IR (KBr) 1200 (S=O?), 1730 (CO_2H), and 3450 (br, NH, OH) cm^{-1}; Anal. Calcd for $C_{18}H_{22}NO_3ClS$: C, 58.77; H, 6.03; N, 3.81. Found: C, 59.28; H, 6.08; N, 3.73.

The same procedure applied to L-4 gave a 56% yield of (2*R*,4*R*)-2-benzyl-3-((2-phenylethyl)sulfonimidoyl)propionic acid (L-6) as the hydrochloride: mp 148.5–150.5 °C; $[\alpha]_D = +4°$ (*c* = 7.5, MeOH); 400-MHz ^1H NMR (CD_3OD) δ 7.3 (m, 10 H), 4.1 (dd, *J* = 10.1, 15.2 Hz, 1 H), 4.05 (m, 2 H), 3.75 (dd, *J* = 2.5, 15.2 Hz, 1 H), 3.4 (m, 1 H), 3.3 (m, 1 H), 3.08 (m, 3 H); 100-MHz ^{13}C NMR (CD_3OD) δ 29.77, 40.04, 47.03, 56.55, 56.97, 127.54, 127.75, 129.54, 129.59, 129.72, 130.36, 139.42, 140.38, and 180.39; IR (KBr) 1200 (S=O?), 1730 (CO_2H), and 3450 (br, NH, OH) cm^{-1}. Anal. Calcd for $C_{18}H_{22}NO_3ClS$: C, 58.77; H, 6.03; N, 3.81. Found: C, 59.10; H, 6.05; N, 3.75.

Similarly obtained were D-5 (mp 145.5–147.5 °C) and D-6 (mp 147–148 °C). Spontaneous recyclization to **3** and **4** occurs in weakly acidic solution (pH ~3).[4] An analytical separation of **5** and **6** by HPLC could not be obtained.

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Supplementary Material Available: X-ray crystallographic data for compounds **3** and **4** (14 pages). Ordering information is given on any current masthead page.

Vilsmeier–Haack Reaction with Glutarimides. Synthesis of 2,6-Dichloro-1,4-dihydropyridine-3,5-dicarboxaldehydes[1]

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4-Aryl-1,4-dihydropyridines are an important class of drugs which are used in the treatment of various cardiovascular disease states.[3-5] It is surprising that for a group of compounds which has been so intensively studied, relatively few useful syntheses thereof are known,[6,7] especially for those which bear substituents other than hydrogen atoms or methyl groups at C-2 and C-6. This publication shows that 4-arylglutarimides, upon reaction with the Vismeier–Haack reagent, are converted into 1,4-dihydro-2,6-dichloro-4-arylpyridine-3,5-dicarboxaldehydes, which may show promise as precursors of still other novel dihydropyridine derivatives.

Kvitko and Panfilova have reported[8] that N-substituted succinimides were converted into 2,5-dichloropyrrole-3,4-dicarboxaldehyde derivatives upon reaction with an excess of the Vilsmeier–Haack reagent. If an analogous reaction were to occur with 4-arylglutarimides, the corresponding 1,4-dihydro-2,6-dichloro-4-arylpyridine-3,5-dicarboxaldehydes would be the expected products. Indeed, Weissenfels and Kubisch[9] have shown that *N*-arylglutarimides, and even glutarimide itself, are converted into the expected dihydropyridine derivatives in the presence of an excess of the Vilsmeier–Haack reagent at 100 °C. Furthermore, Aubert et al.[10] have recently shown that 1-substituted 7-chloro-2,3,4,5-tetrahydroazepin-2-ones are converted into 2,7-dichloro-4,5-dihydroazepine-3,6-dicarboxaldehydes under similar conditions.

Table I. Synthesis of Some Pyridine and Dihydropyridine Derivatives

R	% yield 3	4[a]	5
C_6H_5	72	87	
3-ClC_6H_4	80	98	
3-$NO_2C_6H_4$	61	87	
3-$CF_3C_6H_4$	75	88	94
H	65	56[b]	91

[a] Yield based on **3** unless otherwise specified. [b] Yield based on **1e**.

A study of the reaction of 4-phenylglutarimide (**1a**, Scheme I) with the Vilsmeier–Haack reagent ($POCl_3$–DMF)[11] showed that this imide was consumed under conditions which were much milder than those reported by Weissenfels and Kubisch.[9] For example, after 15 h at room temperature, in the presence of 4 molar equiv of the reagent and subsequent hydrolysis of the reaction mixture with excess aqueous sodium acetate, an orange-colored solid was obtained in over 70% yield. This substance, analyzed for $C_{15}H_{14}Cl_2N_2O$, had no NH stretching absorptions in the infrared spectrum, and the NMR spectrum (90 MHz) showed five singlet absorptions at δ 3.20 (6 H), 5.40 (1 H), 7.28 (5 H), 7.89 (1 H), and 9.95 (1 H). These properties are not consistent with those anticipated for **4a**, but they are compatible with the 3-((dimethylamino)-methylene)-3,4-dihydropyridine structure **3a**, provided that rapid rotation is assumed about the formal $CHNMe_2$ single bond on the NMR time scale (see below). This is a reasonable assumption, in view of the observation by Katritzky et al.,[12] that the dimethylamino moiety of 2,4-dichloro-3-((dimethylamino)methylene)-1,4-cyclohexadiene-1,5-dicarboxaldehyde has a coalescence temperature of −25 °C. Compound **3a** was very sensitive to acidic hydrolysis being rapidly converted into the desired dicarboxaldehyde **4a** with 1 equiv of 0.5 N HCl in THF solution at room temperature.

Under conditions identical to those described above, the meta-substituted 4-arylglutarimides **1b–d** were also converted into the 3,4-dihydro- and the 1,4-dihydropyridine derivatives **3b–d** and **4b–d**, respectively (Table I). In addition, the (*m*-(trifluoromethyl)phenyl-1,4-dihydropyridine derivative **4d** was oxidized to 2,6-dichloro-4-(3-(trifluoromethyl)phenyl)pyridine-3,5-dicarboxaldehyde (**5d**) in over 90% yield, with ceric ammonium nitrate in aqueous acetone.[13]

At this stage it was of interest to reexamine the reaction of glutarimide itself with the Vilsmeier–Haack reagent in the light of the above observations. Repetition of the

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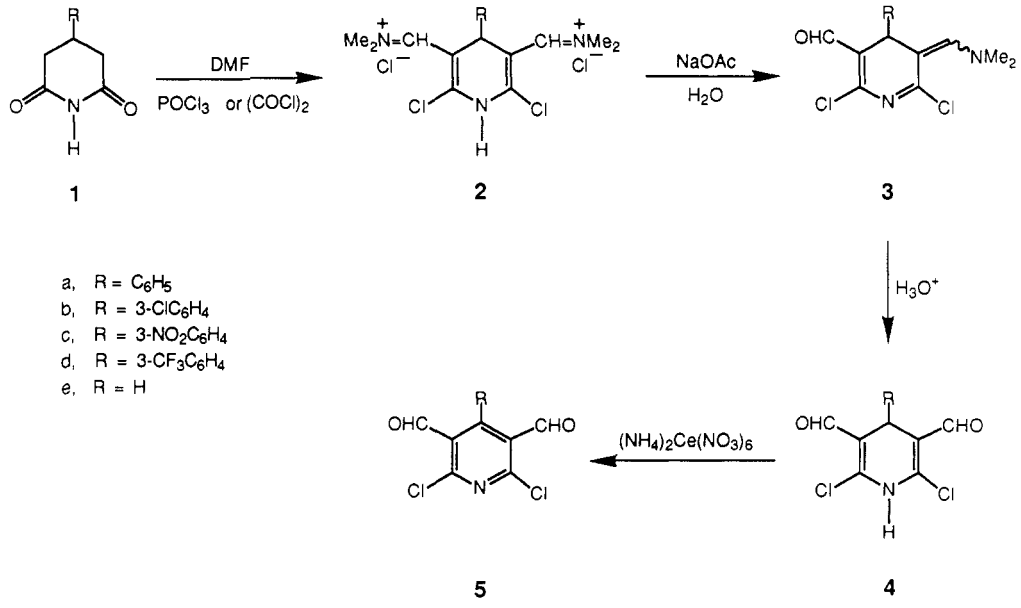
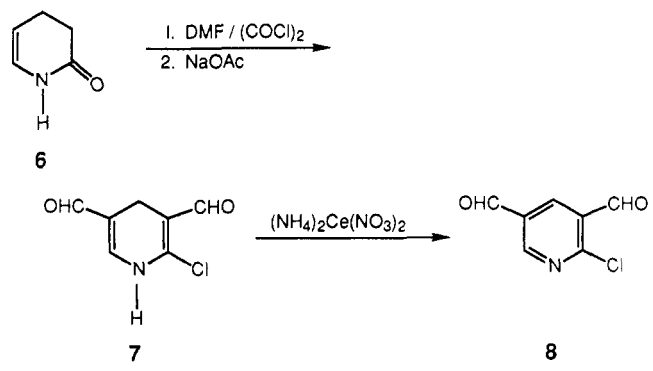
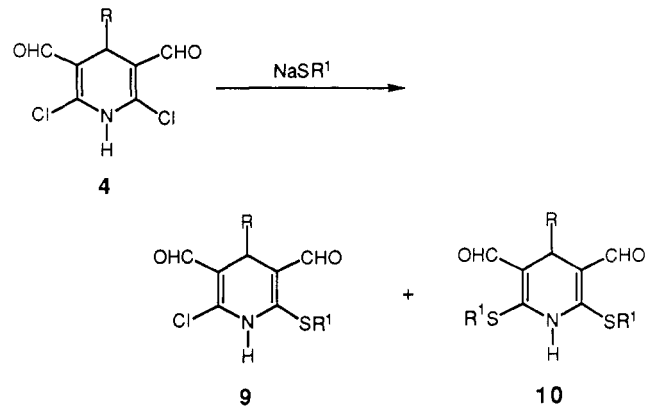
Scheme I



Scheme II



Scheme III



reaction with **1e** under the reported conditions (100 °C, excess (6 equiv) $POCl_3$/DMF in $POCl_3$ as solvent; sodium carbonate hydrolysis)[9] did indeed give the 1,4-dihydropyridine derivative **4e**, but only in about 30% yield. Utilization of the conditions described above for 4-arylglutarimides, followed by prolonged (48 h) hydrolysis of the reaction mixture with excess sodium acetate, gave 2,6-dichloropyridine-3,5-dicarboxaldehyde (**5e**) in 24% yield. If, however, the reaction was conducted with the Vilsmeier–Haack reagent prepared from oxalyl chloride and DMF (i.e. $[Me_2NCHCl]^+Cl^-$) and the reaction mixture was subjected to brief hydrolysis with sodium acetate, not only was the formation of the aerial oxidation product **5e** avoided, but the intermediate, somewhat unstable 3,4-dihydropyridine derivative **3e** could easily be isolated. As expected (see below), the singlet NMR (CD_2Cl_2) absorption for the NMe_2 group at δ 3.28 did split into a doublet on cooling (T_c = 258 ± 2 K; $\Delta G^{\ddagger}$ = 12.3 ± 0.5 kcal/mol). Acidic hydrolysis of **3e**, in the usual way, gave 2,6-dichloro-1,4-dihydropyridine-3,5-dicarboxaldehyde (**4e**) in greater than 50% overall yield. Application of this process to 3,4-dihydro-2-pyridone (**6**, Scheme II) provided 2-chloro-1,4-dihydropyridine-3,5-dicarboxaldehyde (**7**) in 75% yield. In this case, the intermediate 3,4-dihydropyridine, though easily detectable because of its intense color, was much more susceptible to hydrolysis and acid treatment thereof was unnecessary. Both **4e** and **7** were effeciently oxidized to the corresponding pyridine derivatives **5e** and **8** with ceric ammonium nitrate.

The chlorine atoms in **4e** and related compounds are known to be readily displaced by amine derivatives.[11,14,15] It was therefore of interest to determine the susceptibility of the 4-aryl-1,4-dihydropyridine derivatives **4** to displacement of the chloro groups with more powerful nucleophiles. Reaction of the trifluoromethyl derivative **4d** with excess sodium ethoxide in THF or acetonitrile resulted in the immediate formation of the deeply colored sodium salt which remained unchanged even after prolonged periods at reflux temperature. The dihydropyridine could be recovered quantitatively upon quenching with dilute aqueous hydrochloric acid. Reaction of either **4b** or **4d** with an excess (3–5 equiv) of the sodium salt of ethylmercaptan in THF at room temperature gave the monodisplaced products **9b** (R^1 = Et) and **9d** (R^1 = Et, Scheme III). The second chlorine atom could not be displaced even when the monoethylthio derivatives themselves were subjected to the displacement conditions. In contrast, the bisphenylthio compound **10d** (R = SC_6H_5) was readily formed from **4d** and a slight excess (10%) of sodium thiophenolate. The divergent behavior of these nucleophiles is undoubtedly a reflection of the greatly different basicity of ethoxide ($pK_a \approx 16$), ethyl mercaptide (pK_a = 10–11) and thiophenolate (pK_a = 6–8).[16]

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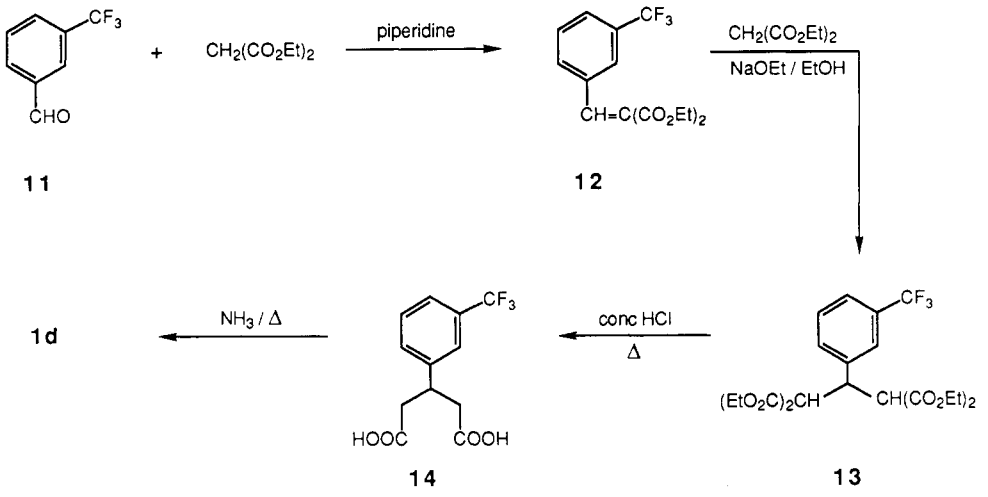
Scheme IV



Syntheses of all of the 4-arylglutarimides used in this study, except **1d**, have been reported. Compound **1d** was prepared by the reaction sequence shown in Scheme IV and described in detail in the Experimental Section. This process is a hybrid of published methodology[17-19] and is generally applicable.

The information disclosed herein may have a number of important consequences especially with regard to the synthesis of novel dihydropyridine derivatives with potential activity as calcium entry blockers.[20]

Experimental Section

The melting points were determined in a Mel-Temp melting point apparatus and are not corrected. The IR spectra were measured in choroform solution, unless stated otherwise, with a Perkin-Elmer Model 1420 infrared spectrophotometer. The ^{1}H NMR spectra were obtained in deuteriochloroform, unless specified otherwise, with a Varian EM-390, a Bruker WM-300, or a Bruker AM-500 NMR spectrometer and are expressed as parts per million (δ) from internal tetramethylsilane. When exchangeable protons were present, the data are given for deuterium oxide exchanged spectra. The UV spectra were measured with a Perkin-Elmer Model 402 spectrophotometer in methanol solution. The high-resolution mass spectrum was obtained with a Finnigan MAT 311A mass spectrometer.

Unless indicated otherwise, all new compounds had elemental analyses within ±0.3 for C and H and ±0.4 for N.

Glutarimide was obtained from the Aldrich Chemical Co. 4-Phenylglutarimide (**1a**),[17] 4-(3-chlorophenyl)glutarimide (**1b**),[18] and 4-(3-nitrophenyl)glutarimide (**1c**)[19] can be prepared as described in the references cited or by the method described below for (**1d**). 3,4-Dihydro-2-pyridone (**6**) was synthesized by the method of Speckamp et al.[22]

The terms "worked up in the usual manner" or "the usual workup" signify that the extract was dried over sodium sulfate and evaporated in vacuo.

4-(3-(Trifluoromethyl)phenyl)glutarimide (1d). A. Diethyl 3-(3-(Trifluoromethyl)benzylidene)malonate (12). A solution of 3-(trifluoromethyl)benzaldehyde (12.0 g, 68.9 mmol) and diethyl malonate (13.5 g, 83 mmol) in benzene (100 mL) containing piperidine(0.5 mL) was heated at reflux temperature for 20 h. The solution was cooled to room temperature, diluted with benzene (100 mL), and washed successively with water, 1 N HCl, and saturated aqueous sodium bicarbonate solution. After the usual workup the crude product was subjected to column chromatographic purification on silica gel (400 g) using hexane–ethyl acetate (95:5) as the eluting solvent. The product (21.3 g, 98%) was obtained as an oil: IR 1728, 1639 cm^{-1}; ^{1}H NMR δ 1.29 (t, 3 H, J = 7.2 Hz), 1.35 (t, 3 H, J = 7.2 Hz), 4.33 (q, 4 H, J = 7.2 Hz), 7.56–7.77 (m, 5 H).

B. Diethyl 2,4-Bis(ethoxycarbonyl)-3-(3-(trifluoromethyl)phenyl)glutarate (13). Diethyl malonate (12.4 mL, 13.1 g, 82 mmol) was added to a solution of sodium ethoxide [prepared from sodium (1.7 g, 75 mmol)] in absolute ethanol (50 mL), and 0.25 h thereafter the diester **12** (20.0 g, 63 mmol) was added with stirring. After 3 h at room temperature, acetic acid (15 mL) was added, and the solution was partitioned between water and dichloromethane. After the usual workup the crude product was purified by column chromatography on silica gel (500 g) using hexane–ethyl acetate (9:1). The product (24.7 g, 82%) was obtained as an oil: IR 1749, 1731 cm^{-1}, ^{1}H NMR δ 0.90–1.26 (m, 12 H), 3.78–4.27 (m, 11 H), 7.33–7.65 (m, 4 H).

C. 3-(3-(Trifluoromethyl)phenyl)glutaric Acid (14). A mixture of the tetraester **13** (20.0 g, 42 mmol) and concentrated hydrochloric acid (100 mL) was heated at reflux temperature for 20 h. The solution was cooled to room temperature, and the product which crystallized was collected by filtration, washed with cold water, and dried in vacuo. The dicarboxylic acid (9.0 g, 78%) had mp 129–131 °C after crystallization from methanol: IR (KBr), 3250, 1705, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 2.69 (d, 2 H, J = 7.2 Hz), 2.73 (d, 2 H, J = 7.2 Hz), 3.69 (quin, 1 H, J = 7.2 Hz), 7.46 (m, 4 H).

The glutaric acid derivative **14** (8.0 g, 28 mmol) was heated to its melting point in an oil bath, and then gaseous ammonia was passed through the melt for 0.5 h. The deep brown colored paste was cooled to room temperature, and the solid that formed was taken up in dichloromethane and applied to a column of silica gel (150 g). Elution with hexane–ethyl acetate (7:3) gave 4-(3-(trifluoromethyl)phenyl)glutarimide (**1d**, 4.6 g, 63%), which, after crystallization from methanol, had mp 163–164 °C: IR (KBr) 3182, 1731, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 2.41–2.90 (m, 4 H), 3.33–3.68 (m, 1 H), 7.53 (m, 4 H), 8.93 (br s, 1 H).

General Procedure for the Synthesis of the 2,6-Dichoro-3,4-((dimethylamino)methylene)-4-aryl-3,4-dihydropyridine-5-carboxaldehydes 3. Phosphorus oxychloride (1.5 mL, 2.39 g, 15.6 mmol) was cautiously added with stirring to anhydrous DMF (1.2 mL, 1.36 g, 15.6 mmol) maintained in a nitrogen atmosphere at 0 °C. The reaction mixture was then stirred at room temperature for 3 h, after which time a solution of the 3-arylglutarimide (3.9 mmol) in anhydrous 1,2-dichloro-

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(20) The 4-aryl compounds **3a–d**, **4a–d**, **9b** (R^1 = Et), **9d** (R^1 = Et), and **10d** (R^1 = Ph) were assayed for binding to a rat cerebral cortex membrane preparation by a published[21] procedure. The bis(phenylthio) compound **10d** (R^1 = Ph) showed modest affinity (pK_i = 6.9) for this membrane preparation; all of the other compounds had a much lower (pK_i ⟨5) level of affinity. Under the conditions of the assay, nitrendipine is bound strongly (pK_i = 9.5) to the membrane preparation.
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Table II. Physical Constants of Some Pyridine and Dihydropyridine Derivatives

compd	mp, °C (solvent)	IR, cm^{-1}	UV, nm (ϵ)	NMR (δ)
3a	166 (hex-CH_2Cl_2)	2835, 1645, 1619	275, 322.5, 462 (23 900, 4090, 12 400)	3.20 (s, 6 H), 5.40 (s, 1 H), 7.28 (s, 5 H), 7.89 (s, 1 H), 9.95 (s, 1 H)
3b	143–144 (hex-CH_2Cl_2)	2827, 1645, 1619	275.5, 321, 460 (27 000, 4620, 13 600)	3.26 (s, 6 H), 5.40 (s, 1 H), 7.18 (m, 4 H), 7.89 (s, 1 H), 9.95 (s, 1 H)
3c	152–153 (hex-CH_2Cl_2)[a]	2825, 1672, 1644, 1615, 1580, 1530, 1348	278, 314, 322, 459 (24 400, 4200, 3500, 8600)	3.27 (s, 6 H), 5.53 (s, 1 H), 7.39–7.71 (m, 2 H), 7.98–8.13 (m, 3 H), 9.93 (s, 1 H)
3d	156 (hex-CH_2Cl_2)	2805, 1646, 1619	275, 311, 320, 460 (24 600, 4000, 4270, 13 600)	3.23 (s, 6 H), 5.49 (s, 1 H), 7.40–7.52 (m, 4 H), 7.90 (s, 1 H), 9.90 (s, 1 H)
3e	152 (acet)	2771, 1635, 1631	215, 279, 494 (20 400, 63 100, 22 900)	3.28 (s, 6 H), 3.70 (s, 2 H), 7.52 (s, 1 H), 9.87 (s, 1 H)
4a	215 (MeOH-EtOAc)	3190, 2709, 1661, 1622, 1594[b]	252, 368, 450 (20 000, 4070, 4270)	5.10 (s, 1 H), 7.57 (m, 5 H), 9.89 (s, 2 H)[c]
4b	220 (acet-hex)	3192, 2700, 1656, 1620[b]	267, 303, 449.5 (29 300, 3920, 12 700)	5.03 (s, 1 H), 7.16 (m, 4 H), 4.34 (s, 2 H)[c]
4c	232 (acet-hex)	3180, 2705, 1652, 1620, 1532, 1350[b]	266.5, 301.5, 450.5 (3200, 34 100, 12 600)	5.18 (s, 1 H), 7.40–7.74 (m, 2 H), 7.97–8.09 (m, 2 H), 9.85 (s, 2 H)
4d	218 (acet-hex)	3113, 2714, 1658, 1622[b]	266, 375, 448 (17 400, 2240, 6020)	5.02 (s, 1 H), 7.49 (m, 4 H), 9.74 (s, 2 H)[d]
4e	178 (acet)[e]	3434, 2822, 1705, 1667, 1628[b]	269.5, 475 (24 500, 8780)	2.95 (s, 2 H), 9.77 (s, 2 H)
5d	115 (hex-CH_2Cl_2)	1699, 1655	208, 275 (25 100, 4680)	7.38 (d, 1 H, J = 8.75 Hz), 7.44 (s, 1 H), 7.63 (t, 1 H), 7.78 (d, 1 H, J = 7.83 Hz), 10.06 (s, 2 H)
5e	159–160 (hex-CH_2Cl_2)[f]	2725, 1687, 1680, 1582	219.5, 272, 296 (9490, 4080, 610)	8.72 (s, 1 H), 10.46 (s, 1 H)

[a] Exact mass (high-resolution mass spectrum) calcd for $C_{15}H_{13}Cl_2N_3O_3$ 353.0334, found 353.0340. [b] Dispersion in KBr. [c] Measured in $CDCl_3$ + DMSO-d_6. [d] Measured in DMSO-d_6. [e] Lit.[9] mp 166–168 °C. [f] Lit.[9] mp 151 °C.

ethane (15–20 mL) was added. Stirring at room temperature was continued for 15 h, and then a solution of sodium acetate (11.8 g, 145 mmol) in water (20 mL) was added cautiously. The mixture thus obtained was stirred at room temperature for an additional 0.5–2 h, and the product was extracted into dichloromethane. After the usual workup, the crude solid product was purified by column chromatography on silica gel (50 g) using hexane–ethyl acetate (1:1 for **3a** and **3b** and 3:2 for **3c** and **3d**) as the eluant. The product yields are given in Table I and the melting points, recrystallization solvents, and spectroscopic properties are found in Table II.

2,6-Dichloro-3-((dimethylamino)methylene)-3,4-dihydropyridine-5-carboxaldehyde (3e). A solution of anhydrous DMF (5.5 mL, 5.1 g, 70 mmol) in dry 1,2-dichloroethane (25 mL) was added dropwise to a stirred solution of oxalyl chloride (6.2 mL, 8.9 g, 70 mmol) in dry 1,2-dichloroethane (25 mL) maintained in a nitrogen atmosphere at 0 °C. The cooling bath was removed and after 3 h at room temperature, a solution of glutarimide (2.0 g, 17 mmol) in the above solvent (20 mL) was added to the stirred mixture. After 15 h at room temperature, a solution of sodium acetate (23 g) in water (50 mL) was added carefully with stirring. After 0.5 h, the mixture was partitioned between water and dichloromethane, and the organic phase was worked up as usual to give a deep red solid (2.6 g, 65%) which, on crystallization from acetone, had mp 152 °C dec. See Table II for spectroscopic data.

General Procedure for the Synthesis of the 2,6-Dichloro-1,4-dihydropyridine-3,5-dicarboxaldehydes (4). A 0.5 N hydrochloric acid solution (1 equiv) was added dropwise to a stirred solution of the (dimethylamino)methylene compound **3** (1 equiv) in THF (10–20 mL/mmol) or in 1:1 THF–acetone (for **3e**) at room temperature. The color of the solution changed from deep red to yellow. Stirring was continued for 0.25–0.5 h, and then the organic solvent was removed in vacuo. The mixture thus obtained was filtered; the solid product was washed with cold water, dried in vacuo, and then crystallized from acetone or acetone–hexane. The product thus obtained (yields are given in Table I) was then recrystallized from the appropriate solvent system for analysis. See Table II for melting points, recrystallization solvents, and spectroscoic data.

Synthesis of 2-Chloro-1,4-dihydropyridine-3,5-dicarboxaldehyde (7). The reaction between 3,4-dihydro-2-pyridone (**6**, 1 equiv) and the Vilsmeier–Haack reagent (4 equiv) was carried out exactly as described for the synthesis of **3e** except that the hydrolysis with sodium acetate (40 equiv) was conducted for 2 h. At this stage the 1,2-dichloroethane was removed in vacuo and the mixture was poured into an ice–water mixture. The crystalline product (75% yield) was collected by filtration, washed with cold water, and dried in vacuo. On recrystallization from DMSO compound **7** had mp 210–212 °C; IR (KBr) 3200, 3135, 2743, 1652, 1633, 1600 cm^{-1}; ^1H NMR (DMSO-d_6 + CF_3CO_2D) δ 3.02 (s, 2 H), 7.17 (s, 1 H), 9.35 (s, 1 H), 9.84 (s, 1 H).

Ceric Ammonium Nitrate Oxidation of 1,4-Dihydropyridine Derivatives. A solution of ceric ammonium nitrate (2 mmol) in water (5 mL) was added dropwise to a stirred solution of the 1,4-dihydropyridine derivative (1 mmol) in acetone (10 mL). Stirring was continued for 0.25–0.5 h, and then the reaction mixture was partitioned between ethyl acetate and water. After the usual workup the crude product was purified by column chromatography on silica gel (20 g) using the solvent system indicated below to elute the product.

2,6-Dichloro-4-(3-(trifluoromethyl)phenyl)pyridine-3,5-dicarboxaldehyde (5d): eluent, hexane–ethyl acetate (4:1); 94% yield; mp 115 °C (hexane–dichloromethane); IR 1699, 1655 cm^{-1}; UV 208, 275 nm (ϵ 25 100, 4680); ^1H NMR (500) δ 7.38 (d, 1 H, J = 8.75 Hz), 7.44 (s, 1 H), 7.63 (t, 1 H), 7.78 (d, 1 H, J = 7.83 Hz) 10.06 (s, 2 H).

2,6-Dichloropyridine-3,5-dicarboxaldehyde (5e): eluant, hexane–ethyl acetate (4:1); 91% yield; mp 159–160 °C (hexane–dichloromethane, lit.[9] mp 151 °C); IR 2725, 1687, 1680, 1582 cm^{-1}; UV 219.5, 272, 296 nm (ϵ 9490, 4080, 610); ^1H NMR δ 8.72 (s, 1 H), 10.46 (s, 1 H).

2-Chloropyridine-3,5-dicarboxaldehyde (8): eluant, hexane–ethyl acetate (9:1); 80% yield; mp 70–71 °C (hexane–dichloromethane); IR 2865, 1710, 1685, 1591 cm^{-1}; ^1H NMR δ 8.68 (d, 1 H, J = 2.3 Hz), 9.10 (d, 1 H, J = 2.3 Hz), 10.20 (s, 1 H), 10.52 (s, 1 H).

Reaction of 4-Aryl-1,4-dihydropyridine Derivatives with Sodium Ethane Thiolate. Ethanethiol (0.5 mL, 0.36 g, 6 mmol) was added to a stirred suspension of sodium hydride (0.144 g, 3 mmol, 50% in mineral oil) in anhydrous THF (5 mL) maintained in an atmosphere of dry nitrogen. After 10 min, a solution of the dihydropyridine derivative (1 mmol) in the same solvent (5 mL) was added, and the solution was stirred at room temperature for 5 h. The solution was then partitioned between saturated aqueous ammonium chloride and ethyl acetate. After the usual workup, the crude product was purified by column chromatography on silica gel (20 g) using the solvent system specified below to elute the pure monoethylthio compound.

2-(Ethylthio)-6-chloro-4-(3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxaldehyde (9b, R^1 = Et): eluant, hexane–ethyl acetate (1:1); 73% yield; solid foam; IR 3188, 2705, 1660, 1608 cm^{-1}; UV 249, 270, 303, 358, 452 nm (ϵ 11 200, 10 700, 9120, 4720, 2400); ^1H NMR δ 1.33 (t, 3 H, J = 7.5 Hz), 2.73–3.13 (m, 2 H), 5.22 (s, 1 H), 7.21 (m, 4 H), 9.93 (s, 1 H), 10.19 (s, 1 H). Anal.

Calcd for $C_{15}H_{13}Cl_2NO_2S$: C, 52.64; H, 3.82; N, 4.09. Found: C, 52.38; H, 3.34; N, 3.88.

2-(Ethylthio)-6-chloro-4-(3-(trifluoromethyl)phenyl)-1,4-dihydropyridine-3,5-dicarboxaldehyde (9d, R^1 = Et): eluant, hexane–ethyl acetate (7:3); 77% yield; solid foam; IR (KBr) 3200, 2705, 1657, 1612 cm^{-1}; UV 248, 269, 360, 450 nm (ϵ 14 100, 12 300, 5880, 3470); ^1H NMR (300) δ 1.31 (t, 3 H, J = 7.4 Hz), 2.83–2.98 (m, 2 H), 7.36–7.54 (m, 4 H), 9.85 (s, 1 H), 10.10 (s, 1 H). Anal. Calcd for $C_{16}H_{13}ClF_3NO_2S$: C, 51.13; H, 3.48; N, 3.72. Found: C, 51.19; H, 3.83; N, 3.72.

2,6-Bis(phenylthio)-4-(3-(trifluoromethyl)phenyl)-1,4-dihydropyridine-3,5-dicarboxaldehyde (10d, R^1 = Ph). Thiophenol (0.25 mL, 0.24 g, 2.2 mmol) dissolved in dry THF (5 mL) was added dropwise to a stirred suspension of sodium hydride (0.210 g, 2.2 mmol; 50% in mineral oil) in the same solvent (5 mL) maintained in a dry nitrogen atmosphere. After 10 min, a solution of **4d** (0.350 g, 1 mmol) in THF (5 mL) was added, and the solution was stirred for 3 h. The reaction mixture was worked up as described above for the mono(ethylthio)compounds. The crude product was purified by column chromatography on silica gel (20 g) using hexane–ethyl acetate (3:1) as the eluant. The bis(phenylthio) compound was obtained as a yellow solid (0.348 g, 75% yield) which, after crystallization from dichloromethane–hexane, had mp 144–145 °C: IR 3441, 1651, 1633, 1597 cm^{-1}; ^1H NMR (300) δ 5.34 (s, 1 H), 7.18–7.56 (m, 14 H), 10.08 (s, 2 H). Anal. Calcd for $C_{26}H_{18}F_3O_2S_2$: C, 62.76; H, 3.64; N, 2.81. Found: C, 62.56; H, 4.01: N, 2.52.

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Registry No. **1a**, 14149-31-6; **1b**, 113675-65-3; **1c**, 5893-43-6; **1d**, 129215-95-8; **1e**, 1121-89-7; **3a**, 129215-96-9; **3b**, 129215-97-0; **3c**, 129215-98-1; **3d**, 129215-99-2; **3e**, 129216-00-8; **4a**, 129216-01-9; **4b**, 129216-02-0; **4c**, 129216-03-1; **4d**, 129216-04-2; **4e**, 81305-72-8; **5d**, 129216-05-3; **5e**, 81319-42-8; **6**, 57147-25-8; **7**, 129216-06-4; **8**, 129216-07-5; **9b** (R^1 = Et), 129216-08-6; **9d** (R^1 = Et), 129216-09-7; **10d** (R^1 = Ph), 129216-10-0; **11**, 454-89-7; **12**, 93098-26-1; **13**, 129216-11-1; **14**, 129216-12-2; $CH_2(CO_2Et)_2$, 105-53-3; ethanethiol, 75-08-1; thiophenol, 108-98-5.

Studies on Thermodynamics for Hydrolysis. 3. Isokinetic Temperature Related to Molecular Location of Reactants in Coaggregates

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The isokinetic (enthalpy–entropy) relationship defined by the linear equation for organic reactions has been discussed in detail by Leffler.[1] About 100 organic reactions have been classified on the basis of the correlation between the isokinetic temperature (β) and the average value of the experimental temperature ($\bar{T}$).

We have attempted to clarify the interrelation between the β value and the reaction field for the hydrolytic cleavages of *p*-nitrophenyl esters. In the course of our study on isokinetic discrimination in relation to the β value the following interesting results were obtained: (a) In the hydrolysis of various phenyl esters catalyzed by L-histidine derivatives and hydroxamic acids, the correlation between β and $\bar{T}$ could be grouped into $\beta > \bar{T}$ for the micellar system, $\beta < \bar{T}$ for the vesicular system, and $\beta \gg \bar{T}$ for the macromolecular system.[2,3] (b) The enantioselective hydrolysis of the long-chain substrate was governed by the entropy of activation, and this was different from the enthalpy-driven hydrolysis of the short-chain substrates.[4] (c) The entropy-driven vesicular systems were changed to be enthalpy driven by the addition of cholesterol[5,6] or micellar surfactants.[6,7]

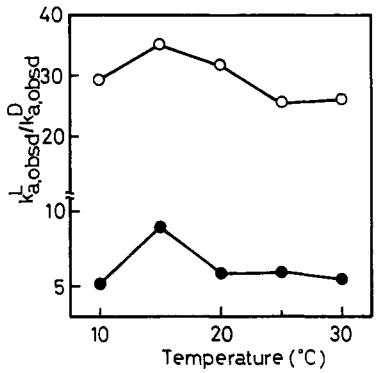

Figure 1. Temperature dependence of enantioselectivity for the hydrolysis of D(L)-S_{12} catalyzed by Z-PheHisLeu (○) and MyrHisLeu (●) in the coaggregate composed of 59 mol % $2C_{14}Br$/41 mol % CTAB at pH 7.6 (0.2 M Tris-KCl buffer) in 3% (v/v) CH_3CN–H_2O; [catalyst] = 2×10^{-4} M, [substrate] = 1×10^{-5} M, [$2C_{14}Br$] = 1×10^{-3} M, [CTAB] = 7×10^{-4} M.

In this paper, we demonstrate the discrimination of the reaction field of micelles, vesicles, and coaggregates composed of 59 mol % ditetradecyldimethylammonium bromide (**4**, $2C_{14}Br$)/41 mol % hexadecyltrimethylammonium bromide (**5**, CTAB) on the basis of β in the enantioselective hydrolysis of *p*-nitrophenyl *N*-(benzyloxycarbonyl)-D(L)-phenylalaninates (**1a**, D(L)-ZS) and *N*-dodecanoyl-D(L)-phenylalaninates (**1b**, D(L)-S_{12}) catalyzed by L-histidine derivatives (*N*-(benzyloxycarbonyl)-L-phenylalanyl-L-histidyl-L-leucine (**2a**, Z-PheHisLeu), *N*-(benzyloxycarbonyl)-L-phenylalanyl-L-histidine (**2b**, Z-PheHis), *N*-tetradecanoyl-L-histidyl-L-leucine (**3a**, MyrHisLeu), and *N*-tetradecanoyl-L-histidine (**3b**, MyrHis)). Moreover, the interrelation between the β values and the molecular location of catalysts in the coaggregates composed of 59 mol % $2C_{14}Br$/41 mol % CTAB will be discussed.

Results and Discussion

Temperature Dependence of Enantioselectivity. The morphology of the coaggregates composed of 59 mol % $2C_{14}Br$/41 mol % CTAB was found to be spherical single- and double-walled vesicles by electron microscopy and light-scattering measurements.[8] The temperature dependence of enantioselectivity (reflected in $k^L_{a,obsd}/k^D_{a,obsd}$) for the hydrolysis of D(L)-S_{12} catalyzed by Z-PheHisLeu and MyrHisLeu in the coaggregates is shown in Figure 1. It is noteworthy that the pronounced maxima

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