sponding to Schiff base formation, followed by a much slower decay of this band concomitant with a new absorption maximum at 290 nm. This spectral change is identical with those observed in water[20] or methanol,[21] confirming that cyclization takes place. The reaction product was spectroscopically identical with an authentic sample of the tetrahydropyrido[3,4-*d*]imidazole (**3**).[22] It has been shown by Mackay and Shepherd that the cyclization product is an inhibitor of histidine decarboxylase.[17] In reversed micelles, the rate of cyclization was also appreciably affected by the water content (Figure 1). The apparent pseudo-first-order rate constant k_{obsd} consists of the formation constant for the Schiff base, K, and the specific rate constant for the cyclization, k_c (eq 1). The K value of Schiff base formation between pyridoxal and histidine cannot be determined accurately because of the subsequent rapid cyclization. However, since the K value for Schiff base formation is not appreciably affected by the structure of the amino acid in the reversed micelle,[8] the specific rate constant of the cyclization k_c could be evaluated by adopting the K value obtained for Schiff base formation between pyridoxal and alanine. As shown in Figure 2, the k_c value so obtained diminished with decrease in the R value. This means that the cyclization can be effectively retarded by a decrease in the pool size of the reversed micelle. In addition, the cyclization rate constant in the reversed micelle is much smaller than that observed in bulk water ($k_c = 2.8 \times 10^{-2}$ s^{-1}). This is attributable to the altered micropolarity and/or the restriction effect on the mobility of the substrate in the restricted reaction field provided by the micelle. As the core size expands, the micropolarity in the interior core approaches that of bulk water,[14] which should be unfavorable for Schiff base formation but not for cyclization.

$$k_{obsd} = k_c \frac{K[\text{histidine}]}{K[\text{histidine}] + 1} \quad (1)$$

Since the cyclization reaction is subject to base catalysis,[23] the effect of hydroxide ion concentration on the reaction rate was studied in the reversed micelles as well as in methanol. The variation of k_{obsd} as a function of hydroxide ion concentration was linear, and the specific second-order rate constants for the base catalysis are 154 and 0.023 M^{-1} s^{-1} in the 0.10 M AOT/0.77 M H_2O/heptane reversed micelle and in methanol, respectively. Thus the effect of hydroxide ion is accentuated above 6700 times in the micelle. The local high concentration of hydroxide ion in the micellar core is no doubt responsible in part for the large rate increase. However, even if this local concentration effect (72-fold) is taken into account, the hydroxide ion is still 93 times more effective as a catalyst in the micelle. The hydroxide ion in the anionic reversed micellar core is in part free from both the interaction with the head group of the anionic surfactant and from hydration due to a lack of sufficient water molecules, both effects leading to an increase in the activity of hydroxide ion.

Matsushima has reported that copper(II) or zinc(II) effectively inhibits the cyclization of the histidine–pyridoxal Schiff base.[24] Unlike these transition-metal ions,[24] magnesium(II) ion was a poor inhibitor of the cyclization in bulk water because of extensive hydration and/or its lesser ability to coordinate with a common ligand. In reversed micelles, however, even magnesium(II) ion was effective in suppressing the cyclization by chelation with the Schiff base. The addition of 1.0×10^{-4} M magnesium(II) ion (equimolar to pyridoxal) to the 0.10 M CTACl/0.17 M H_2O/1.5 mM NaOH/chloroform reversed micelle shifts the absorption maximum of the Schiff base from 419 to 380 nm because of complexation.[12] Under these conditions, the cyclization was inhibited by a factor of 2.4. The inhibitory effect is presumably due to the "naked" character of the metal ion in the reversed micelles.[3,5]

In summary, the bimolecular pyridoxal–histidine Schiff base formation was remarkably enhanced, while the subsquent unimolecular cyclization was effectively retarded, in reversed micelles with a decrease in the R value. This reaction control is attributed to "multiple field assistance",[11] where the microscopic polarity, the local concentration (proximity), and/or the mobility of substrates (microviscosity) are simultaneously altered. In addition, the respective effects of hydroxide or magnesium(II) ion in promoting or inhibiting cyclization of the Schiff base originates from the less hydrated character of these ions in the specific reaction field provided by reversed micelles.

Experimental Section

Materials. Pyridoxal hydrochloride was obtained from Wako Pure Chemicals Co., Ltd., Tokyo. 4-[3-Hydroxy-5-(hydroxymethyl)-2-methyl-4-pyridyl]-4,5,6,7-tetrahydropyrido[3,4-*d*]imidazole-6-carboxylic acid (**3**) was prepared according to the literature.[22] Purifications of AOT [sodium 1,2-bis[[(2-ethylhexyl)oxy]carbonyl]-1-ethanesulfonate][3] and CTACl (hexadecyltrimethylammonium chloride)[10] have been described.

Methods. Formation of the Schiff base from pyridoxal and amino acids was monitored spectrophotometrically on a Hitachi 124 or 200–10 spectrophotometer at 25.0 °C.[8] Rates of cyclization of the histidine Schiff base were determined by following the disappearance of the Schiff base absorption at 419 nm, and the apparent first-order constants were calculated by the Guggenheim method.[22]

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Registry No. 1, 66-72-8; 2, 85850-73-3; histidine, 71-00-1.

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(23) Bruice, T. C.; Lonbardo, A. *J. Am. Chem. Soc.* **1969**, *91*, 3009.
(24) Matsushima, Y. *Chem. Pharm. Bull.* **1968**, *16*, 2143.
(25) Guggenheim, E. A. *Phil. Mag.* **1926**, *2*, 538.

A Mild Two-Step Method for the Hydrolysis/Methanolysis of Secondary Amides and Lactams

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During the course of another investigation we required a mild method for the hydrolysis of lactams into their corresponding acyclic ω-amino acid derivatives. As will be detailed below, the method also proved to be equally effective for the hydrolysis of secondary amides. While many classical methods exist for the hydrolysis of primary and tertiary amides,[1,2] the efficient hydrolysis of secondary

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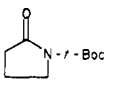
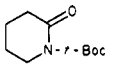
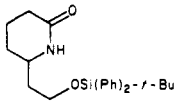
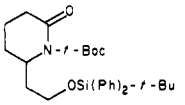
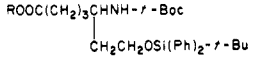
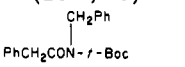
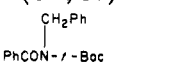
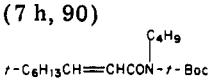
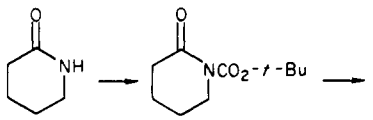
Table I

entry	substrate	N-t-Boc derivative (time, % yield)[a]	cleaved product	acid (R = H)[a,b] (time, % yield)	ester (R = Me)[a] (time, % yield)
1		 (6 h, 96)	$ROOC(CH_2)_3NH$-t-Boc	(20 min, 96)	(30 min, 96)
2		 (8 h, 84)	$ROOC(CH_2)_4NH$-t-Boc	(30 min, 90)	(15 min, 94)
3		 (15 h, 86)		(1 h, 85)	(30 min, 96)
4	$PhCH_2CONHCH_2Ph$	 (6 h, 87)	$PhCH_2COOR$	(1 h, 91)	(25 min, 96)
5	$PhCONHCH_2Ph$	 (7 h, 90)	PhCOOR	(6 h, 83)	(10 min, 94)
6	$t\text{-}C_6H_{13}CH{=}CHCONHC_4H_9$	 (72 h, 78)	$t\text{-}C_6H_{13}CH{=}CHCOOR$	(24 h, 80)	(2 h, 85)

[a] Yields reported are for chromatographically pure materials. [b] Yields refer to methyl esters derived from the corresponding acids by treatment with ethereal diazomethane.

amides has been more problematic and requires specialized conditions.[3-6]

We report herein that *N*-*t*-Boc derivatives of lactams and amides, prepared through the agency of di-*tert*-butyl dicarbonate,[7] suffer regioselective hydrolysis, employing lithium hydroxide or methanolysis under mild conditions, leading to the corresponding ω-amino acids or esters, respectively.[8] For example, δ-valerolactam (1) can be converted [$(t\text{-}BuO_2C)_2O$, Et_3N, DMAP, 25 °C, 8 h] in 84% yield into the *N*-*t*-Boc derivative **2**, which upon treatment with 3.0 equiv of lithium hydroxide in aqueous tetrahydrofuran at room temperature, provides in 90% yield carboxylic acid **3** (R = H). Use of 1.1 equiv of sodium



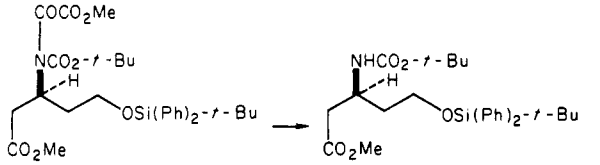
1 2

$ROOCCH_2CH_2CH_2CH_2NHCO_2$-t-Bu

3

methoxide in methanol at 0 °C afforded methyl ester **3** (R = Me) in 94% yield. Overall yields for this process are generally high (see Table I). Several points merit additional comment. The *N*-*t*-Boc derivatives were chosen over alternative acyl carbamates (e.g., *N*-Cbz function) in order to render the "amide" carbonyl more susceptible to nucleophilic attack than the "carbamate" carbonyl. Previous studies employing the *N*-Cbz protecting group have shown that both carbonyl sites undergo hydrolytic opening depending on the reaction conditions.[8a,b] It was our hope that the *tert*-butyl group would exert a steric influence on the course of the hydrolysis/methanolysis reactions, thus forcing "amide" hydrolysis to occur regioselectively.

Table I contains a representative sampling of lactams and amides that have been subjected to this method. Aliphatic as well as aromatic amides are efficiently hydrolyzed by this procedure (entries 4, 5). The highly functionalized methyl *N*-*tert*-butoxycarbonyl oxalamate derivative **4** provided a near-quantitative yield of ester **5**



4 5

upon exposure to sodium methoxide in methanol at 0 °C for 5 min. Unsaturation at the α-position is also unexceptional except for the fact that somewhat longer reaction times are required to introduce the *N*-*t*-Boc group (entry 6). The only limitations that we have encountered is the effect of substitution α to the amide nitrogen. In the lactam cases (entry 3) this substitution again poses no problem except that longer reaction times are required to introduce the *t*-Boc group. In the amide cases, however, α-substitution next to nitrogen (for example α-phenethylamides) greatly suppresses introduction of the *t*-Boc group.

In summary, this method for the hydrolysis/alcoholysis of secondary amides and lactams should find utility in those cases where a mild and efficient method is necessary. Furthermore, the method leaves the ω-amino function in

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a protected form, thus permitting further elaboration of the carboxylic acid residue.

Experimental Section

General Procedure for Formation of *N*-*t*-Boc Derivatives. To a 0.50 M solution of *N*-benzylbenzamide (2.0 g, 9.47 mmol) in methylene chloride were added triethylamine (1.32 mL, 9.47 mmol), di-*tert*-butyl dicarbonate (4.13 g, 18.94 mmol), and 4-(dimethylamino)pyridine (1.16 g, 9.47 mmol). The solution was stirred for 7 h at 25 °C under an argon atmosphere. The volatiles were removed, and the residue was purified by rapid chromatography on silica gel. Elution with hexane/ether (6:1) afforded 2.63 g (90%) of the desired *N*-*tert*-butoxycarbonyl-*N*-benzylbenzamide: IR ($CHCl_3$) 1725, 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.08 (s, 9 H), 4.96 (s, 2 H), 7.24–7.64 (m, 10 H).

General Procedure for Hydrolysis of *N*-*t*-Boc Derivatives. To a 0.20 M solution of *N*-*tert*-butoxycarbonyl-*N*-benzylbenzamide (1.09 g, 3.51 mmol) in tetrahydrofuran was added 10.54 mL (10.54 mmol) of a 1.0 N solution of lithium hydroxide. The solution was stirred for 6 h at 25 °C. After removal of tetrahydrofuran in vacuo, the basic aqueous residue was acidified by the addition of 10% acetic acid and extracted with ether. Drying ($MgSO_4$) and concentration afforded 883 mg of crude material. The acid was characterized by esterification: the crude acid was dissolved in 10.0 mL of ether and treated with excess ethereal diazomethane. After 10 min the excess diazomethane was quenched with glacial acetic acid, and the volatiles were removed in vacuo. Chromatography (silica gel, pentane/ether, 20:1) afforded 396 mg (83%) of methyl benzoate.

General Procedure for Methanolysis of *N*-*t*-Boc Derivatives. A solution of *N*-*tert*-butoxycarbonyl-*N*-benzylbenzamide (981 mg, 3.15 mmol) in 1.40 mL of methanol, under an argon atmosphere, was cooled to 0 °C. To this solution was added 1.75 mL (3.47 mmol) of a 2.0 M solution of sodium methoxide in methanol. After 10 min the solution was poured into brine and extracted with ether. After drying ($MgSO_4$) and concentration, the residue was chromatographed on silica gel. Elution with pentane/ether, 20:1, afforded 402 mg (94%) of methyl benzoate.

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Registry No. 1, 675-20-7; 2, 85908-96-9; 3 (R = H), 27219-07-4; 3 (R = Me), 85908-97-0; 4, 85908-98-1; 5, 85908-99-2; $PhCH_2CONHCH_2Ph$, 7500-45-0; $PhCONHCH_2Ph$, 1485-70-7; *t*-$C_6H_{13}CH{=}CHCONHC_4H_9$, 85909-00-8; $PhCH_2CON(CH_2Ph)$-*t*-Boc, 85909-01-9; $PhCON(CH_2Ph)$-*t*-Boc, 85909-02-0; *t*-$C_6H_{13}CH{=}CHCON(C_4N_9)$-*t*-Boc, 85909-03-1; $HOOC(CH_2)_3NH$-*t*-Boc, 57294-38-9; $MeOOC(CH_2)_3NH$-*t*-Boc, 85909-04-2; $HOOC(CH_2)_3CH[CH_2CH_2OSi(Ph)_2$-*t*-Bu$]NH$-*t*-Boc, 85909-05-3; $MeOOC(CH_2)_3CH[CH_2CH_2OSi(Ph)_2$-*t*-Bu$]NH$-*t*-Boc, 85909-06-4; $PhCH_2COOH$, 103-82-2; $PhCH_2COOMe$, 101-41-7; PhCOOH, 65-85-0; PhCOOMe, 93-58-3; *t*-$C_6H_{13}CH{=}CHCOOH$, 14812-03-4; *t*-$C_6H_{13}CH{=}CHCOOMe$, 14952-06-8; γ-butyrolactam, 616-45-5; 5-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-δ-valerolactam, 85909-07-5; *N*-(*tert*-butoxycarbonyl)-γ-butyrolactam, 85909-08-6; *N*-(*tert*-butoxycarbonyl)-5-[2-[(*tert*-butyldiphenylsilyl)oxy]-ethyl]-δ-valerolactam, 85909-09-7.

Synthesis of 3,6-Dimethylcholanthrene[1]

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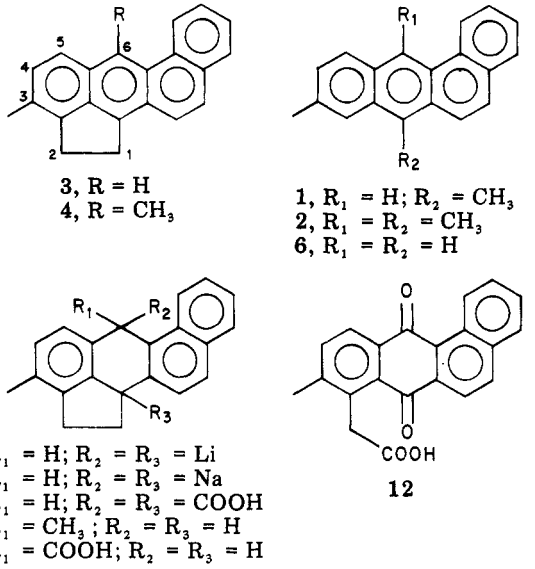
7-Methylbenz[*a*]anthracene (7-MBA, **1**; Chart I) is the most potent carcinogenic monomethylbenz[*a*]anthracene[3] and is undoubtedly a planar hydrocarbon.[4] The addition of a methyl group at position 12 to afford 7,12-dimethylbenz[*a*]anthracene (7,12-DMBA, **2**) not only increases the carcinogenic potency[5] but renders the molecule nonplanar[6] because of the steric effect of the 12-methyl group. We were interested to see whether the introduction of a methyl group at position 6 of 3-methylcholanthrene (3-MC, **3**) would increase the carcinogenic activity of 3-MC and cause 3,6-dimethylcholanthrene (3,6-DMC, **4**) to be nonplanar.[7]

Chart I



Alkali metals are known[8,9] to add across the meso positions in anthracene[10] (**5**), benz[*a*]anthracene[8] (BA, **6**), and 3-MC,[8] giving rise to intensely colored anionic intermediates. Alcoholysis of these intermediates was shown[8] to be an excellent route to the corresponding dihydrohydrocarbons. But the scope of alkylation (reductive alkylation) has been limited by low yields, complexity of products, and over alkylation.[11]

Subtle differences in color and reactivity were noticed between the disodio and the dilithio derivatives.[12] Thus

(1) Research supported by Grant CA07934 from the National Cancer Institute.

(2) Postdoctoral Research Associate.

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(6) For the latest X-ray structure and discussion of DMBA, see D. W. Jones and J. M. Sowden, *Cancer Biochem. Biophys.*, 281 (1976).

(7) Recent preliminary reports by Drs. J. A. and E. C. Miller, McArdle Laboratory for Cancer Research, Dr. W. Levin et al., Hoffmann-La Roche, M. S. Newman, Ohio State University, and D. Jerina et al., National Institute of Arthritis, NIH, indicate that **4** is considerably more tumorigenic than 3-MC.

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(10) (a) W. Schlenk, J. Appenrodt, A. Michael, and A. Thal, *Ber. Ntsch. Chem. Ges.* 47, 473 (1914); (b) O. Blum and K. Ehninger, *Justus Liebigs. Ann. Chem. 463*, 134 (1928).

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