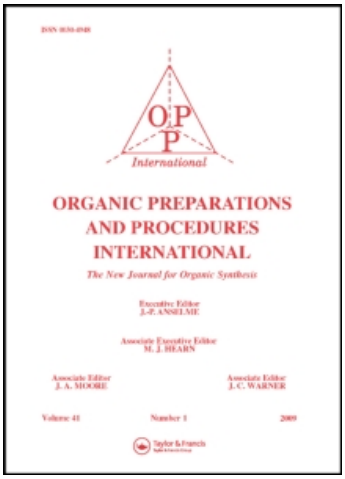

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

CHEMICAL TRANSFORMATION OF DIHYDRO- AND TETRAHYDRO-1,5-BENZODIAZEPIN-2-ONES INTO AMIDINES

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To cite this Article Puodziunaite, Benedikta Dale , Vertelyte, Lina , Janciene, Regina and Stumbreviciute, Zita(1997) 'CHEMICAL TRANSFORMATION OF DIHYDRO- AND TETRAHYDRO-1,5-BENZODIAZEPIN-2-ONES INTO AMIDINES', Organic Preparations and Procedures International, 29: 6, 689 — 696
To link to this Article: DOI: 10.1080/00304949709355250
URL: http://dx.doi.org/10.1080/00304949709355250

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CHEMICAL TRANSFORMATION OF DIHYDRO- AND TETRAHYDRO-1,5-BENZODIAZEPIN-2-ONES INTO AMIDINES

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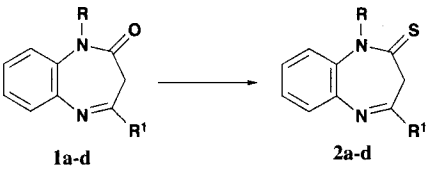
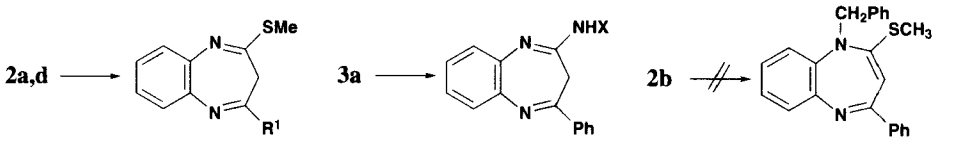
As a result of our interest in the chemistry of 1,5-benzodiazepines, we have investigated the synthesis of cyclic amidines. The present paper describes the preparation of new diversely substituted 3H- and 2,3-dihydro-1H-1,5-benzodiazepine amidines.



	R	R^1
1a, 2a	H	Ph
1b, 2b	CH_2Ph	Ph
1c, 2c	CH_2-CH=CH_2	Ph
1d, 2d	H	Me



3a R^1 = Ph
3b R^1 = Me

4a X = NHCOPh
4b X = NHCOMe
4c X = NH_2

3b

The desired hydrazino amidines **4a-c** were obtained from dihydro-1,5-benzodiazepinone derivatives **1a-d** *via* the route shown in the Scheme. Compounds **1a-d** were prepared according to the literature methods.[1] Lactams **1a-c** were transformed into the corresponding thiolactams **2a-c** using Lawesson's reagent. The interaction of **1d** with thionation agents did not proceed smoothly. The variation of the reaction temperature, time, solvents and agents led to the formation of **2d**, albeit in low yield (Table 1) which may be explained by the fact that compound **1d** is thermally less stable than **1a**.[2]

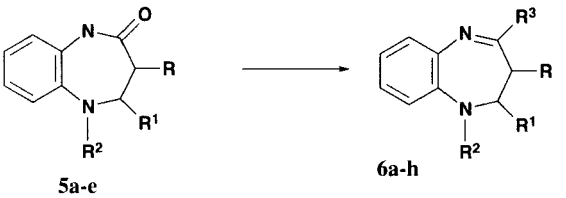
It has previously been reported that in the reaction of **2a** with acethydrazide, a thermal sigmatropic-[1,3] rearrangement of the seven-membered heterocycle to benzimidazol-2-thione is possible.[3] Therefore, thiolactams **2a,d** were activated by conversion into the corresponding iminothioethers **3a,d** by treatment with methyl iodide and potassium carbonate. The tautomeric iminothioether **3b** could be formed from N-substituted thiolactam **2b** when in the formation of the thiolic form there takes part the hydrogen atom of methylene group nearest to C=S, as it was observed in the analogous dihydro-1,5-benzodiazepinthione derivatives.[4] An attempt to prepare iminothioether **3b** by the alkylation of 1-N-benzyl derivative **2b** with methyl iodide and sodium hydride was unsuccessful. The reaction of **3a** with excess of hydrazides or hydrazine afforded amidines **4a-c**.

Table 1. Reaction Conditions for Synthesis of Compound **2d**

No.	Compd **1d** (mmol)	Thionation reagent (mmol)	Solvent	Temp. (°C)	Time (min)	Yield (%)
1.	10	P_2S_5 (12)	dry pyridine	115	50	21 (A)
2.	10	P_2S_5 (12)[a]	dry dioxane	80	120	10[b] (A)
3.	10	P_2S_5 (12)	dry dioxane	105	45	21[b] (A)
4.	10	P_2S_5 (12)	dry toluene	110	20	24 (A)
5.	20	Lawesson's reagent (10)	dry toluene	80	60	11 (B)
6.	20	Lawesson's reagent (10)	dry toluene	35	30	24 (B)

a) At the presence of 100 mmol of $NaHCO_3$; b) purified by column chromatography (silica gel or neutral aluminum oxide).

The desired title N-substituted amidines **6a-h** were obtained from the reaction of tetrahydro-1,5-benzodiazepinone derivatives **5a-e** with amines in the presence of titanium tetrachloride and anisole (refluxing toluene), using a literature procedure.[5] The starting compounds **5a,b,e**



5a-e **6a-h**

	R	R^1	R^2
5a	Me	H	H
5b	H	Me	H
5c	H	Ph	H
5d	H	Me	CH_2Ph
5e	H	H	COPr

	R	R^1	R^2	R^3
6a	Me	H	H	
6b	H	Me	H	
6c	H	Ph	H	
6d	H	Me	CH_2Ph	
6e	H	Me	H	
6f	H	Ph	H	
6g	H	H	COPr	
6h	H	Me	H	NHPr

and **5c** were prepared by the known methods.[6,1a] The IR spectra of compounds **6a-h** exhibit a characteristic absorption in the region 3350-3100 cm^{-1} (NH stretching). An additional band at 1570-1560 cm^{-1} is assigned to the C=N stretching and the spectra do not exhibit a strong band of carbonyl bond, except for compound **6g**. All the compounds synthesized herein are characterized by elemental analysis and ^1H NMR spectra.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes with a PTP apparatus and are uncorrected. IR spectra were recorded as KBr pellets or in Nujol mul on 71 IR spectrophotometer. ^1H NMR spectra were recorded on a Hitachi R-22 spectrometer operating at 90 MHz with HMDSO as an internal reference and chemical shifts are expressed as δ (ppm). TLC was performed on *Silufol* UV_{254} silica gel plates in the systems of eluents (v/v): Method A. benzene/ether/methanol (4:2:1); Method B. benzene/ethyl acetate (9:1); C. chloroform/ethyl acetate/ methanol (14:7:1).

TABLE 2. IR and ^1H NMR Spectral Data of Compounds **2a-d, 3a,d** and **4a-c**

Cmpd	IR (cm^{-1})	^1H NMR[a] (δ) ppm, *J* (Hz)
2a	3150, 3130, 1615, 1570, 1530	12.05 (bs, 1H, NH); 8.40-8.05, 7.60-7.06 (m, 9H, Ar); 3.89 (s, 2H, CH_2)
2b	1610, 1585	8.44-8.22, 7.60-6.92 (m, 14H, Ar); 5.73 (d,1H, CH_2N, ^2J = 15.7 Hz); 5.52 (d, 1H, CH_2N); 4.90 (d, 1H, CH_2, ^2J = 11.8 Hz); 3.42 (d, 1H, CH_2)
2c	1665, 1605, 1565	8.49-8.18, 7.74-7.00 (m, 9H, Ar); 6.20-5.50 (m, 1H, CH); 5.30-4.75 (m, 4H, $2CH_2$); 4.81 (d, 1H, CH_2C=S, ^2J = 12.1 Hz); 3.28 (d, 1H, CH_2C=S)
2d	3130, 1640, 1580, 1535	10.01 (bs, 1H, NH); 7.43-7.03 (m, 4H, Ar); 3.52 (s, 2H, CH_2); 2.36 (s, 3H, CH_3)
3a	1570, 1585	8.14-7.95, 7.60-7.03 (m, 9H, Ar); 3.35 (s, 2H, CH_2); 2.42 (s, 3H, CH_3S)
3d	1630, 1600, 1570	7.43-7.02 (m, 4H, Ar); 2.88 (s, 2H, CH_2); 2.43 (s, 3H, CH_3S); 2.25 (s, 3H, CH_3)
4a	3185, 3050, 1645, 1605, 1560, 1535	10.19 (bs, 1H, NH); 9.40 (bs, 1H, NH); 8.30-6.80 (m, 14H, Ar); 3.49 (bs, 2H, CH_2)
4b	3195, 3150, 3045, 1630, 1610, 1590, 1540	9.73 (bs, 1H, NH); 9.06 (bs, 1H, NH); 8.30-7.93, 7.71-7.00 (m, 9H, Ar); 3.47 (s, 2H, CH_2); 2.07, 1.87 (s, 3H, CH_3)
4c	3360, 3290, 3225, 3120, 1615, 1550, 1500	7.84-6.42 (m, 9H, Ar); 6.06 (s, 1H, CH); 5.29-5.80 (bs, 4H, 2NH, NH_2)[b]

a) Cmpd **2b,c,d, 3a,d** in $CDCl_3$; **4a,b** in DMSO-d_6; **2a** in DMSO-d_6/$CDCl_3$ (1:2); **4c** in DMSO-d_6/$CDCl_3$ (1:4). b) observed as tautomeric form.

4-Phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-thione (2a). A suspension of 4.04 g (10 mmol) of Lawesson's reagent in 100 mL of dry toluene was refluxed with stirring until the solution became

clear. Then the solution was allowed to cool to 40°, and a warm solution of 4.7 g (20 mmol) of **1a** in 60 mL of dry toluene was added. The reaction mixture was heated at 80° until it became clear; then product **2a** began to precipitate as colorless needles. The reaction mixture was allowed to cool to ambient temperature. The precipitate was collected and washed with cool *n*-propanol. The toluene filtrate was sequentially washed with water, 10% of aqueous Na_2CO_3, water and dried over Na_2SO_4. The solvent was concentrated *in vacuo* to 50 mL volume. After cooling, an additional amount of product was obtained.

TABLE 3. Data of Compounds **5d** and **6a-h**

Compd	Yield (%)	mp. °C (solv.)[a]	^{1}H NMR[b] (δ) ppm, *J* (Hz)
5d	75	124-126 (A)	8.75 (bs, 1H, NH); 7.34 (s, 5H, Ar); 7.30-6.90 (m, 4H, Ar); 4.27 (s, 2H, $\underline{CH_2}$Ar); 3.94 (m, 1H, CH); 2.53-1.98 (m, 2H, CH_2CO); 1.06 (d, 3H, CH_3, ^3J6.0)
6a	10	157-159 (B)	7.29-6.50 (m, 4H, Ar); 3.97 (bs, 1H, NH); 3.82-3.42 (m, 8H, morph.); 3.50-2.80 (m, 3H, CH_2CH); 1.15 (d, 3H, CH_3, ^3J6.0)
6b	30	156-158 (C)	7.13-6.62 (m, 4H, Ar); 4.00 (m, 1H, CH); 3.82-3.45 (m, 8H, morph.); 2.99 (bs, 1H, NH); 2.44 (dd, 1H, $\underline{CH_2}$CH, ^2J13.9, ^3J5.1); 2.19 (dd, 1H, $\underline{CH_2}$CH, ^2J13.9, ^3J7.6); 1.22 (d, 3H, CH_3, ^3J6.0)
6c	35	132-134 (C)	7.63-7.18, 7.10-6.62 (m, 9H, Ar); 5.14 (dd, 1H, CH); 3.76-3.03 (m, 8H, morph.); 2.88 (dd, 1H, $\underline{CH_2}$CH, ^2J13.8, ^3J5.1); 2.67 (dd, 1H, $\underline{CH_2}$CH, ^2J13.8, ^3J5.5)
6d	65	123-125 (B)	7.43-6.81 (m, 9H, Ar); 4.19 (s, 2H, CH_2N); 3.89-3.15 (m, 9H, morph., CH); 2.27 (dd, 1H, $\underline{CH_2}$CH, ^2J14.0, ^3J5.8); 2.09 (dd, 1H, $\underline{CH_2}$CH, ^2J14.0, ^3J11.0); 0.98 (d, 3H, CH_3, ^3J6.0)
6e	31	197-199 (D)	7.32-6.85 (m, 4H, Ar); 4.06 (m, 1H, $\underline{CH}CH_3$); 3.82 (m, 1H, CHN); 2.76 (dd, 1H, CH_2C=, ^2J13.6, ^3J5.2); 2.43 (dd, 1H, CH_2C=, ^2J13.6, ^3J5.2); 2.05-0.95 (m, 10H, $(CH_2)_5$); 1.30 (d, 3H, CH_3, ^3J6.3)
6f	38	207-209 (D)	7.57-6.85 (m, 9H, Ar); 5.16 (m, 1H, $\underline{CH}$Ar); 3.69 (m, 1H, CHN); 3.04 (dd, 1H, CH_2C=, ^2J13.8, ^3J4.8); 2.81 (dd, 1H, CH_2C=, ^2J13.8, ^3J6.1); 2.10-0.80 (m, 10H, $(CH_2)_5$)
6g	32	200-203 (D)	7.75-7.28 (m, 4H, Ar); 5.18-4.71 (m, 1H, CH_2N); 4.05-3.44 (m, 2H, CHN,CH_2N); 3.02-2.52 (m, 2H, CH_2C=); 2.51-1.05 (m, 14H, $(CH_2)_5$, $COCH_2CH_2$); 0.76 (t, 3H, CH_3)
6h	35	193-195 (D)	7.34-6.85 (m, 4H, Ar); 4.06 (m, 1H, CH); 3.45 (t, 2H, CH_2N, ^3J6.6); 2.79 (dd, 1H, $\underline{CH_2}$CH, ^2J13.5, ^3J5.5); 2.46 (dd, 1H, $\underline{CH_2}$CH, ^2J13.5, ^3J6.3); 1.75 (m, 2H, $\underline{CH_2}CH_3$); 1.30 (d, 3H, $\underline{CH_3}$CH, ^3J6.3); 1.07 (t, 3H, CH_3, ^3J6.0)

a) Solvent of crystallization: A = benzene, B = ethyl ether, C = ethyl acetate, D = methanol/ethyl ether. b) Solvents: cmpd **5d, 6a-d** in $CDCl_3$; **6e-h** in CD_3OD.

Crystallization of the combined precipitates from *n*-propanol gave 4.0 g (80%) of **2a**, mp. 222-224°, lit.[7] mp. 222°; R_f = 0.87 (A).

1-Benzyl-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-thione (2b).- A suspension of 1.5 g (3.7 mmol) of Lawesson's reagent in 40 mL of dry toluene was refluxed with stirring until clear solution was obtained. After that it was allowed to cool to 40°, a warm solution of 2.4 g (7.4 mmol) of **1b** in 20 mL of dry toluene was added. The reaction mixture was heated at 90-100° until TLC analysis indicated reaction was complete (about 2.5 h). The cool mixture was sequentially washed with water,

TABLE 4. Elemental Analysis Data of Compounds **2c, d, 3d, 4a-c, 5d** and **6a-h**

Cmpd	Molecular Formula	C		H		N	
		Calcd	Found	Calcd	Found	Calcd.	Found
2c	$C_{18}H_{16}N_2S$	73.94	74.21	5.51	5.77	9.58	9.72
2d	$C_{10}H_{10}N_2S$	63.13	63.97	5.29	5.17	14.72	15.02
3d	$C_{11}H_{12}N_2S$	64.67	64.99	5.92	6.19	13.71	13.41
4a	$C_{22}H_{18}N_4O$	74.56	74.84	5.12	5.43	15.81	15.53
4b	$C_{17}H_{16}N_4O$	69.84	69.89	5.51	5.56	19.16	19.23
4c	$C_{15}H_{15}N_4$	71.69	72.00	6.01	5.70	22.29	22.40
5d	$C_{17}H_{18}N_2O$	76.66	77.01	6.81	7.08	10.52	10.32
6a	$C_{14}H_{19}N_3O$	68.54	68.20	7.81	7.76	17.13	17.33
6b	$C_{14}H_{19}N_3O$	68.54	68.77	7.81	8.00	17.13	17.26
6c	$C_{19}H_{21}N_3O$	74.24	74.59	6.89	7.19	13.67	13.74
6d	$C_{21}H_{25}N_3O$	75.19	75.24	7.51	7.58	12.53	12.47
6e	$C_{16}H_{23}N_3 \cdot HCl$	65.40	65.66	8.23	8.31	14.30	14.13
6f	$C_{21}H_{25}N_3 \cdot HCl$	70.87	70.81	7.36	7.20	11.81	11.90
6g	$C_{19}H_{27}N_3O \cdot HCl$	65.22	65.46	8.07	8.21	12.01	12.20
6h	$C_{13}H_{19}N_3 \cdot HBr$	52.36	52.63	6.76	6.98	14.09	14.08

10% of aqueous Na_2CO_3, water and dried over Na_2SO_4. The solvent was removed *in vacuo*. Crystallization of the thick oily residue from EtOAc gave 1.8 g (70%) of **2b** as colorless crystals, mp. 126-127°, lit.[8] mp. 127-128°; R_f = 0.98 (A).

1-Allyl-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-thione (2c).- The product was synthesized from **1c** (2.9 g, 10.5 mmol) according the procedure described for **2b**. After 6 h at 100°, TLC analysis did not indicate completion of reaction. The solution was concentrated under reduced pressure to ca 20 mL and filtered through a short plug of silica gel (100 g). The first fraction was eluted with EtOAc, evaporated and the residue was crystallized twice from EtOH to afford 1.4 g (57%) of **2c** as yellow crystals, mp. 105-107°; R_f = 0.88 (A). The second fraction was eluted with MeOH and after evaporation gave 0.5 g (17%) of **1c,** mp. 102-104°, lit.[1b] mp. 108°; R_f = 0.75 (A).

4-Methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-thione (2d). Method A.- A suspension of 3.9 g (18 mmol) of P_2S_5 in 50 mL of dry pyridine was refluxed with stirring for 2 h and 2.6 g (15 mmol) of **1d**

was added. The resulting brown reaction mixture was refluxed for 50 min and concentrated to dryness *in vacuo*. The dark oily residue was dissolved in 200 mL of $CHCl_3$. The solution was washed with water and dried over Na_2SO_4. Removal of the solvent afforded an orange solid, which was crystallized from toluene to afford 0.58 g (21%) of **2d**, mp. 189-190°; $R_f = 0.70$ (A) and $R_f = 0.45$ (B). The experiments were repeated in dioxane and toluene (see Table 1).

Method B.- A suspension of 4.04 g (10 mmol) of Lawesson's reagent in 100 mL of dry toluene was refluxed with stirring until the solution became clear. After that it was allowed to cool to 40°, a warm solution of 3.48 g (20 mmol) of **1d** in 60 mL of dry toluene was added. A red dark oil formed at once. The reaction mixture was heated at 35° for 30 min and allowed to cool with stirring to room temperature. The toluene solution was decanted from the oil, sequentially washed with water, 10% of aqueous Na_2CO_3, water and dried over Na_2SO_4. Concentration of solution *in vacuo* to ca 40 mL and cooling gave the precipitate (0.9 g) of **2d**. This experiment was performed at higher temperature (see Table 1). TLC analysis of analytical examples of **2d**, obtained in all experiments, exhibited an admixture with R_f= 0.60 and R_f= 0.4 (A and B systems). The elemental analysis of carbon atoms of **2d** exhibited 0.8% more of calculated value.

2-Methylthio-4-phenyl-3H-1,5-benzodiazepine (3a). A mixture of 5.0 g (19.8 mmol) of **2a,** 5.52 g (40 mmol) of K_2CO_3 and 2.46 mL (40 mmol) of methyl iodide in 100 mL of dry THF was stirred at room temperature for 20 h (TLC). Filtration and evaporation of the solvent *in vacuo* gave a brown oily residue which solidified on standing. Crystallization from hexane afforded 3.2 g (61%) of **3a** as pale orange crystals, mp. 86-87°, lit.[7] mp. 87-88°; $R_f = 0.94$ (A).

2-Methylthio-4-methyl-3H-1,5-benzodiazepine (3d). Compound **3d** was synthesized from 3.8 g (19.8 mmol) of **2d** according to the procedure described for **3a**. The resulting crude oily product was purified by column chromatography on silica gel (L 40/100) (v/v, 1:1 Hex/EtOH). Evaporation of the solvent and drying of the residue under reduced pressure at 35° overnight left 2.58 g (64%) of **3d** as a yellow oily material, $R_f = 0.85$ (A).

2-(2'-Benzoylhydrazino-1)-4-phenyl-3H-1,5-benzodiazepine (4a). A solution of 2.6 g (10 mmol) of **3a** and 4.08 g (30 mmol) of benzoylhydrazine in 50 mL of dry ethanol was heated at 60-70° for 2 h (TLC). The reaction mixture was allowed to cool. The formed white precipitate was collected and crystallized from EtOH to give 2.4 g (67%) of **4a**, mp. 181-183°; $R_f = 0.52$ (A).

2-(2'-Acethydrazino-1)-4-phenyl-3H-1,5-benzodiazepine (4b). The compound was synthesized from 1.53 g (5.76 mmol) of **3a** and 1.25 g (17 mmol) of acethydrazide according to the procedure described for **4a**. Crystallization from acetone/petroleum ether (1:1) afforded 0.97 g (59%) of **4b** as pale yellow plates, mp. 199-201°; $R_f = 0.42$ (A).

2-Hydrazino-4-phenyl-3H-1,5-benzodiazepine (4c). A solution of 1.0 g (3.75 mmol) of **3a** and 3.6 mL (113 mmol) of hydrazine in 40 mL of ethanol was refluxed for 2 h (TLC). The solvent was removed *in vacuo* and 30 mL of water was added. The resulting white crystals were collected and recrystallized from EtOH to give 0.6 g (63%) of **4c**, mp. 122-124°; $R_f = 0.50$ (A).

Reaction of Thiolactam 2b with Methyl Iodide. A mixture of 1.7 g (5 mmol) of **2b** and 0.16 g (6 mmol) of sodium hydride in 50 mL of dry toluene was refluxed for 2 h with stirring. After cooling to room temperature a solution of 3.1 mL (50 mmol) of methyl iodide in the same solvent (10 mL) was added dropwise. The mixture was refluxed for an additional 20 h (TLC analysis indicated the presence of **2b**). To the well stirred and cooled reaction mixture 50 mL of water was added. The organic layer was separated and dried over Na_2SO_4. Removal of the solvent *in vacuo* afforded a white solid (1.0 g). ^1H NMR spectrum of this solid indicated the mixture of **1b** (15%), $R_f = 0.83$ and $R_f = 0.67$ and **2b**, $R_f = 0.98$ and $R_f = 0.83$ (A and B). The reaction of **2b** with dimethyl sulfate at the presence of KOH in dioxane/MeOH solution led also to the mixture of **2b** and desulfurated **1b**.

Substituted 2,3-Dihydro-1H-1,5-benzodiazepin-4-amines (6a-h). General Procedure.- A solution of 5 mL of morpholine (cyclohexylamine) or of 4.4 mL of propylamine in 10 mL of dry toluene was added slowly to externally cooled (-15°) and stirred solution of 1.2 mL (10.9 mmol) of $TiCl_4$, 2 mL of anisole in 40 mL of dry toluene, protected from moisture. 10 mmol of the corresponding lactam (**5a-e**) and a further solution of 3 mL (or 2.2 mL) of the suitable amine in 5 mL of dry toluene were then added. The resulting mixture was then refluxed with stirring for 2-6 h when TLC analysis indicated that the reaction was complete (C system). The precooled mixture was treated with 3 mL of concentrated ammonium hydroxide and 3 mL of *i*-propanol. After stirring, the resulting suspension was filtered. The filtrate was washed with two-three 20 mL portions of water, dried over Na_2SO_4, filtered and then evaporated to dryness *in vacuo*. The residue was recrystallized from an appropriate solvent to give the amidine (**6a-d**) as a solid or the residue was treated with hydrochloric or hydrobromic acid in the mixture of methanol and ethyl ether to give the corresponding salt of the amidine (**6e-h**). The data for the products are summarized in the Table 3.

5-Benzyl-4-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (5d).- A mixture of 3.5 g (20 mmol) of **5b**, 2.52 g of $NaHCO_3$ and 0.2 mL (80 mmol) of benzyl chloride in 200 mL of dry methanol was refluxed for 48 h. After cooling the reaction mixture was filtered. Removal of the solvent furnished a crude residue which was dissolved in chloroform. The solution was washed with water, dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo*. Crystallization of the residue gave **5d** as colorless crystals (Table 3).

Acknowledgement.- This investigation has been supported by research grant from Lithuanian Science and Studies Foundation. We wish to thank Miss Z. Talaikyte for her help in discussing IR spectra.

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N-ACETYL-α,β-DEHYDROAMINO ACID *N'*-METHYLAMIDES AND *N',N'*-DIMETHYLAMIDES†

Submitted by (02/06/97)

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α,β-Dehydroamino acids belong to a large group of nonstandard amino acids, which occur in a number of entities of microbial, plant and animal origin. They are a focus of enormous interest due to their applicability to peptide and protein engineering. An α,β-dehydroamino acid incorporated into a peptide chain forms the system involving three rigid groups located on atom C^{α}: the α,β-double bond flanked by two adjacent amide bonds. As a consequence, these amino acids provide conformational constraint to the peptide backbone and restrict the orientation of the side chain β-substituent(s), and hence generate often specific peptide secondary structures (for recent reviews on α,β-dehydropeptides, see Ref. 1-3). However, relatively little effort has been directed to explore the stereoelectronic interactions of bond $C^{\alpha}=C^{\beta}$ with neighboring peptide bonds.[4] To address this question, we prepared *N*-acetyl-α,β-dehydroamino acid *N'*-methylamides and report herein the synthesis of Ac-(*Z*)-ΔAbu-NHMe, Ac-(*Z*)-ΔLeu-NHMe and Ac-ΔVal-NHMe,[5] the new members of the unsaturated amide series, whose conformational preferences and electronic density perturbation we recently investigated.[4] We also