heated under reflux under N_2 for 12 h. The pH was brought to 5 by the addition of 3 M HCl, and the solution was placed in the refrigerator overnight. The solid was filtered off, washed with water, and dried in the vacuum oven: yield 0.95 g (3.01 mmol, 48%); mp 258–260 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.29–1.36 (m, 2 H), 1.48–1.58 (m, 2 H), 2.05 (s, 3 H, CH_3), 2.21 (t, 2 H, J = 7.1 Hz, Het-CH_2), 2.62 (t, 2 H, J = 7.5 Hz, ArCH_2), 3.79 (s, 3 H, $COOCH_3$), 6.00 (br s, 2 H, NH_2), 7.29 and 7.82 (AA′BB′, 4 H, aromatic protons), 11.32 (br s, 1 H, N-3 H); HRMS calcd for $C_{17}H_{21}N_3O_3$ 315.1583, found 315.1576. Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.71; H, 6.77; N, 13.16.

4-(4-(6-Amino-3,4-dihydro-2-methyl-4-oxopyrimidin-5-yl)butyl)benzoic Acid (22). A solution of ester **22** (750 mg, 2.38 mmol) in 1 M NaOH (30 mL) was heated under reflux for 2 h. After cooling, the pH was brought to 5 by the addition of 1 M HCl, and the precipitate was filtered off, washed with water, and dried to give 480 mg (1.59 mmol, 67%) of **22** as a white powder; mp 278–280 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.30–1.37 (m, 2 H), 1.49–1.58 (m, 2 H), 2.05 (s, 3 H, CH_3), 2.22 (t, 2 H, J = 7.2 Hz, het-CH_2), 2.61 (t, 2 H, J = 7.5 Hz, ArCH_2), 6.00 (br s, 2 H, NH_2), 7.26 and 7.80 (AA′BB′, 4 H, aromatic protons), 11.40 (br s, 1 H, N-3 H), 12.75 (br s, 1 H, COOH); HRMS calcd for $C_{16}H_{19}N_3O_3$ 301.1426, found 301.1438. Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found: C, 63.89; H, 6.31; N, 13.71.

Diethyl *N*-(4-(4-(6-Amino-3,4-dihydro-2-methyl-4-oxopyrimidin-5-yl)butyl)benzoyl)-L-glutamate (23). A solution of acid **22** (450 mg, 1.49 mmol), 4-methylmorpholine (230 mg, 2.27 mmol), and 2-chloro-4,6-dimethoxy-1,3,5-triazine (320 mg, 2.00 mmol) in DMF (15 mL) was stirred at rt under N_2 for 30 min. Diethyl L-glutamate hydrochloride (481 mg, 2.00 mmol) and 4-methylmorpholine (200 mg, 1.98 mmol) were added, and the solution was allowed to stir at rt under N_2 for 2.5 h. The solvent was removed in vacuo, and CH_2Cl_2 (100 mL) was added to the residue. The solution was washed with water (100 mL) and brine (100 mL), and after drying over anhydrous $MgSO_4$, the solvent was evaporated and the residue chromatographed using 7% MeOH/CH_2Cl_2 as eluent to give 350 mg (0.72 mmol, 48%) of **23**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (t, 3 H, J = 7.1 Hz, $COOCH_2CH_3$), 1.26 (t, 3 H, J = 7.1 Hz, $COOCH_2CH_3$), 1.44–1.50 (m, 2 H), 1.59–1.69 (m, 2 H), 2.03–2.13 (m, 1 H, glutamate C_β-H), 2.16–2.26 (m, 1 H, glutamate C_β-H), 2.21 (s, 3 H, CH_3), 2.31–2.50 (m, 4 H, het-CH_2 and glutamate C_γ-H_2), 2.64 (t, 2 H, J = 7.4 Hz, $C_6H_4CH_2$), 4.07 (q, 2 H, J = 7.1 Hz, $COOCH_2CH_3$), 4.19 (q, 2 H, J = 7.1 Hz, $COOCH_2CH_3$), 4.72–4.77 (m, 1 H, glutamate C_α-H), 4.85 (br s, 2 H, NH_2), 7.16 and 7.68 (AA′BB′, 4 H, aromatic protons), 7.22 (d, 1 H, J = 7.6 Hz, CONH); HRMS calcd for $C_{25}H_{34}N_4O_6$ 486.2478, found 486.2492. Anal. Calcd for $C_{25}H_{34}N_4O_6$: C, 61.71; H, 7.04; N, 11.51. Found: C, 61.50; H, 6.92; N, 11.46.

***N*-(4-(4-(6-Amino-3,4-dihydro-2-methyl-4-oxopyrimidin-5-yl)butyl)benzoyl)-L-glutamic Acid (24).** A solution of diester **23** (250 mg, 0.51 mmol) in 1 M NaOH (15 mL) was stirred at rt for 24 h. The pH was brought to 5 by the addition of 1 M HCl, and the precipitate was allowed to stand for 15 min. The suspension was centrifuged and the water decanted off. The remaining solid was centrifuged twice with ethanol and once with ether before being filtered off and dried in the vacuum oven: yield 150 mg (0.35 mmol, 68%); mp 190–192 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.29–1.35 (m, 2 H), 1.48–1.58 (m, 2 H), 1.87–2.01 (m, 2 H, glutamate C_β-H_2), 2.05 (s, 3 H, CH_3), 2.21 (t, 2 H, J = 7.2, glutamate C_γ-H_2), 2.31 (t, 2 H, J = 7.3 Hz, het-CH_2), 2.60 (t, 2 H, J = 7.3 Hz, $C_6H_4CH_2$), 4.31–438 (m, 1 H, glutamate C_α H), 6.04 (s, 2 H, NH_2), 7.24 and 7.74 (AA′BB′, 4 H, aromatic protons), 8.45 (d, 1 H, J = 7.6 Hz, CONH), 11.32 (br s, 1 H, N-3 H), 12.46 (br s, 2 H, COOH); FABMS calcd for $C_{21}H_{27}N_4O_6$ (MH^+) 431.1931, found 431.1946.

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Registry No. **3**, 5604-46-6; **4**, 142979-46-2; **5**, 142979-47-3; **6**, 142979-48-4; **7**, 142979-49-5; **8**, 61266-36-2; **9**, 15403-22-2; **10**, 141618-99-7; **11**, 142979-50-8; **12**, 142979-51-9; **14**, 124656-56-0; **15**, 142979-52-0; **16a**, 142979-53-1; **16b**, 142979-61-1; **17a**, 142979-54-2; **17b**, 142979-62-2; **18a**, 142979-55-3; **18b**, 142979-63-3; **19a**, 142979-56-4; **19b**, 142979-64-4; **20**, 142979-57-5; **21**, 142979-58-6; **22**, 142979-59-7; **23**, 142979-60-0; **24**, 143006-13-7; $PhCH_2NHMe$, 103-67-3; $H_3CCOCH_2CH_2COCH_3$, 110-13-4; 4-$IC_6HyCOOMe$, 619-44-3; $HC{\equiv}CCH_2OH$, 107-19-7; Ph_3P, 603-35-0; H-Glu(OEt)-OEt·HCl, 1118-89-4; $EtOCOCH_2CN$, 105-56-6; $H_3CC(NH_2){=}NH{\cdot}HCl$, 124-42-5.

Supplementary Material Available: ^{1}H NMR spectra and ^{13}C NMR, IR, and mass spectral data of the compounds reported in this paper (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Dehalogenation of α-Halo Aldehydes via α-Halo Aldimines and 2-Aza-1,3-dienes

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Introduction

The selective removal of halogens α to a carbonyl moiety yielding the parent carbonyl compound has received considerable attention. An array of procedures for the reductive dehalogenation of α-halo ketones has been developed, including the use of zinc in acetic acid,[1] metal carbonyls,[2-4] transition metals,[5] tributyltin hydride,[6] iodide ion,[7,8] nickel boride,[9] tellurium reagents,[10,11] samarium iodide,[12] lithium diisopropylamide,[13] iodophosphines,[14] the combination of phenylsilane and catalytic amounts of molybdenum hexacarbonyl and triphenylphosphine,[15] and many other reagents.[15,16] Few of these reagents are applicable for the dehalogenation of α-halo aldehydes because of competitive reactions mainly centered at the reactive aldehyde carbon. However, 1,3-dimethyl-2-phenylbenzimidazoline has been found recently to be a powerful and chemoselective reducing agent for the mild reductive dehalogenation of a variety of α-halo carbonyl compounds, including α-halo aldehydes.[17]

In the present paper a new method for the dehalogenation of α-halo aldehydes employing very common chemicals is disclosed.

Discussion of the Results

The dechlorination of α-halo aldehydes consists of a sequence of reactions by which an α-chloro aldehyde **1** is converted into a N-benzylic α-chloro aldimine **3**, which is subjected to base-induced 1,4-dehydrochlorination[18] and subsequent hydrolysis (Scheme I). α-Chloro aldehydes **1** are cleanly converted into α-chloro aldimines **3** by reaction with 1 molar equiv of benzylamine or *p*-chlorobenzylamine in CH_2Cl_2 in the presence of $MgSO_4$ as drying agent at room temperature for 2 h. These N-benzylic α-chloro aldimines **3** are sufficiently pure for use in the next step. *N*-Benzylaldimines **3** contain an active methylene function at the benzylic position, allowing deprotonation by potassium *tert*-butoxide. The resulting me-

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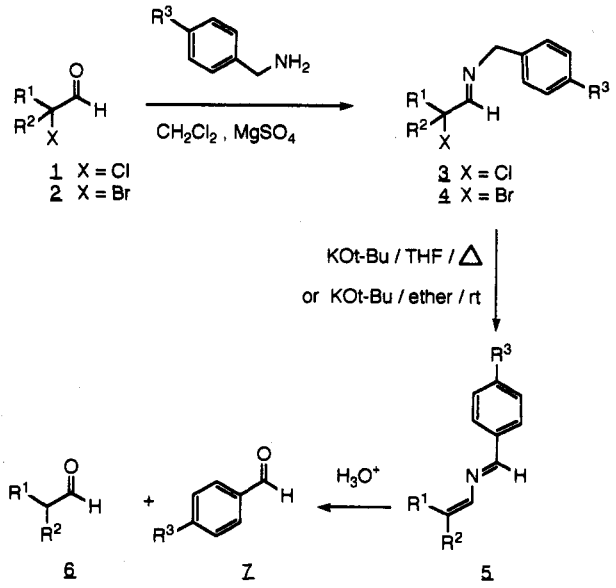
Table I. Dehalogenation of α-Chloro Aldehydes 1 and α-Bromo Aldehyde 2 into Aldehydes 6

R^1	R^2	R^3	X	α-halo aldimine 3[a] and 4[b] yield (%) from 1 and 2	2-aza-1,3-diene 5 yield (%) from 3 and 4	aldehyde 6[f] yield (%) from 5
Et	Et	H	Cl	**3a**:85	**5a**:87[c]	**6a**:93
Et	Et	Cl	Cl	**3b**:86	**5b**:85[c]	**6a**:87
$(CH_2)_5$		H	Cl	**3c**:92	**5c**:78[d]	**6b**:94
$(CH_2)_5$		Cl	Cl	**3d**:88	**5d**:80[d]	**6b**:83
Me	Me	H	Cl	**3e**:91	**5e**:91[d]	**6c**:90
Et	Et	H	Br	4:89	**5a**:94[e]	**6a**:93

[a] Reaction conditions: α-chloro aldehyde 1 and 1 molar equiv of the benzylamine (R^3 = H, Cl) in CH_2Cl_2 (10% 1 w/v) in the presence of $MgSO_4$ at room temperature for 2 h. [b] Reaction conditions: α-bromo aldehyde 2 and 1 molar equiv of benzylamine in CH_2Cl_2 in the presence of $MgSO_4$ at room temperature for 2 h. [c] Reaction conditions: compound 3 and 1.4 equiv of potassium *tert*-butoxide in THF under reflux for 1 h. [d] Reaction conditions: compound 3 and 1.4 equiv of potassium *tert*-butoxide in ether at room temperature overnight (most reactions go to completion within 2 h). [e] Reaction conditions: compound 4 and 1.4 equiv of potassium *tert*-butoxide in ether (reflux 1 h). [f] Reaction conditions: hydrolysis with 2 equiv of aqueous 4 N HCl and CH_2Cl_2 as a second phase (reflux 1 h).

Scheme I



someric 2-azaallylic anion eliminates a chloride anion to form 2-aza-1,3-dienes **5**, originating from a net 1,4-dehydrochlorination. Again, this reaction leads to reaction products **5** which are of sufficient purity for further use in the next step. 2-Aza-1,3-dienes **5** can be considered as the combination of an imine and an enamine. Therefore, by hydrolysis they lead to ammonia and the two carbonyl compounds. The hydrolysis of 2-aza-1,3-dienes **5** is conveniently performed by reflux (1 h) in a biphase system containing aqueous 4 N HCl and CH_2Cl_2. The resulting carbonyl compounds, i.e., aldehydes **6** and benzaldehydes **7**, are obtained in good yield in approximately a 1:1 ratio. The applicability of this sequence of reactions requires a good separation of aldehydes **6** from the aromatic aldehydes **7**. 2-Ethylbutanal (**6a**) ($R^1 = R^2$ = Et) and isobutyraldehyde (**6c**) ($R^1 = R^2$ = Me) are easily separable from benzaldehyde (**7**) (R^3 = H) by distillation. Higher aliphatic aldehydes, e.g., cyclohexanecarboxaldehyde (**6b**) (R^1–$R^2 = (CH_2)_5$), have boiling points closer to the one of benzaldehyde. Therefore, the use of *p*-chlorobenzylamine in the synthetic sequence is recommended because it gives a better separation of **6** and **7**. This sequence of reactions certainly tolerates the use of other benzylamines, which can be choosen in such a way as to obtain a good separation of the desired aldehyde **6** and the byproduct **7**.

Also, α-bromo aldehydes are subject to a similar debromination into the reduced aldehydes, as exemplified for the conversion of 2-bromo-2-ethylbutanal (**2**) ($R^1 = R^2$ = Et) into 2-ethylbutanal (**6a**). 2-Bromo-2-ethylbutanal (**2**) ($R^1 = R^2$ = Et) was reacted with benzylamine in CH_2Cl_2 in the presence of $MgSO_4$ to afford α-bromo aldimine **4** ($R^1 = R^2$ = Et; R^3 = H) (89%), which was always contaminated by small amounts of starting material and an unidentified reaction product. The contaminant apparently did not interfere in further reaction steps. The reaction of α-bromo aldimine **4** with potassium *tert*-butoxide in ether under reflux for 1 h afforded the 1,4-dehydrobromination product **5a** in 94% yield. As reported above, 2-aza-1,3-diene **5a** was hydrolyzed by aqueous HCl (2 equiv, 4 N) into 2-ethylbutanal (**6a**) in 93% yield (Table I). The results of the conversion of **1** and **2** into **6** are summarized in Table I.

The overall process from **1** and **2** to **6** constitutes a transamination, which delivers the target aldehydes **6** free from side reactions. These reactions can be run without purification of the intermediates **3**, **4**, and **5**. This sequence of reactions, entailing a useful dehalogenation procedure of α-halo aldehydes, is certainly amenable to other aldehyde substrates and offers a good alternative to the already known dechlorination methods.

Experimental Section

Synthesis of α-Chloro Aldimines 3. A solution of 0.05 mol of α-chloro aldehyde **1** in 75 mL of CH_2Cl_2 was treated in one portion with 0.05 mol benzylamine or 4-chlorobenzylamine. After the addition of 0.1 mol of anhydrous $MgSO_4$, the mixture was stirred at room temperature for 2 h. The heterogenous reaction mixture was filtered and evaporated in vacuo to give α-chloro aldimines **3** in sufficient purity to be used in the next dehydrohalogenation step. Yields are given in Table I.

***N*-(2-Chloro-2-ethyl-1-butylidene)benzylamine (3a)** ($R^1 = R^2$ = Et; R^3 = H): bp 102–103 °C (0.1 mmHg); ^{1}H NMR (CCl_4) δ 0.96 (6 H, t, J = 7 Hz, Me_2), 1.97 (4 H, ≈q, J = 7 Hz, $(CH_2)_2$),

(1) Zimmerman, H. E.; Mais, A. *J. Am. Chem. Soc.* **1959**, *81*, 3644.
(2) Alper, H.; Patter, L. *J. Org. Chem.* **1979**, *44*, 2568.
(3) Luk, T. H.; Lai, C. H.; Lei, K. L.; Tam, S. W. *J. Org. Chem.* **1979**, *44*, 641.
(4) Alper, H. *Tetrahedron Lett.* **1975**, 2257.
(5) McMurry, J. E. *Acc. Chem. Res.* **1974**, *7*, 281.
(6) Bock, D. A.; Brady, W. T. *J. Org. Chem.* **1979**, *44*, 101.
(7) Olah, G. A.; Arvanaghi, M.; Vankar, Y. D. *J. Org. Chem.* **1980**, *45*, 3531.
(8) Gemal, A. L.; Luche, J. L. *Tetrahedron Lett.* **1980**, 3195.
(9) Sarma, J. C.; Borbaruah, M.; Sharma, R. P. *Tetrahedron Lett.* **1985**, *26*, 4657.
(10) Engman, L.; Cava, M. P. *J. Org. Chem.* **1982**, *47*, 3946.
(11) Petragnani, N.; Comasseto, J. V. *Synthesis* **1986**, 1.
(12) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.
(13) Dubois, J.-E.; Lion, C.; Dugast, J.-Y. *Tetrahedron Lett.* **1983**, *24*, 4207.
(14) Denis, J, N.; Krief, A. *Tetrahedron Lett.* **1981**, *22*, 1431.
(15) Perez, D.; Greenspoon, N.; Keinan, E. *J. Org. Chem.* **1987**, *52*, 5570 and references cited therein.
(16) De Kimpe, N.; Verhé, R. *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines*; Patai, S., Rappoport, Z., Eds.; J. Wiley: Chichester (U.K.), 1988.
(17) Chikashita, H.; Ide, H.; Itoh, K. *J. Org. Chem.* **1986**, *51*, 5400.
(18) De Kimpe, N.; Yao, Z.; Boeykens, M.; Nagy, M. *Tetrahedron Lett.* **1990**, *31*, 2771.

4.51 (2 H, d, J = 1.2 Hz, NCH_2), 7.23 (5 H, s, C_6H_5), 7.71 (1 H, t, J = 1.2 Hz, C*H*=N); ^{13}C NMR ($CDCl_3$) δ 8.8 (q, Me_2), 32.0 (t, $(CH_2)_2$), 64.0 (t, NCH_2), 77.0 (s, *C*Cl), 126.9 (d, para C), 127.7 and 128.4 (each d, meta and ortho C's), 138.8 (s, =*C*CH_2), 165.8 (d, *C*H=N); IR (NaCl) 1666 cm^{-1} (C=N); mass spectrum m/z (relative intensity) no M^+, 195/7 (McLafferty, $-C_2H_4$; 18), 188 (-Cl; 10), 180/2 (9), 133 (50), 132 (5), 118 (3), 105 (2), 104 (2), 91 (100), 89 (2), 69 (14), 65 (10). Anal. Calcd for $C_{13}H_{18}ClN$: N, 6.26; Cl, 15.85. Found: N, 6.39; Cl, 15.63.

***N*-(2-Chloro-2-ethyl-1-butylidene)-4-chlorobenzylamine (3b) ($R^1 = R^2 = Et$; $R^3 = Cl$)**: ^1H NMR (CCl_4) δ 0.95 (6 H, t, J = 7 Hz, $(CH_3)_2$), 1.98 (4 H, ≈q, J = 7 Hz, $(CH_2)_2$), 4.54 (2 H, d, J = 1.2 Hz, NCH_2), 7.20 and 7.30 (each 2 H, each d, AB, J = 9 Hz, C_6H_4), 7.76 (1 H, t, J = 1.2 Hz, C*H*=N); ^{13}C NMR ($CDCl_3$) δ 8.8 (q, Me_2), 32.1 (t, $(CH_2)_2$), 63.2 (t, NCH_2), 76.9 (s, *C*Cl), 128.6 and 129.0 (each d, ortho and meta C's), 132.8 (s, =*C*Cl), 137.6 (s, =*C*-CH_2), 166.2 (d, *C*H=N); IR (NaCl) 1667 cm^{-1} (C=N); mass spectrum m/z (relative intensity) no M^+, 222/24 (33), 206/08 (100), 192/4 (12), 178 (8), 177 (6), 171 (7), 151/3 (12), 138/40 (23), 125 (11), 89 (16), 69 (7), 45 (6). Anal. Calcd for $C_{13}H_{17}Cl_2N$: N, 5.42; Cl 27.46. Found: N, 5.56; Cl, 27.29.

***N*-[(1-Chloro-1-cyclohexyl)methylidene]benzylamine (3c) (R^1-$R^2 = (CH_2)_5$; $R^3 = H$)**: bp 101–105 °C (0.4 mmHg); ^1H NMR ($CDCl_3$) δ 1.1–2.3 (10 H, m, $(CH_2)_5$), 4.57 (2 H, d, J = 1.2 Hz, NCH_2), 7.21 (5 H, s, C_6H_5), 7.72 (1 H, t, J = 1.2 Hz, C*H*=N); ^{13}C NMR ($CDCl_3$) δ 22.2 (t, $(CH_2)_2$), 25.2 (t, CH_2), 36.9 (t, $(CH_2)_2$), 63.6 (t, CH_2N), 73.0 (s, *C*Cl), 126.8 (d, para C), 127.6 and 128.3 (each d, meta and ortho C's), 138.9 (s, C quat. arom.), 165.9 (d, H*C*=N); IR (NaCl) 1670 cm^{-1} (C=N); mass spectrum m/z (relative intensity) 235/37 (M^+; 1), 200 (39), 180/2 (6), 133 (36), 132 (6), 91 (100), 81 (21), 65 (10). Anal. Calcd for $C_{14}H_{18}ClN$: N, 5.94; Cl, 15.04. Found: N, 5.99; Cl, 15.21.

***N*-[(1-Chlorocyclohexyl)methylidene]-4-chlorobenzylamine (3d) (R^1-$R^2 = (CH_2)_5$; $R^3 = Cl$)**: ^1H NMR ($CDCl_3$) δ 1–2.2 (10 H, m, $(CH_2)_5$), 4.63 (2 H, d, J = 1.2 Hz, NCH_2), 7.33 (4 H, s, C_6H_4), 7.88 (1 H, t, J = 1.2 Hz, C*H*=N); ^{13}C NMR ($CDCl_3$) δ 22.2 (t, $(CH_2)_2$), 25.2 (t, CH_2), 36.9 (t, $(CH_2)_2$), 62.9 (t, NCH_2), 72.8 (s, *C*Cl), 128.5 and 128.9 (each d, meta and ortho C's), 132.6 (s, 4-Cl*C*=); 137.6 (s, CH_2C=), 166.3 (d, *C*H=N); IR (NaCl) 1668 cm^{-1} (C=N); mass spectrum m/z (relative intensity) 269/71/73 (M^+; 3), 234/36 (40), 214/16/18 (5), 167/69 (35), 125/27 (100), 89 (10), 81 (40). Anal. Calcd for $C_{14}H_{17}Cl_2N$: N, 5.18; Cl 26.24. Found: N, 5.03; Cl, 26.30.

***N*-(2-Chloro-2-methyl-1-propylidene)benzylamine (3e)** ($R^1 = R^2 = Me$; $R^3 = H$). Identical in all aspects with previously reported data.[19]

Conversion of α-Chloro Aldimines 2 into 2-Aza-1,3-dienes 5. A solution of 0.05 mol of α-chloro aldimine **2** in 150 mL of dry ether or dry THF (see Table I) was treated with 0.07 mol of potassium *tert*-butoxide. The reaction mixture was stirred under reflux for 1 h (THF) or at room temperature overnight (ether), after which it was poured into water. Extraction with ether gave, after drying with K_2CO_3, an oily reaction mixture, which consisted of pure 2-aza-1,3-diene **5**. These 2-aza-1,3-dienes **5** were characterized by spectroscopic methods and were used as such in the next hydrolysis step. High vacuum distillation does not offer any advantage.

***N*-(Benzylidene)-2-ethyl-1-butenylamine (5a) ($R^1 = R^2 = Et$; $R^3 = H$)**: bp 115–118 °C (0.65 mmHg); ^1H NMR ($CDCl_3$) δ 1.04 (3 H, t, J = 7.5 Hz, CH_3), 1.07 (3 H, t, J = 7.5 Hz, CH_3), 2.12 (2 H, q, J = 7.5 Hz, CH_2C=), 2.63 (2 H, q, J = 7.5 Hz, CH_2C=), 6.48 (1 H, s, br, C*H*=C), 7.0–7.3 (3 H, m, meta and para H's), 7.4–7.8 (2 H, m, ortho H's), 7.90 (1 H, s, br, CH=N); ^{13}C NMR ($CDCl_3$) δ 12.8 and 13.3 (each q, Me_2), 22.9 and 27.0 (each t, $(CH_2)_2$), 128.1 and 128.5 (each d, meta and ortho C's), 130.1 (d, para C), 137.2 (s, quat. arom. C), 136.4 (d, C=*CN*), 146.5 (s, Et_2C=), 156.6 (d, *C*H=N); IR (NaCl) 1642 cm^{-1} (C=N); mass spectrum m/z (relative intensity) 187 (M^+, 20), 172 (72), 158 (11), 155 (7), 144 (14), 143 (11), 118 (5), 117 (24), 115 (7), 110 (5), 105 (6), 104 (56), 91 (32), 90 (28), 89 (24), 79 (5), 78 (4), 77 (17), 69 (16), 67 (10), 65 (11), 63 (9), 55 (16), 53 (13), 51 (11), 42 (6), 41 (100), 40 (11), 39 (24). Anal. Calcd for $C_{13}H_{17}N$: N, 7.48. Found: N, 7.66.

(19) De Kimpe, N.; Verhé, R.; De Buyck, L.; Hasma, H.; Schamp, N. *Tetrahedron* **1976**, *32*, 2457.

***N*-(4-Chlorobenzylidene)-2-ethyl-1-butenylamine (5b) ($R^1 = R^2 = Et$; $R^3 = Cl$)**: ^1H NMR ($CDCl_3$) δ 1.04 (6 H, t, J = 7 Hz, Me_2), 2.11 and 2.57 (each 2 H, each q, J = 7 Hz, $(CH_2)_2C$=C), 6.43 (1 H, s, br, C=C*HN*), 7.14 (2 H, d, J = 8.5 Hz, ortho CH's), 7.48 (2 H, d, J = 8.5 Hz, meta CH's), 7.77 (1 H, s, C*H*=N); ^{13}C NMR ($CDCl_3$) δ 12.8 and 13.3 (each q, Me_2), 23.1 and 27.2 (each t, $(CH_2)_2$), 128.7 and 129.2 (each d, ortho and meta C's), 135.8 and 135.9 (each s, C_1 and C_4 of the aromatic ring), 136.3 (d, C=*CHN*), 147.1 (s, Et_2C=C), 154.7 (d, *C*H=N); IR (NaCl) 1648 cm^{-1} (C=N); mass spectrum m/z (relative intensity) 221/23 (M^+; 40), 206/08 (100), 192/94 (15), 178 (9), 177 (7), 171 (9), 141/43 (20), 138/40 (30), 125 (13), 89 (30), 69 (13), 67 (9), 63 (9), 55 (9), 53 (7), 41 (63). Anal. Calcd for $C_{13}H_{16}ClN$: N, 6.32; Cl, 15.99. Found: N, 6.19, Cl, 15.78.

***N*-(Benzylidenecyclohexylidenemethylamine (5c) (R^1-$R^2 = (CH_2)_5$; $R^3 = H$)**: bp 97–100 °C (0.3 mmHg); ^1H NMR ($CDCl_3$) δ 1–2 (6 H, m, $(CH_2)_3$, 2–2.4 (2 H, m, CH_2C=), 2.5–2.9 (2 H, m, CH_2C=C), 6.54 (1 H, s, br, =C*HN*), 7.1–7.5 (3 H, m, meta and para H's), 7.5–7.8 (2 H, m, ortho H's), 8.00 (1 H, s, C*H*=N); ^{13}C NMR ($CDCl_3$) δ 27.0, 27.7, 28.6, 28.6 and 34.1 (all t, all CH_2), 128.1 and 128.4 (each d, meta and ortho C's), 130.1 (d, para C), 134.9 (d, =*C*HN), 137.2 (s, C quat. arom.), 143.2 (s, CH_2C=), 156.6 (d, *C*H=N); IR (NaCl) 1658 cm^{-1} (C=N); mass spectrum m/z (relative intensity) 199 (M^+; 100), 198 (48), 170 (30), 157 (40), 156 (95), 122 (32), 117 (60), 106 (16), 104 (24), 91 (44), 90 (52), 89 (32), 79 (20), 77 (20), 67 (16), 65 (12), 55 (16), 53 (12), 51 (12). Anal. Calcd for $C_{14}H_{17}N$: N, 7.03. Found: N, 6.89.

***N*-(Chlorobenzylidene)cyclohexylidenemethylamine (5d) (R^1-$R^2 = (CH_2)_5$; $R^3 = Cl$)**: bp 135–138° C (0.3 mmHg) (substantial decomposition occurred upon distillation); mp 49 °C; ^1H NMR ($CDCl_3$) δ 1–2 (6 H, m, $(CH_2)_3$), 2–2.4 (2 H, m, C*H*$_2$C=), 2.5–3 (2 H, m, C*H*$_2$C=), 6.67 (1 H, s, br, =C*H*N), 7.40 (2 H, d, C*H*'s at 3-position), 7.78 (2 H, d, C*H*'s at 2-position), 8.11 (1 H, s, C*H*=N); ^{13}C NMR ($CDCl_3$) δ 26.9, 27.7, 28.6, 28.6 and 34.1 (all t, all CH_2), 128.7 and 129.2 (each d, meta and ortho C's), 134.8 (d, =*C*HN), 135.7 and 135.9 (each s, 2 × C quat. arom.), 143.9 (s, CH_2C=), 154.9 (d, *C*H=N); IR (NaCl) 1650 cm^{-1} (C=N); mass spectrum m/z (relative intensity) 233/35 (M^+; 100), 232/34 (54), 204/06 (28), 190/92 (84), 151/3 (42), 140 (18), 138 (18), 125 (28), 124 (20), 122 (28), 95 (15), 89 (42), 79 (18), 88 (17), 67 (17). Anal. Calcd for $C_{14}H_{16}ClN$: N, 5.99; Cl, 15.17. Found: N, 5.90; Cl, 14.96.

***N*-(Benzylidene)-2-methyl-1-propenylamine (5e) ($R^1 = R^2 = Me$; $R^3 = H$)**: bp 80–83 °C (0.5 mmHg). Identical in all aspects to the previously reported data.[19]

Hydrolysis of 2-Aza-1,3-dienes 5 into Aldehydes 6 and Benzaldehydes 7. A solution of 0.05 mol of 2-aza-1,3-diene **5** in 100 mL of CH_2Cl_2 was refluxed under vigorous stirring for 1 h with 25 mL of 4 N aqueous HCl. After the mixture was cooled, the organic phase was washed with brine. After drying ($MgSO_4$), the solvent was evaporated at atmospheric pressure using a short Vigreux column. Aldehydes **6** and **7** were separated by distillation. For example, the mixture of isobutyraldehyde (**6c**) ($R^1 = R^2 = Me$) and benzaldehyde (**7**) ($R^3 = H$), obtained from the hydrolysis of 2-aza-1,3-diene **5e**, was distilled to give isobutyraldehyde (90%, bp 61–62 °C) and benzaldehyde (83%, bp 101–103 °C (15 mmHg)). Alternatively, this mixture of aldehydes was separated by column chromatography (silica gel Silpearl, 70–140 μm, Kavalier Votice, Czechoslovakia, 60-cm length, i.d. 3 cm) with toluene as eluent (TLC monitoring the C_6H_6–ether (7:3); benzaldehyde R_f 0.83, isobutyraldehyde R_f 0.58). Aldehydes **6** were identical in all aspects with commercial samples.

Synthesis of α-Bromo Aldimine 4 ($R^1 = R^2 = Et$; $R^3 = H$). A stirred solution of 5.37 g (0.03 mol) of 2-bromo-2-ethylbutanal (**2**) ($R^1 = R^2 = Et$) in 50 mL of CH_2Cl_2 was treated with 3.21 g (0.03 mol) of benzylamine. Anhydrous $MgSO_4$ (0.06 mol, 7.2 g) was added, and stirring at room temperature was continued for 2 h. Evaporation in vacuo afforded α-bromo aldimine **4** ($R^1 = R^2 = Et$; $R^3 = H$) (7.16 g; 89%) which was contaminated by small amounts of starting material and an unidentified compound. The α-bromo aldimine **4** was used as such in the next dehydrobromination step: ^1H NMR ($CDCl_3$) δ 0.97 (6 H, t, J = 7 Hz, 2Me), 2.10 (4 H, q, J = 7 Hz, $2CH_2$), 4.57 (2 H, d, J = 1.3 Hz, NCH_2), 7.20 (5 H, s, C_6H_5), 7.79 (1 H, t, J = 1.3 Hz, CH=N); ^{13}C NMR ($CDCl_3$) δ 10.0 (q, 2Me), 32.1 (t, $2CH_2$), 63.6 (t, NCH_2), 75.4 (s, CBr), 126.8 (d, para C), 127.6 and 128.3 (each d, ortho and meta C's), 139.0 (s, C_{quat}), 165.3 (d, CH=N); IR (NaCl) 1660 cm^{-1}

(C=N); mass spectrum m/z (relative intensity) no M^+, 238/40 (Me^{*+} - Et; 1), 223/5 (1), 188 (-Br; 3), 133 (31), 91 (100), 86 (6), 84 (8), 82 (6), 81 (4), 80 (6), 79 (4), 69 (17), 65 (21), 55 (6), 49 (15), 44 (81), 43 (11), 41 (21). Anal. Calcd for $C_{13}H_{18}BrN$: N, 5.22; Br, 29.79. Found: N, 5.13; Br, 29.56.

Dehydrobromination of α-Bromo Aldimine 4 ($R^1 = R^2$ = Et; R^3 = H). α-Bromo aldimine 4 was dehydrobrominated with potassium *tert*-butoxide (1.4 equiv) in dry ether under reflux for 1 h. Workup was performed as described above in the general synthesis of 2-aza-1,3-dienes 5 from α-chloro aldimines 3. *N*-Benzylidene-2-ethyl-1-butenylamine (5a) was obtained in 94% yield: bp 72-80 °C (0.1 mmHg). See spectroscopic data above.

Unique Carbamation of 2-(2-Pyridyl)-1,3-propanediol by Phosgenation Followed by Ammonolysis†

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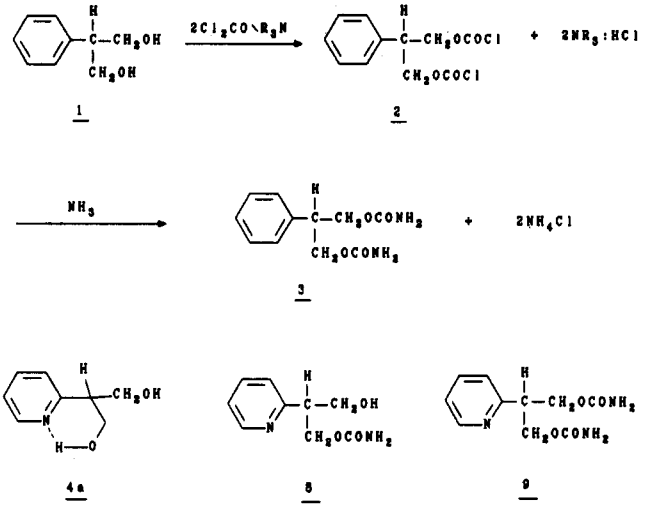
2-Phenyl-1,3-propanediol dicarbamate (3, felbamate) has been developed as a new antiepileptic drug in our laboratories.[1,2] 2-Phenyl-1,3-propanediol (1) has been used as an important intermediate in the synthesis of 3 by a two-step procedure, phosgenation followed by ammonolysis as shown in Scheme I.[3] The administration of 3 in solution to animals or human subjects has been difficult due to the poor solubility of 3 in water.[4] To synthesize not only water-soluble but also more active felbamate backups or analogs, the first series of analogs selected was 2-(2-pyridyl)-substituted dicarbamates. During synthesis of the 2-(2-pyridyl)-1,3-propanediol dicarbamate, we observed that the two-step carbamation of 2-(2-pyridyl)-1,3-propanediol (4) even with an excess of phosgene provides only formation of 2-(2-pyridyl)-1,3-propanediol monocarbamate (8), not the dicarbamate (9).

Accordingly, we undertook a detailed study of the carbamation reaction mechanism of the representative substrate, 2-(2-pyridyl)-1,3-propanediol (4), compared to that with 2-phenyl-1,3-propanediol (1) under mild, controlled reaction conditions. The results of these investigations are reported.

The phosgenation reaction mixture was 0.65 M in phosgene and 0.5 M in the functional group (FG) in substrate 4 in tetrahydrofuran (THF) unless otherwise indicated. The ammonolysis reaction mixture was 10 M in ammonia and 0.2 M in FG in substrate in THF. The addition of substrate to phosgene was carried out at both 0 and -30 °C for 0.25 h. The ammonolysis was carried out at both 0 and -70 °C for 0.25 h unless otherwise indicated. The phosgenation aliquots removed at 0.25 h were monitored by thin-layer chromatography (TLC) analysis before and after the ammonolysis for the reaction progress including disappearance of starting material.

The synthesis of 2-alkyl-1,3-propanediol dicarbamate starting with 2-alkyl-1,3-propanediol has been reported by various methods.[5-7] One simple carbamation method is to perform a two-step procedure combining the phosgenation and then the ammonolysis. For example, addition of phosgene to 1 in a 4:1 molar ratio results in the expected

Scheme I



formation of 2-phenyl-1,3-propanediyl bis(chloroformic acid ester) (2) as indicated in Scheme I.[3,8] The phosgenation reaction required room temperature (rt) for 16 h in toluene with antipyrine as a hydrogen chloride trapping agent and 1 h in THF.[3] The intermediate, 2, readily reacts with ammonia to yield 2-phenyl-1,3-propanediol dicarbamate (3).

In a similar manner, the preliminary phosgenation between 2-(2-pyridyl)-1,3-propanediol (4) and phosgene in a 4:1 molar ratio in THF with triethylamine (TEA) was performed at 0 °C but formed immediate precipitates along with disappearance of 4 as monitored by TLC analysis. This is probably due to formation of a coordinating bond of the electrophilic phosgene to the 2-pyridyl moiety in the substrate 4. With pyridine, the corresponding phosgenation with a phosgene to 4 ratio of 12:1 resulted in the expected precipitates with no starting material, 4. To the precipitates were introduced additional amounts of pyridine, making a homogenous solution. The solution was stirred at 0 °C for 18 h. Indeed, as shown in Table I, ammonolysis of this solution in pyridine with gaseous ammonia at 0 °C resulted in quantitative formation of only one product corresponding to 2-(2-pyridyl)-1,3-propanediol monocarbamate (8) without formation of the dicarbamate (9) as expected. Therefore, a systematic mechanistic study including optimal preparation of 8 was performed under various reaction conditions (solvents, temperatures, molar ratios of reactants, and trapping agents). The results are summarized in Table I.

It has been previously reported that the reactions of pyridine with acyl chloride form salt complexes of *N*-acylpyridinium.[9] These salts can be isolated although they are highly reactive, being rapidly hydrolyzed even by atmospheric moisture.[10,11] Addition of 4 with TEA, trapping

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† This paper is dedicated to Professor Herbert C. Brown on the occasion of his 80th birthday.

(1) Porter, R. J. *Epilepsia* **1989**, *30* (1), 29.
(2) Swinyard, E. A.; Sofia, R. D.; Kupferberg, H. J. *Epilepsia* **1986**, *27* (1), 27.
(3) (a) Choi, Y. M. U.S. Patent No. 5,091,595, 1992. (b) Choi, Y. M. U.S. Patent No. 4,982,016, 1991. (c) Choi, Y. M.; Kucharczyk, N.; Sofia, R. D. *J. Labelled Compd. Radiopharm.* **1986**, *23*, 545.
(4) These are unpublished results.
(5) Ludwig, B. J.; Powell, L. S.; Berger, F. M. *J. Med. Chem.* **1969**, *12*, 462.
(6) Loev, B.; Kormendy, M. F. *J. Org. Chem.* **1963**, *28*, 3421.
(7) Berger, F. M.; Ludwig, B. J. U.S. Patent No. 3,054,022, 1963.
(8) March, J. *Advanced Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1977; p 361.
(9) Smith, D. M. *Comprehensive Organic Chemistry*; Pergamon Press: New York, 1979; Vol. 4, p 6.
(10) Cook, D. *Can. J. Chem.* **1962**, *40*, 2362.
(11) Adkins, H.; Thompson, Q. E. *J. Am. Chem. Soc.* **1949**, *71*, 2242.

0022-3263/92/1957-5764$03.00/0