

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

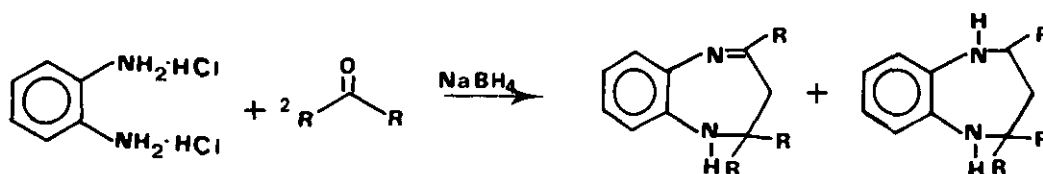
Hilda R. Morales, Arturo Bulbarela, and Rosalinda Contreras*

Centro de Investigación y de Estudios Avanzados del I.P.N.
Departamento de Química. Apartado Postal 14-740. 07000-México, D.F.

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 compounds¹. 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).

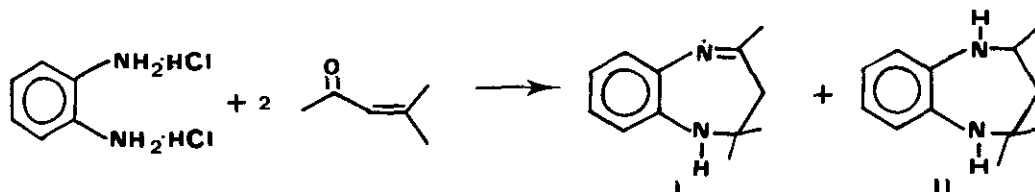
In all cases the products were characterized by spectroscopic methods: IR, MS, and ^1H NMR (Table I); ^{13}C NMR (Table II).



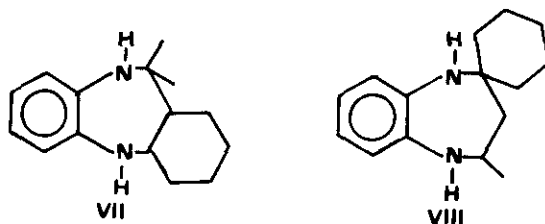
Although many examples of dihydro- and tetrahydro-1,5-benzodiazepines are known,²⁻⁵ their synthesis has been generally carried out by reaction of o-phenylenediamine with either α,β -unsaturated carbonyl compounds or the corresponding β -halo-carbonyl compounds⁶.

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 ¹³C 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.



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

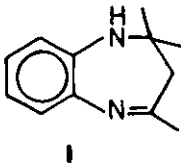
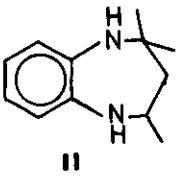
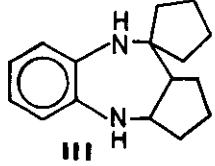
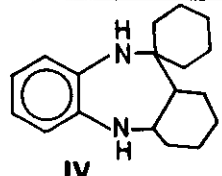
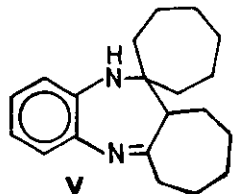
EXPERIMENTAL

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 NaBH₄.

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°C⁹) 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.

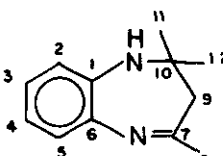
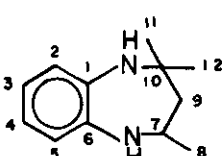
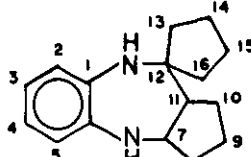
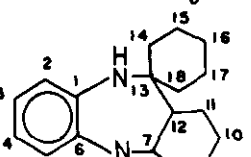
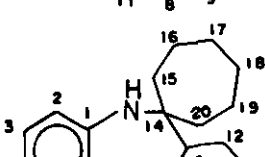
Ketone ^a , 1,5-benzodiazepines	yield ^b [%]	mp [°C] ^c	IR (KBr) ^d	¹ H NMR	MS m/e (M ⁺)
Acetone  I	20	120-121	3500 3293 1650	1.35, s (6H) 2.2, s (2H) 2.35, s (3H) 2.95, b (1H) 6.65-7.3, m (4H)	188
 II	50	56-58	3500	1.1, s (3H) 1.22, d (3H) J=(6H _z) 1.38, s (3H) 1.5-1.95, m (2H) 3.3, m (1H) 3.7, b (2H)	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) $\nu = \text{cm}^{-1}$; 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	121.5	125.4	171.8	67.84	45.2	30.41	29.71
	140.6	121.8	126.9					
	137.7	119.8	121.2	51.5	51.8	47.9	32.94	24.0
	140.4		121.7					26.3
	137.8	119.6	120.6	C ₁₂ 65.4	C ₇ 58.4	C ₁₁ 54.2	C _{8,13,16} 35.4	C _{9,10,14,15} 22.3
	139.7		130.0				37.9	23.2
							38.4	23.6
								24.8
	136.5	118.8	121.0	C ₁₃ 54.6	C ₇ 50.1	C ₁₂ 49.5	C _{8,18,14} 34.0	C _{9,10,11,15,16,17} 19.9 22.1
	141.0	120.4	121.1				35.1	20.3 25.7
							35.6	21.6 26.8
	137.4	121.3	125.5	C ₇ 179.0	C ₁₄ 72.4	C ₁₃ 54.2	C _{8,15,20} 40.9	C _{9,10,11,12,16,17,18,19} 22.5 28.9
	139.8	121.6	127.7				38.4	23.2 29.5
							38.1	26.4 29.7
								28.4 30.1

a) Chemical shifts in columns were not assigned.

ACKNOWLEDGMENT

The authors are grateful to Conacyt México for financial support and Dr. R.L. Santillán for critical reading.

REFERENCES

- 1a. H.R. Morales, M. Pérez-Juárez, L. Cuéllar, L. Mendoza, H. Fernández and R. Contreras, Synth. Commun., 1984, 14, 1213.
- b. R. Contreras, L. Cuéllar, H. Fernández, R. González, M. Pérez and H.R. Morales, Congress Abs., Rev. Soc. Quim. Mex., 1984, 25, 241.
2. O.E. Fancher and G. Nichols, U.S. Pat., 2,899,359, Chem. Abs., 1960, 54, 598. U.S. Pat., 302,951, Chem. Abs., 1962, 57, 8592.
3. H. Stetter, Chem. Ber., 1953, 86, 161.
4. W. Ried and P. Stahlhofen, Chem. Ber., 1957, 90, 815.
5. W. Ried and E. Torinus, Chem. Ber., 1959, 92, 2902.
6. G.A. Archer and L.H. Sternbach, Chem. Rev., 1968, 68, 773.
7. P.W.W. Hunter and G.A. Webb, Tetrahedron, 1972, 28, 5573.
8. P.W.W. Hunter and G.A. Webb, Tetrahedron, 1973, 29, 147.
9. J.B. Ekeley and R.J. Wells, Chem. Ber., 1905, 2259.

Received, 4th September, 1985