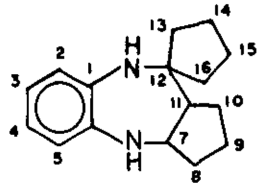
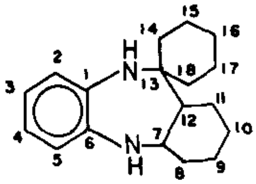
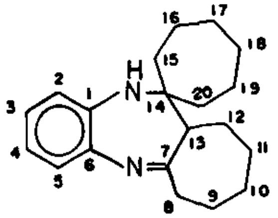
The reaction mixture was stirred for 24 h at room temperature, diluted with 10 ml (20 mmol) of 2N NaOH, and then extracted with CH_2Cl_2. The extract was dried over sodium sulfate and concentrated to give 2.2 g of crude product as a brown oil which was chromatographed on a silica gel column (hexane/ethyl acetate 9:1) to yield 0.20 g (20%) of I, mp 120-121°C (lit. 124°C[9]) and 0.52 g (50%) of II, mp 56-58°C. The same procedure was followed for the synthesis of III-V (Table I).

Table I. Data of 1,5-Benzodiazepines Prepared.

Ketone[a],	1,5-benzodiazepines	yield[b] [%]	mp [°C][c]	IR (KBr)[d]	^{1}H NMR	MS m/e (M^+)
Acetone	 **I**	20	120-121	3500 3293 1650	1.35, s (6H) 2.2, s (2H) 2.35, s (3H) 2.95, b (1H) 6.65-7.3, m (4H)	188
	 **II**	50	56-58	3500	1.1, s (3H) 1.22, d (3H) J=(6H_z) 1.38, s (3H) 1.5-1.95, m (2H) 3.3, m (1H) 3.7, b (2H)	190
Cyclo-pentanone	 **III**	68	72-74	3500	1.1-2.3, m (15H) 3.3, b (2H) 3.6, b (1H) 6.7, m (4H)	242
Cyclo-hexanone	 **IV**	60	97-99	3450	0.8-2.4, m (19H) 3.1, b (2H) 3.7, b (1H) 6.7, m (4H)	270
Cyclo-heptanone	 **V**	40	134-135	3500 3295 1700	0.8-2.95, m (23H) 3.6, b (1H) 7.0, m (4H)	296

a) As the other starting material o-phenylenediamine dihydrochloride is used;
b) yield based on o-phenylenediamine dihydrochloride; c) uncorrected;
d) ν = cm^{-1}; e) $CDCl_3$ (TMS).

Table II ^{13}C-NMR ($CDCl_3$/TMS)^a δ[ppm]

	$C_{1,6}$	$C_{2,5}$	$C_{3,4}$	C_7	C_{10}	C_9	C_8	$C_{11,12}$	
	137.9 140.6	121.5 121.8	125.4 126.9	171.8	67.84	45.2	30.41	29.71	
	137.7 140.4	119.8	121.2 121.7	51.5	51.8	47.9	32.94	24.0 26.3	
				C_{12}	C_7	C_{11}	$C_{8,13,16}$	$C_{9,10,14,15}$	
	137.8 139.7	119.6	120.6 130.0	65.4	58.4	54.2	35.4 37.9 38.4	22.3 23.2 23.6 24.8	
				C_{13}	C_7	C_{12}	$C_{8,18,14}$	$C_{9,10,11,15,16,17}$	
	136.5 141.0	118.8 120.4	121.0 121.1	54.6	50.1	49.5	34.0 35.1 35.6	19.9 20.3 21.6	22.1 25.7 26.8
				C_7	C_{14}	C_{13}	$C_{8,15,20}$	$C_{9,10,11,12,16,17,18,19}$	
	137.4 139.8	121.3 121.6	125.5 127.7	179.0	72.4	54.2	40.9 38.4 38.1	22.5 23.2 26.4 28.4	28.9 29.5 29.7 30.1

a) Chemical shifts in columns were not assigned.

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