Benzodiazepines. VIII.[1] Diborane Reduction of Benzodiazepin-2-ones

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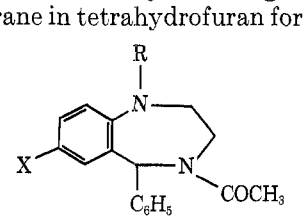
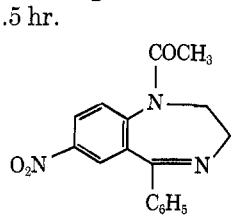
The reduction of 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones **1** with diborane gives the corresponding dihydro- or tetrahydrobenzodiazepines **2** or **3**, depending on molecular structures or reaction conditions. This reduction can also be carried out conveniently by using the sodium borohydride–boron trifluoride etherate reagent. This method is especially suitable for nitro-substituted benzodiazepinone and 1-alkyl-substituted benzodiazepinone derivatives where lithium aluminum hydride causes side reactions.

Diborane has been shown to be an effective reducing agent for the selective reduction of an amide carbonyl group in the presence of a nitro, ester, carbamate, or halogen group.[2] In connection with synthetic routes to 2,3-dihydrobenzodiazepines **2**, we have examined the diborane reduction of 1,3-dihydrobenzodiazepin-2-ones **1** in which both amide and C=N double bond groups are present. Feuer and coworkers have reported that the C=N double bonds of alkyl and α-monoaryl oximes are readily reduced with diborane at 25°, while diaryl ketoximes such as benzophenone oxime, in which the C=N double bond system is analogous to that of **1**, are not reduced even after 12 hr at 66°.[3]

As shown in Table I, the reduction of **1** with diborane gave the corresponding dihydro- or tetrahydrobenzodiazepines **2** or **3**, depending on molecular structures or reaction conditions. The product ratios obtained in the reductions were determined by nmr spectroscopy. In these reductions similar results were realized either in treating **1** with 1 *M* solution of diborane in tetrahydrofuran or in adding **1** to the reagent, conveniently prepared by the treatment of boron trifluoride etherate with sodium borohydride in tetrahydrofuran. In preliminary experiments with **1a** it was found necessary to use temperatures below 5° and a large excess of the reagent to obtain a maximum yield of **2a** (Table I). Dihydrobenzodiazepine (**2a**) was isolated by extraction of the crude acetylation mixture with 0.1 *N* hydrochloric acid after acetylation of the contaminating tetrahydrobenzodiazepine (**3a**) to the less basic 4-acetyl derivative (**4a**). Complete reduction of **1a** to **3a** was achieved by refluxing with a larger excess of diborane in tetrahydrofuran for 7.5 hr.



4a, X = Cl; R = CH_3
d, X = NO_2; R = $COCH_3$



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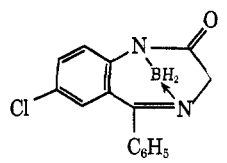
Reduction of 1-unsubstituted benzodiazepin-2-one **1b** gave **2b** and **3b** in a ratio of 1:2 even under conditions favoring selective reduction to **2b**. The lower ratio of **2b** to **3b** is perhaps best explained by assuming an initial reaction of the amide hydrogen in **1b** and diborane[2a,4] to give an amidoborane intermediate such as **6**. The



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C=N double bond in this intermediate **6** would be readily reduced because the positive charge on C-5 would be increased resulting from coordination of N-4 with the boron atom in the molecule. A similar explanation has been proposed by Kornet and coworkers[2b] to explain the lack of selectivity in the diborane reduction of N-monosubstituted amido ester, methyl hippurate.

In contrast to the present procedure, Sternbach and coworkers[5a] have shown that reduction of **1a** with lithium aluminum hydride gives, as the only isolable product, **3a** in 20% yield, whereas reduction of **1b**[5b] gives **2b** in 71% yield. Recently, Steinman[6] has reported the selective reduction of **1a** with lithium aluminum hydride at 0° to give 7-chloro-2,3-dihydro-2-hydroxy-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (**7**) in 40% yield. We repeated his procedure and found that the formation of **7** was nearly quantitative as the primary reaction at −50° and a further reaction took place at room temperature to give an insoluble dimer (**8**)[7,8] as the major product without observable forma-

(1) Paper VII: S. Inaba, K. Ishizumi, T. Okamoto, and H. Yamamoto, *Chem. Pharm. Bull.*, **20**, 1628 (1972).

(2) (a) H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, **86**, 3566 (1964); (b) M. J. Kornet, P. A. Thio, and S. I. Tan, *J. Org. Chem.*, **33**, 3637 (1968); (c) W. V. Curran and R. B. Angier, *ibid.*, **31**, 3867 (1966); (d) E. R. Bissell and M. Finger, *ibid.*, **24**, 1256 (1959); (e) Z. B. Papanastassiou and R. J. Bruni, *ibid.*, **29**, 2870 (1964); (f) G. R. Pettit, S. K. Gupta, and P. A. Whitehouse, *J. Med. Chem.*, **10**, 692 (1967).

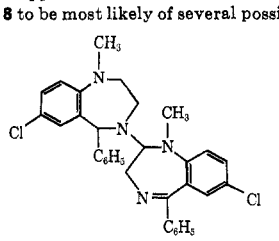
(3) (a) H. Feuer, B. F. Vincent, Jr., and R. S. Bartlett, *J. Org. Chem.*, **30**, 2877 (1965); (b) H. Feuer and D. M. Braunstein, *ibid.*, **34**, 1817 (1969).

(4) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **82**, 681 (1960).

(5) (a) L. H. Sternbach, E. Reeder, and G. A. Archer, *J. Org. Chem.*, **28**, 2456 (1963); (b) T. S. Sulkowski and S. J. Childress, *ibid.*, **28**, 2150 (1963).

(6) M. Steinman, German Patent 1,958,742 (1970); *Chem. Abstr.*, **73**, 66637*b* (1970).

(7) The compound **8** was a dimer of the same empirical formula as **2a**. The mass spectrum of **8** showed the molecular ion (M^+) at *m/e* 540 and was similar to that of **7** in the region below *m/e* 286. The ir spectrum indicated a band at 1595 cm^{-1} (C=N) and nothing corresponding to NH or OH group. Attempted reduction of **8** with lithium aluminum hydride in refluxing tetrahydrofuran and acetylation with acetic anhydride in pyridine gave only starting material. However, oxidation with chromic acid in acetic acid at 50° led to the isolation of the known 6-chloro-1,2-dihydro-1-methyl-4-phenylquinazolin-2-one (A)[8b] in 40% yield. Under same conditions **3a** gave A in about 20% yield, whereas **2a** and **7** gave **1a** in nearly quantitative yield. For the oxidation of benzodiazepines **2a** and **3a**, see ref 8. Therefore, the structure **3a** appeared to be contained in **8**. From these facts we considered structure **8** to be most likely of several possible structures.



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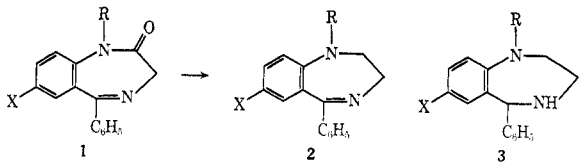
(8) (a) R. I. Fryer, G. A. Archer, B. Brust, W. Zally, and L. H. Sternbach, *J. Org. Chem.* **30**, 1308 (1965); (b) A. M. Felix, J. V. Earley, R. I. Fryer, and L. H. Sternbach, *J. Heterocycl. Chem.*, **5**, 731 (1968).

TABLE I

REDUCTION OF DIHYDROBENZODIAZEPIN-2-ONES WITH DIBORANE



1 2 3

Compd[a]	X	R	Reducing agent	Mole ratio, B_2H_6/compd	Temp, °C	Time, hr	Product ratio,[b] 2:3	Yield, % 2	Yield, % 3
1a	Cl	CH_3	$NaBH_4$-BF_3	8[c]	−15	22	86:14	75	11[d]
1a	Cl	CH_3	$NaBH_4$-BF_3	8[c]	0	3.5	86:14	75	
1a	Cl	CH_3	$NaBH_4$-BF_3	6[c]	5	4	86:14	70	
1a	Cl	CH_3	$NaBH_4$-BF_3	4[c]	10	3.5	76:24[e]		
1a	Cl	CH_3	B_2H_6	6	−10	2	87:13	62[f]	
1a	Cl	CH_3	B_2H_6	10	Reflux	7.5			95
1b	Cl	H	B_2H_6	4	−14	2.5	33:67	26[g]	47[h]
1b	Cl	H	$NaBH_4$-BF_3	8[c]	Reflux[i]	3			77
1c	NO_2	CH_3	B_2H_6	6	−8	1.8		77[f]	*j*
1c	NO_2	CH_3	NaBH -BF_3	8[c]	Reflux[i]	2			83[k]
1d	NO_2	H	B_2H_6	4	−13	3	71:29	39[l]	21[m]
1d	NO_2	H	$NaBH_4$-BF_3	8[c]	Reflux[i]	2			65

[a] 5 mmol. [b] Determined by nmr analysis. [c] Calculated assuming that the diborane is quantitatively generated in accordance with the amount of sodium borohydride used. [d] Isolated as the acetyl derivative **4a**. [e] Tlc analysis showed a small amount of starting material remaining in the mixture. [f] Purified by recrystallization. [g] Crystallized from pentane–ether. [h] Isolated as the hydrochloride by treatment of the filtrate with ethanolic hydrogen chloride. [i] Before refluxing, the reaction temperature was maintained at 25° with a reaction time of 2–3 hr. [j] Tlc analysis of the mother liquor indicated the presence of a small amount of the tetrahydro derivative **3c**. [k] Isolated as the hydrochloride. [l] Isolated as the acetyl derivative **5** which was reconverted into **2d** in 87% yield on heating with 1 *N* sodium hydroxide solution in methanol. [m] Isolated as the diacetyl derivative **4d**.

tion of **2a** and **3a**. Consequently, the present procedure is particularly useful for the preparation of 1-alkyl-substituted dihydrobenzodiazepines such as **2a**,[9] which cannot be obtained in a satisfactory yield by N-methylation of **2b** under ordinary conditions.[1,5a,10]

A further advantage is that the mildness of the reagent makes possible the presence of a variety of other substituents less susceptible to the reducing action of the reagent. Thus, under mild conditions 1-methyl-7-nitrobenzodiazepinone **1c** was reduced almost exclusively to the corresponding dihydrobenzodiazepine **2c**, and the 1-unsubstituted derivative **1d** to a 71:29 mixture of **2d** and **3d**. The reduction products **2d** and **3d** were converted into the 1-acetyl and 1,4-diacetyl derivatives **5** and **4d**, respectively, by treatment with acetic anhydride. The basic compound **5** was separated from **4d** by extraction of the crude acetylation mixture with dilute hydrochloric acid and reconverted into **2d** by hydrolysis with base.

The reduction of **1c** and **1d** proceeded with higher degree of selectivity than of the corresponding chloro derivatives **1a** and **1b**. This is, presumably, due to the effect of the strongly electron-withdrawing nitro group which decreases the basicity of N-4 making it less susceptible to the diborane attack.

More vigorous treatment of **1c** and **1d** led to the complete reduction to the respective tetrahydro derivatives **3c** and **3d**.

(9) An indirect reductive synthesis for **2a**, involving conversion of **1a** into the corresponding 2-thione derivative, followed by Raney nickel desulfurization, has been reported: G. A. Archer and L. H. Sternbach, *J. Org. Chem.*, **29**, 231 (1964).

(10) In contrast, the corresponding 2-one derivative **1a** is readily prepared by N-methylation of **1b**: L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *ibid.*, **27**, 3788 (1962).

Experimental Section

Infrared spectra were measured on a Hitachi Model EPI-G3 spectrophotometer and nmr spectra on a Varian T-60 instrument using tetramethylsilane as an internal standard. Mass spectra were taken on a Shimadzu LKB instrument with the direct sample inlet system and ionizing potential at 70 eV. All melting points were determined in open capillary tubes and are uncorrected.

General Procedures.—Each of the reduction reactions was carried out in a dry 100-ml three-necked flask, equipped with a magnetic stirrer, thermometer, and condenser. The 1 *M* solution of diborane in tetrahydrofuran (THF) was prepared as described by Brown.[11] The sodium borohydride–boron trifluoride etherate reagent was prepared by adding 15% excess boron trifluoride etherate to sodium borohydride in THF, in accordance with the equation $3NaBH_4 + 4BF_3 \cdot OEt_2 \rightarrow 2B_2H_6 + 3NaBF_4$. The reduction products were extracted with ether or chloroform. The drying agent used for organic solutions was anhydrous sodium sulfate.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (2a). A. By Sodium Borohydride–Boron Trifluoride Etherate Reduction of 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (1a).—The following procedures are representative of the reduction with sodium borohydride–boron trifluoride etherate. To a stirred suspension of 2.28 g (60 mmol) of pulverized sodium borohydride in 35 ml of THF was added dropwise a solution of 13.0 g (92 mmol) of boron trifluoride etherate in 10 ml of THF below 10°. The mixture was stirred at room temperature for 1 hr. To the resulting reagent (40 mmol as diborane) was added a solution of 1.43 g (5 mmol) of **1a** in 10 ml of THF over a period of 5 min at −15 to −12.5°. Stirring was continued for 22 hr at −15°, and the reaction mixture was cautiously poured into 100 ml of ice–water. The mixture was acidified with 20 ml of concentrated hydrochloric acid, refluxed for 30 min, and cooled. The resulting red solution was made basic with aqueous ammonia. The THF layer was separated, and the aqueous layer was extracted with ether. The organic layers were combined, washed with water, dried, and

(11) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **81**, 6428 (1959).

evaporated. The oily residue (1.4 g) was shown by nmr in CCl_4 to be composed of **2a** (86%) and **3a** (14%). This mixture was dissolved in 5 ml of acetic anhydride and stirred at room temperature for 4 hr. The resulting solution was diluted with 30 ml of ice–water, made basic with aqueous ammonia, and then extracted with ether. The ether extracts were combined and reextracted with 0.1 *N* hydrochloric acid. The acidic solution was then made basic with aqueous ammonia and extracted with ether. The ether extracts were combined, dried, and evaporated. The oily residue was crystallized from hexane to give 1.02 g (75%) of **2a**, mp 99.5–101.0°.

The ether layer which had been separated from the acidic layer was washed with water, dried, and evaporated. The residue (243 mg) was chromatographed over 15 g of silica gel with ethyl acetate. Evaporation of homogeneous fractions and crystallization of the residue from pentane gave 172 mg (10.9%) of **4a**, mp 98.5–102.5°.

This product was shown to be identical with a sample prepared by treatment of **3a** with acetic anhydride.

When the above acetylation of the crude mixture was carried out at 5–10° using 1 ml of acetic anhydride in 10 ml of toluene, similar results were obtained.

B. By Diborane Reduction of 1a.—The following procedures are representative of the reduction with diborane. Compound **1a** (1.43 g, 5 mmol) was added in one portion to a stirred solution of 30 ml of 1 *M* diborane in THF cooled to −15°. After further stirring at −10° for 2 hr, the reaction mixture was cautiously poured into 100 ml of ice–water, acidified with 20 ml of concentrated hydrochloric acid, and refluxed for 1 hr. The resulting red solution was cooled and made basic with aqueous ammonia. The THF layer was separated, and the aqueous layer was extracted with ether. The organic layers were combined, washed with water, dried, and evaporated. The residue (1.35 g) was analyzed by nmr as a 87:13 mixture of **2a** and **3a**. Recrystallization of the crude product from hexane gave 0.70 g of **2a**, mp 99.5–101.0°. A second crop (0.14 g) was obtained from the mother liquor. Total yield was 0.84 g (62%).

7-Chloro-2,3-dihydro-2-hydroxy-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (7).—To a well-stirred suspension of 0.46 g of lithium aluminum hydride in 20 ml of THF was added a solution of 2.85 g of **1a** in 15 ml of THF over a period of 38 min at −50°. The mixture was stirred at −52 to −40° for 4 hr. The excess of lithium aluminum hydride was decomposed by cautious addition of 5 ml of water followed by 20 ml of saturated aqueous sodium chloride. The THF layer was separated, and the aqueous layer was extracted with ether. The organic layers were combined, dried, and evaporated to give 2.80 g (97.5%) of **7**, mp 138–145°. An analytical sample was obtained as colorless plates after recrystallization from ether: mp 148–151° (lit.[6] mp 120–122°, 125–126°, 136–138°); ir (Nujol) 3080 (OH), 1610 cm^{-1} (C=N); mass spectrum *m/e* 286 (M^+), 268 (M − H_2O), 257 (M − CHO), 241, 228.

Anal. Calcd for $C_{16}H_{15}ClN_2O$: C, 67.02; H, 5.27; Cl, 12.36; N, 9.77. Found: C, 66.97; H, 5.24; Cl, 12.57; N, 9.50.

When reduction was carried out using the same conditions (reverse addition at 0°) as described in the literature,[6] the crude **7** was obtained in 80% yield, mp 128–134° dec (lit.[6] mp 125–126°).

Reduction of 1a with Lithium Aluminum Hydride at Room Temperature.—Compound **1a** (2.85 g) was treated with 0.76 g of lithium aluminum hydride at −50° as described above. Conversion into **7** was nearly complete in 6.5 hr as indicated by tlc analysis (silica gel, ethyl acetate). The temperature was, then, allowed to rise to room temperature within 1.5 hr. After stirring for 1 hr, the reaction mixture was cooled to −50° and worked up as described above to give 3.55 g of an amorphous solid. Crystallization from ether afforded 0.63 g (23.3%) of the dimer **8**, mp 265–267° dec. An analytical sample was obtained as colorless prisms after recrystallization from THF, mp 281.5–285° dec.

TABLE II

MELTING POINTS AND CHARACTERIZATIONS OF BENZODIAZEPINES[a]

Compd	Mp, °C	Recrystn solvent	Lit. mp, °C
2a[b]	100–101	Hexane	102–103[c]
3a	66–68	Pentane	60–62[d]
4a	104.5–106.5	Ligroin–pentane	106–108[e]
2b[b]	173–173.5	EtOH	173–173.5[c]
3b HCl	253.5–254 dec	EtOH	259–260[d]
2c	185.5–186.5	*i*-PrOH	187–188[f]
3c[g]	96–99	*i*-PrOH	
3c HCl	295–297 dec	EtOH	
2d[b]	210–211	MeOH	209–211[c]
3d[h]	237–240	EtOH	
4d[i]	170	*i*-PrOH	
5[j]	160–160.5	*i*-PrOH	

[a] Satisfactory analytical data (±0.4% for C, H, N, and Cl) were reported for all new compounds listed in the table: Ed. [b] The product was identified with an authentic sample[1] by comparison of the ir and nmr spectra. [c] Reference 1. [d] Reference 5a. [e] R. I. Fryer and L. H. Sternbach, U. S. Patent 3,625,957 (1971). [f] L. H. Sternbach, G. A. Archer, and E. Reeder, *J. Org. Chem.*, **28**, 3013 (1963). [g] Ir (Nujol) 3310 cm^{-1} (NH); nmr ($CDCl_3$) δ 2.22 (s, 1, NH), 3.04 (s, 3, CH_3), 2.80–3.55 (m, 4, CH_2CH_2), 5.30 (s, 1, CH). [h] Ir (Nujol) 3325, 3230 cm^{-1} (NH); nmr (C_5D_5N) δ 2.96–3.40 (m, 4, CH_2 and 2 NH), 3.84 (m, 2, CH_2), 5.40 (s, 1, CH). [i] Ir (Nujol) 1664, 1648 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.60 and 1.88 (3, CH_3), 2.25 (s, 3, CH_3), 2.80–4.70 (m, 4, CH_2CH_2), 6.20 (s, 1, CH). [j] Ir (Nujol) 1650 cm^{-1} (CO); nmr ($CDCl_3$) δ 2.00 (s, 3, CH_3), 3.00–5.30 (m, 4, CH_2CH_2).

Anal. Calcd for $C_{32}H_{30}Cl_2N_4$: C, 70.98; H, 5.58; Cl, 13.09; N, 10.35. Found: C, 71.00; H, 5.65; Cl, 12.92; N, 10.34.

An examination of the ether filtrate by tlc indicated the presence of other, unidentified products, but none of these corresponded to authentic samples of **2a** and **3a**.

1-Acetyl-2,3-dihydro-7-nitro-5-phenyl-1*H*-1,4-benzodiazepine (5) and 1,4-Diacetyl-7-nitro-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (4d).—Compound **1d** (1.41 g, 5 mmol) was treated with 20 ml of a 1 *M* solution of diborane in THF at −13° for 3 hr. The reaction product (1.25 g) was shown by nmr (C_5D_5N) to be composed of **2d** (71%) and **3d** (29%). This crude mixture (0.95 g) was suspended in 8 ml of acetic anhydride and heated under reflux for 3 hr. The reaction mixture was cooled, diluted with 20 ml of ice–water, made basic with aqueous ammonia, and extracted with chloroform. The chloroform layer was extracted with 1.2 *N* hydrochloric acid. The acidic solution was then made basic with aqueous ammonia and extracted with ethyl acetate. The ethyl acetate solution was washed with water, dried, and evaporated. Recrystallization of the residue from isopropyl alcohol gave 0.46 g (39.1%) of **5**, mp 158.5–160°.

The chloroform layer that separated from the acidic layer was washed with water, dried, and evaporated. The residue, dissolved in a small volume of ethyl acetate, was placed on a column of 30 g of silica gel. Elution with ethyl acetate and recrystallization from isopropyl alcohol gave 0.28 g (20.8%) of **4d**, mp 169–170°.

See Table II for characterizations of benzodiazepines.

Registry No.—**1a**, 439-14-5; **1b**, 1088-11-5; **1c**, 2011-67-8; **1d**, 146-22-5; **2a**, 2898-12-6; **2a** dimer, 36493-03-5; **2b**, 1694-78-6; **2c**, 2898-19-3; **2d**, 2898-03-5; **3a**, 4267-07-6; **3b**, 10456-83-4; **3b** HCl, 2890-23-5; **3c**, 36508-54-0; **3c** HCl, 36508-55-1; **3d**, 36508-56-2; **4a**, 21647-87-0; **4d**, 36508-58-4; **5**, 36508-59-5; **7**, 28739-21-1; diborane, 19287-45-7.