DIASTEREOSELECTIVE SYNTHESIS OF HEXAHYDRO-3H-OXAZOLO[3,4-a]PYRIDIN-3-ONE DERIVATIVES BY CYCLIZATION OF α-ACYLAMINORADICAL-OLEFIN SYSTEM

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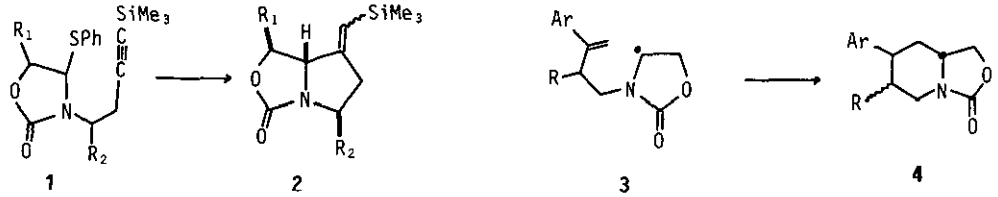
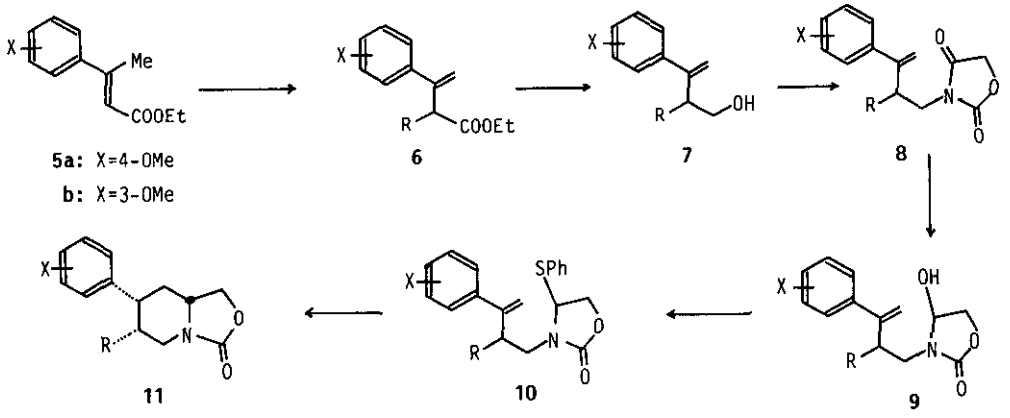
Abstract —— The substituent effect in α-acylaminoradical-olefin cyclization was examined. Treatment of 4-phenylthiooxazolidin-2-ones (**10a-f**) with tri-n-buytltin hydride in the presence of AIBN yielded 6,7-cis-6,8a-trans-6-alkyl-7-arylhexahydrooxazolo[3,4-a]pyridin-3-ones (**11a-f**), respectively, with high diastereoselectivity.

Radical cyclization is rapidly becoming an important method for a construction of bicyclic systems.[1,2] α-Acylaminoradical cyclization at an unsaurated component affords N-heterocycles through a formation of carbon-carbon bond at the α-position of nitrogen.[3,4] Previously, we reported a synthesis of 1- and 5-substituted tetrahydropyrrolo[1,2-c]oxazoles (**2a,b**)[5] by the reaction of **1a,b** with tri-n-butyltin hydride in the presence of azobisisobutyronitrile (AIBN). The diastereoselectivity in a formation of these bicyclic compounds can be attributed to the substituent effect of a substituent at the α-position to nitrogen or to radical carbon. The diastereoselectivity in a formation of **2b** can be accounted for by allylic strain phenomena.[6] However, in these radical cyclization reactions, little attention has been paid to the substitutent effect with regard to a substituent on the position adjacent to double bond as in **3**.[7] We investigated a substituent effect on α-acylaminoradical cyclization by the use of the type of compounds (**3**) whether cyclization proceeded with diastereoselectivity in a formation of **4** which would be potentially useful in a synthesis of several member of morphine-based structural variants such as benzomorphane and related copmpounds.[8]



a: R_1=Me, R_2=H
b: R_1=H, R_2=Me

At first, we prepared 4-phenylthiooxazolidin-2-ones (**10a-f**), used as precursors for generation of radical species, by starting from ethyl β-aryl-β-methylacrylate (**5a,b**) according to the method reported previously.[7,9] Deprotonation of **5a** with lithium diisopropylamide (LDA) followed by addition of the corresponding alkyl halide yielded α-alkylated esters (**6a-d**). Reduction of **6a-d** with $LiAlH_4$ in ether afforded the alcohols (**6a-d**), condensation of which with oxazolidine-2,4-dione by Mitsunobu's method[10] yielded the corresponding N-substituted oxazolidine-2,4-diones (**7a-d**), respectively. Reduction of **7a-d** with $NaBH_4$, followed by treatment of **9a-d** with diphenyl disulfide in the presence of tri-n-butylphosphine[7] gave the correspodning 4-phenylthio derivatives (**10a-d**), respectively. In a smilar way, the 4-phenylthiooxazolidin-2-ones (**10e,f**) were also prepared by starting with **5b** through **6e,f**, **7e,f**, **8e,f**, **9e,f** respectively.

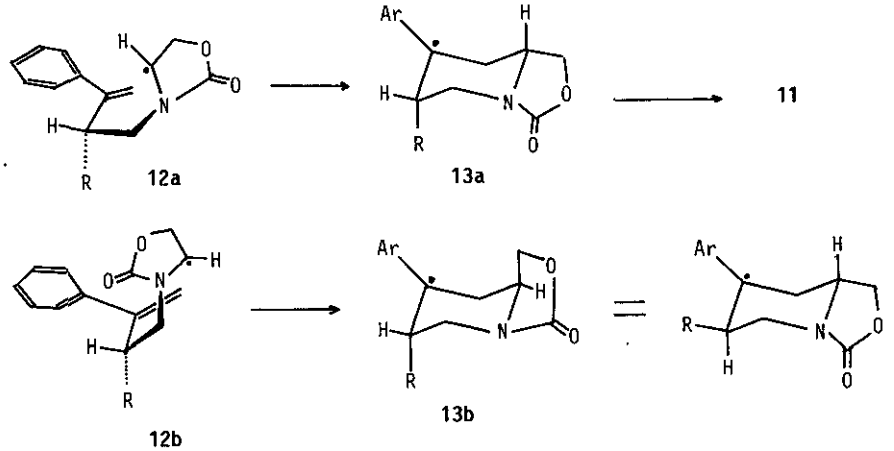


5a: X=4-OMe
b: X=3-OMe

6 **7** **8** **9** **10** **11**

For **6-11**

a: X=4-OMe, R=Me
b: X=4-OMe, R=Et
c: X=4-OMe, R=$CH_2CH=CH_2$
d: X=4-OMe, R=$CH_2C_6H_5$
e: X=3-OMe, R=Me
f: X=3-OMe, R=Et



12a **13a** **11**

12b **13b**

A solution of **10a** in benzene was heated with tri-n-butyltin hydride in the presence of AIBN resulted in a formation of hexahydrooxazolo[3,4-a]pyridine (**11a**) as a single diastereomer. The relative configuration of **11a** was determined based on the Dreiding model study and Karplus relation[11] for the signals due to $NC\underline{H}_2$ and $PhC\underline{H}$ which were clearly visible in its ^1H nmr ($CDCl_3$, 400 MHz) spectra. Of $NC\underline{H}_2$, the equatorial oriented proton resonated at δ 3.78 (dd, $\underline{J}$=1.42, 13.14 Hz) and the axial one at 3.22 (dd, $\underline{J}$=3.47, 13.14 Hz). Signals due to $PhC\underline{H}$ appeared at δ 2.98 (ddd, $\underline{J}$=3.42, 3.48, 12.85 Hz) owing to one large diaxial and two small axial-equatorial coupling constants. These facts indicates that phenyl group is equatorially and methyl group is axially oriented. The methyl signals which appearted at considerably high field, δ 0.75 (d, $\underline{J}$=7.03 Hz) also support this assignment. The same reaction by the use of **11b-f** gave the corresponding hexahydrooxazolo[3,4-a]pyridine derivatives (**11b-f**), respectively.

Diastereoselectivity in this cyclization reaction can be accounted for by the effect of $A^{1,2}$ strain[6] in the transition state for the radical cyclization. Of the two possible transition states (**12a,b**), **12a** giving **13a** should be more preferable to **12b** giving **13b** because of the considerably severe steric repulsion caused by and phenyl group and oxazolidinone ring in **12b**. The successive C-H bond formation via delivery of H from the less hindered face to **13a** gave **11**. Thus a highly diastereoselective synthesis of hexahydro-3H-oxazolo[3,4-a]pyridine derivatives was achieved.

EXPERIMENTAL

All melting points were determined on a Yanagimoto hot-stage apparatus and uncorrected. ^1H-nmr spectra were recorded on a Varian EM-390 (90 MHz) and a Bruker AM-400 (400 MHz) istrument in $CDCl_3$ with Me_4Si as an internal standard. Ir spectra were run on a 260-30 Hitachi Infrared spectrophotometer. Mass spectra (ms) were obtained with a Hitachi RMU-7L instrument. Tetrahydrofuran (THF) and ether were distilled from sodium-benzophenone before use.

General Procedure for an α-Alkylation of Esters (5a,b) —— To a stirred solution of lithium diisopropylamide (prepared from 5.10 g of diisopropylamine and 64 ml of 1.6 M hexane solution of n-butyllithium in 50 ml of THF at -78°C as usual) was added a solution of **5a,b** (11.0 g, 50 mmol) in THF (30 ml) at -78°C. After the stirring had been continued at the same temperature for 0.5 h, methyl iodide (10.3 g, 70 mmol) was added [ethyl iodide (11.2 g, 70 mmol) was used for preparation of **6b,f**, and allyl bromide (8.5 g, 70 mmol) was used for **6c** and benzyl bromide (9.4 g, 55 mmol) was used for **6d**]. After the stirring had been continued at room temperature for 2 h, the mixture was poured into water (100 ml) and extracted with benzene. The extract was washed with brine, dried (Na_2SO_4) and evaporated to give **6a-f** as an oil in all entries. Yields and physical

data are shown in the Table 1. Only characteristic signals are given for their ^{1}H-nmr spectra.

General Procedure for a Preparation of 7a-f —— To a stirred solution of of $LiAlH_4$ (1.9 g, 50 mmol) in ether (60 ml) was added a solution of **6a-f** (25 mmol) in ether (50 ml) under below 0°C. After the stirring had been continued at the same temperture for 1.5 h, the mixture was decomposed with aqueous 10 % NaOH. Inorganic precipitate was removed by filtration and the filtrate was evaporated to leave **7a-f** as an oil in all entries. Yields and physical properties are shown in the Table 1. Only characteristic signals are given for their ^{1}H-nmr spectra.

Table 1. Yields and Physical Properties of **6** and **7**

6a	92 % yield; ir ($CHCl_3$) 1720 cm^{-1}; ms m/z 234 (M^+); ^{1}H-nmr ($CDCl_3$) δ 1.13 (3H, t, J=7 Hz), 1.31 (3H, d, J=7 Hz), 3.61 (1H, q, J=7 Hz), 3.74 (3H, s), 4.06 (2H, q, J=7 Hz), 5.11 (1H, s), 5.28 (1H, s)
6b	88 % yield; ir ($CHCl_3$) 1720 cm^{-1}; ms m/z 248 (M^+); ^{1}H-nmr ($CDCl_3$) δ 0.92 (3H, t, J=8 Hz), 1.18 (3H, t, J=7 Hz), 3.37 (1H, t, J=7 Hz), 3.76 (3H, s), 4.10 (2H, q, J=7 Hz), 5.16 (1H, s), 5.28 (1H, s)
6c	88 % yield; ir ($CHCl_3$) 1720 cm^{-1}; ms m/z 260 (M^+); ^{1}H-nmr ($CDCl_3$) δ 1.18 (3H, t, J=7 Hz), 3.58 (1H, dd, J=7, 8 Hz), 3.78 (3H, s), 4.13 (2H, q, J=7Hz). 5.22 (1H, s), 5.36 (1H, s)
6d	82 % yield; ir ($CHCl_3$) 1720 cm^{-1}; ms m/z 310 (M^+); ^{1}H-nmr ($CDCl_3$) δ 1.09 (3H, t, J=7 Hz), 2.82-3.33 (2H, m), 3.70-3.84 (1H, m), 3.77 (3H, s), 4.07 (2H, q, J=7 Hz), 5.23 (1H, s), 5.31 (1H, s)
6e	87 % yield; ir ($CHCl_3$) 1720 cm^{-1}; ms m/z 234 (M^+); ^{1}H-nmr ($CDCl_3$) δ 1.16 (3H, t, J=8 Hz), 1.37 (3H, d, J=7 Hz), 3.30 (1H, q, J=7 Hz), 3.80 (3H, 3), 4.08 (2H, q, J=7 Hz), 5.21 (1H, s), 5.40 (1H, s)
6f	84 % yield; ms m/z 248 (M^+); ^{1}H-nmr ($CDCl_3$) δ 0.93 (3H, t, J=7 Hz), 1.20 (3H, t, J=7Hz), 3.77 (3H, s), 4.11 (2H, q, J=7 Hz), 5.24 (1H, s), 5.37 (1H, s)
7a	92 % yield; ms m/z 192 (M^+); ^{1}H-nmr ($CDCl_3$) δ 1.14 (3H, d, J=7 Hz). 2.68-2.72 (1H, m), 3.48-3.64 (2H, broad, signal), 3.77 (3H, s), 5.02 (1H, s), 5.26 (1H, s)
7b	88 % yield; ms m/z 206 (M^+); ^{1}H-nmr ($CDCl_3$) δ 0.90 (3H, t, J=8 Hz), 1.37-1.67 (2H, m), 2.50-2.83 (1H, m), 3.60 (2H, broad signal), 3.76 (3H, s), 5.01 (1H, s), 5.30 (1H, s)
7c	85 % yield; ms m/z 260 (M^+); ^{1}H-nmr ($CDCl_3$) δ 2.29-3.00 (3H, m), 3.67 (2H, broad signal), 3.80 (3H, s), 5.04 (1H, s), 5.33 (1H, s)
7d	83 % yield; ms m/z 268 (M^+); ^{1}H-nmr ($CDCl_3$) δ 3.54 (2H, broad signal), 3.71 (3H, s), 5.02 (1H, s), 5.28 (1H, s)
7e	85 % yield; ms m/z 192 (M^+); ^{1}H-nmr ($CDCl_3$) δ 1.13 (3H, d, J=7 Hz), 2.73-2.97 (1H, m), 3.77 (3H, s), 5.07 (1H, s), 5.30 (1H, s)
7f	86 % yield; ms m/z 206 (M^+); ^{1}H-nmr ($CDCl_3$) δ 0.92 (3H, t, J=8 Hz), 2.53-2.83 (1H, m), 3.83 (3H, s), 5.10 (1H, s), 5.38 (1H, s)

General Procedure for a Synthesis of 8a-f —— To a stirred mixture of **7a-f** (0.03 mol), triphenylphosphine (7.86 g, 30 mmol), oxazolidine-2,4-dione (3.03 g, 30 mmol) in THF (60 ml) was added a

solution of diisopropyl azodicarboxylate (6.06 g, 30 mmol) in THF (15 ml) under ice-cooling. After the stirring had been continued at room temperature for 14 h, the solvent was evaporated. The remaining residue was chromatographed on silca gel (30 g) by using benzene-hexane (1:3) as an eluant. Removal of the solvent afforded **8a-f** as an oil in all entries. Yields and physical properties are shown in the Table 2. Only characteristic signals are given for ^{1}H-nmr spectra.

Table 2. Yields and Physical Properties of **8a-f**

8a	70 % yield; m/z 275.114 (M^+, calcd for $C_{15}H_{17}NO_4$ m/z 275.116); ir ($CHCl_3$) 1810, 1725; ^{1}H-nmr ($CDCl_3$) δ 1.18 (3H, d, J=6 Hz), 3.78 (3H, s), 4.35 (2H, s), 5.07 (1H, s), 5.26 (1H, s)
8b	68 % yield; m/z 289.129 (M^+, calcd for $C_{16}H_{19}NO_4$ m/z 289.131); ir ($CHCl_3$) 1810, 1728 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 0.93 (3H, t, J=7 Hz), 3.80(3H, s), 4.38 (2H, s), 5.08 (1H, s), 5.36 (1H, s)
8c	72 % yield; m/z 301.129 (M^+, calcd for $C_{17}H_{19}NO_4$ m/z 301.131); ir ($CHCl_3$) 1810, 1730 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 3.80 (3H, s), 4.38 (2H, s), 5.11 (1H, s), 5.34 (1H, s)
8d	70 % yield; m/z 351.148 (M^+, calcd for $C_{21}H_{21}NO_4$ m/z 351.147); ir ($CHCl_3$) 1803, 1722 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 3.80 (3H, s), 4.12 (2H, s), 5.17 (1H, s), 5.27 (1H, s),
8e	70 % yield; m/z 275.115 (M^+, calcd for $C_{15}H_{17}NO_4$ m/z 275.116); ir ($CHCl_3$) 1810, 1725 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.53 (3H, d, J=7 Hz), 3.83 (3H, s), 4.12 (2H,s), 5.17 (1H, s), 5.27 (1H, s)
8f	72 % yield; m/z 289.129 (M^+, calcd for $C_{16}H_{19}NO_4$ m/z 289.131); ir ($CHCl_3$) 1810, 1725 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 0.96 (3H, t, J=7 Hz), 3.82 (3H, s), 4.36 (2H, s), 5.18 (1H, s), 5.46 (1H, s)

General Procedure for a Synthesis of 10a-f —— To a stirred solution of **8a-f** (20 mmol) in MeOH (100 ml) was added $NaBH_4$ (3.4 g, 0.1 mol) in small portions at below 0°C. After the stirring had been continued at the same temperature for 4 h, the solvent was evaporated. The resulting residue was diluted with water and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated to give 4-hydroxyoxazolidin-2-ones (**9a-f**). The remaining residue was used for the following reaction without purification. A mixture of **9a-f** (15 mmol), diphenyl disulfide (3.27 g, 15 mmol), n-Bu_3P (3.03 g, 15 mmol) and benzene (40 ml) was stired at room temperature for 24 h. After removal of the resulting residue was chromatographed on silica gel. Elution with hexane gave unreacted diphenyl disulfide and n-Bu_3P. Successive elution with hexane-AcOEt (9:1) gave **10a-f** as an oil in all entries as a mixture of diastreomers in yields shown below. Their M^+ ion peaks were not give in EI ms, but weak M^++1 ion peaks were given in all entries. Yields and ir spectra are as follows.

10a —— 70 % yield; ir ($CHCl_3$) 1735 cm^{-1}. **10b** —— 63 % yield; ir ($CHCl_3$) 1742 cm^{-1}.

10c —— 68 % yield; ir ($CHCl_3$) 1735 cm^{-1}. **10d** —— 67 % yield; ir ($CHCl_3$) 1740 cm^{-1}.

10e —— 66 % yield; ir ($CHCl_3$) 1741 cm^{-1}. **10f** —— 65 % yield; ir ($CHCl_3$) 1741 cm^{-1}.

General Procedure for a Synthesis of Hexahydrooxazolo[3,4-a]pyridine (11a-f) —— To a stirred solution of **10a-f** (3 mmol) and azobisisobutyronitrile (15 mg) in benzene (200 ml) was added dropwisely a solution of n-Bu_3SnH (1.4 g, 4.8 mmol) in benzene (100 ml) under reflux. After addition of the reagent, the mixture further heated under reflux for 3 h and then the solvent was evaporated. The resulting residue was chromatographed on silica gel. Elution with hexane afforded decomposed stannic compound and successive elution with CH_2Cl_2 afforded **11a-f**. Yields, physical properties and analytical data are listed in the Table 3. Only characteristic signals are given for ^{1}H-nmr spectra (400 MHz).

Table 3. Yields and Physical Properties of **11a-f**

11a 57 % yield; mp 142-143°C; ms m/z 261 (M^+); ^{1}H-nmr ($CDCl_3$) δ 0.75 (3H, d, J=7.0 Hz), 1.74 (1H, ddd, J=3.53, 3.53, 12.85 Hz), 1.90-1.91 (1H, m), 2.09 (1H, broad signal, $W_{1/2}$=13 Hz), 2.98 (1H, ddd, J=3.42, 3.48, 12.85 Hz), 3.22 (1H, dd, J=3.47, 13.14 Hz), 3.78 (1H, dd, J=1.42, 13.14 Hz), 3.80 (3H, s), 3.83 (1H, broad signal, $W_{1/2}$= 31 Hz), 4.04 (1H, dd, J=6.42, 8.50 Hz), 4.50 (1H, dd, J=8.50, 8.50 Hz); ir ($CHCl_3$) 1740 cm^{-1}.
Anal. Calcd for $C_{19}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36.
Found: C, 69.23; H, 7.34; N, 5.33

11b 60 % yield; mp 165-166°C; ms m/z 275 (M^+); ^{1}H-nmr ($CDCl_3$) δ 0.81 (3H, t, J= 7.40 Hz), 3.00 (1H, dt, J=12.12, 4.01 Hz), 3.08 (1H, dd, J=3.48, 13.14 Hz), 3.80 (3H, s), 4.01 (1H, dd, J=6.53, 8.34 Hz), 4.50 (1H, t, J=8.34 Hz), signals due to two NCH are conceled to beneath OCH_3); ir ($CHCl_3$) 1740 cm^{-1}.
Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09.
Found: C, 71.09; H, 7.82; H, 5.14.

11c 60 % yield; mp 107-108°C; ms m/z 287 (M^+); ^{1}H-nmr ($CDCl_3$) δ 3.06 (2H, d, J=12.99 Hz), 3.84 (1H, m), 3.99 (1H, d, J=13.28 Hz), 4.04 (1H, d, J=6.62, 8.42 Hz), 4.51 (1H, t, J=8.42, 8.42 Hz); ir ($CHCl_3$) 1740 cm^{-1}.
Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87.
Found: C, 71.18; H, 7.37; N, 4.90.

11d 62 % yield; mp 171-172°C; ms m/z 337 (M^+); ^{1}H-nmr ($CDCl_3$) δ 2.98 (1H, dd, J=3.64, 13.31 Hz), 3.12 (1H, ddd, J=4.20, 4.20, 11.48 Hz), 3.85 (3H, s), 4.12 (1H, dd, J=6.43, 8.46 Hz), 4.56 (1H, dd, J=8.46, 8.46 Hz), signals due to two NCH are concealed beneath OCH_3); ir (CHC_3) 1740 cm^{-1}.

11e 58 % yield; mp 92-93°C; ms m/z 261 (M^+); ^{1}H-nmr ($CDCl_3$) δ 3.00 (1H, dt, J=12.80, 3.40 Hz), 3.23 (1H, dd, J=3.55, 13.07 Hz), 3.78 (1H, d, J=13.07 Hz), 3.80 (3H, s), 4.05 (1H, dd, J=6.45, 8.48 Hz), 4.51 (1H, t, J=8.48 Hz); ir ($CHCl_3$) 1740 cm^{-1}.
Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36.
Found: C, 68.86; H, 7.26; N, 5.35.

11f 63 % yield; mp 119-120°C; ms m/z 275 (M^+); ^{1}H-nmr ($CDCl_3$) δ 0.82 (3H, t, J=7.30 Hz), 3.01 1H, dt, J=12.31, 4.01 Hz), 3.09 (1H, dd, J=3.48, 13.34 Hz), 3.81 (3H, s,), 4.02 (1H, dd, J=6.41, 8.39 Hz), 4.50 (1H, t, J=8.39 Hz); ir ($CHCl_3$) 1740 cm^{-1}.
Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09.
Found: C, 69.81; H, 7.70; N, 5.10.

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Received, 5th February, 1988