Synthesis of Novel Imidazole-4,5-dicarboxylic Acid Derivatives

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A convenient general method for the synthesis of unsymmetrical imidazole-4,5-dicarboxylic acid derivatives is described. The key intermediates are 5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1′,5′-*d*]pyrazine-1,6-dicarboxylic acid, -1,6-dicarboxylic ester and -1,6-dicarboxamide.

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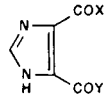
The physiological importance of compounds incorporating the imidazole nucleus has stimulated considerable work in the synthesis of the mono- or dicarboxylic acid derivatives of imidazole [1a-i]. Symmetrical derivatives of imidazole-4,5-dicarboxylic acid (**1**), such as dicarboxylic ester, dicarboxamide and dicarbohydrazide, have been prepared [1a-1e]. However unsymmetrical imidazole 4,5-dicarboxylic acid derivatives have been rarely investigated [1c]. This report presents a convenient general method for the synthesis of novel imidazole 4,5-dicarboxylic acid derivatives, as shown in general formulas **2-5**.



2, X = OH, Y = OR_1 (R_1 = C_2H_5)

3, X = OH, Y = NR_2R_3

- **a**, Y = $NHCH_2CH(CH_3)_2$
- **b**, Y = $NHCH_2Ph$
- **c**, Y = $N(C_2H_5)_2$
- **d**, Y = $NHCHCOOCH_3$ (CH_2Ph)
- **e** Y = $NHCH_2CH_2SO_3Na$

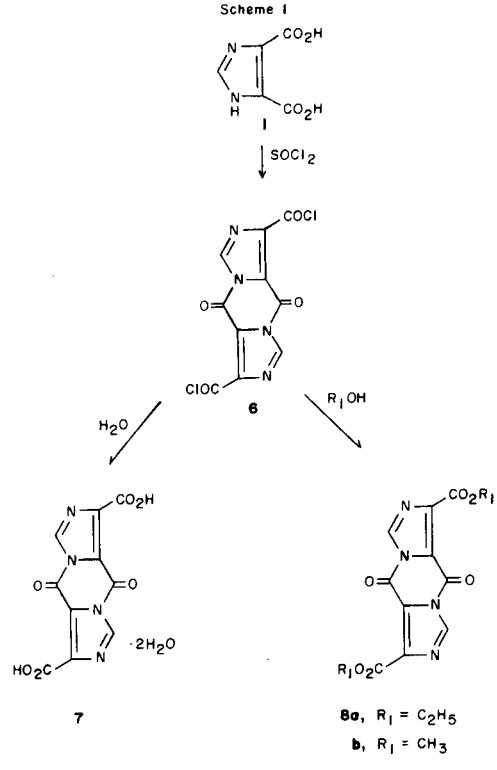
4, X = OR_1, Y = NR_2R_3

- **a**, X = OC_2H_5, Y = $NHCH_2PhCl_2$ (O, P)
- **b**, X = OCH_3, Y = $NHOCH_2Ph$

5, X = NR_2R_3, Y = NR_4R_5

- **a**, X = $NHCH_2CH(CH_3)_2$, Y = NHPh
- **b**, X = $NHCH_2CH(CH_3)_2$, Y = $NHCH_2PhCl_2$ (O, P)
- **c**, X = $NHCH_2Ph$, Y = $N(C_2H_5)_2$

Scheme I



The key intermediate in this method is the novel diimidazopyrazine derivative **7**, which can be derived from **1** *via* **6** as shown in Scheme 1. The synthetic method of **7** has been reported in a preceding paper [2].

Compound **7** is not highly stable. Since it has two moles of water of crystallization, the hydrolysis to **1** proceeds gradually even stored in a refrigerator. Consequently, it is preferable to prepare **7** just prior to use.

Compound **2** (R_1 = C_2H_5) was obtained in moderate yield by heating **7** with ethanol under reflux, followed by recrystallization from ethanol.

The treatment of **7** with amine affords the corresponding monoamide **3**. A typical example is as follows. Compound **7** was heated with two equivalent moles of amine in dichloromethane at 40° in the presence of triethylamine. After concentration of the mixture, the residue was dissolved in water and acidified. A precipitate was collected by filtration to give the crude product. Since compound **7** has water of crystallization as mentioned above, the hydrolysis of **7** to **1** occurs as a side reaction. Consequently, the crude product thus obtained contains **1**. However it is possible to remove **1** by treatment with tetrahydrofuran (THF), because compound **3** is soluble in hot THF, while **1** is quite insoluble in THF.

The reaction has been successfully carried out with primary amines such as isobutylamine, benzylamine, or phenylalanine methyl ester in high yield. In some cases this reaction can be achieved in water. For example, taurine was allowed to react with **7** in water maintaining the *p*H at 6.0-7.5 to give a desired product, after isolation by crystallization from acidic water. However the reaction with se-

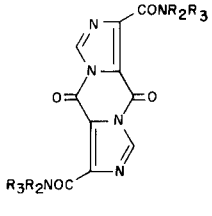
condary amine such as diethylamine resulted in a low yield. Moreover, the attempts to prepare monoanilide of **1** were unsuccessful. These differences are ascribed to the steric effect and in the case of the reaction with aniline, the less nucleophilicity of the N of aniline is also an influential factor. In these cases the hydrolysis of **7** proceeds predominantly.

The derivative **4** was prepared by the reaction of **8** with the corresponding amine. For example 2,4-dichlorobenzylamine or *O*-benzylhydroxylamine was allowed to react with **8** in dichloromethane under reflux to give the corresponding **4** in high yield.

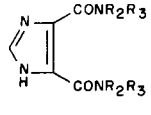
The structure of **4** ws confirmed by nmr, ms spectrum and elemental analyses. The ir spectrum [3] of **4** shows no ν CO attributable to ester group above 1700 cm^{-1}. While at about 1690 cm^{-1} the band of the ester group is observed. Since ethyl imidazole-4-carboxylate [4] shows ν CO due to ester group at 1717 cm^{-1}, the shift of ν CO to a low-wavenumber in the ir spectrum seems to be due to the influence of a neighboring carboxamide group. A detailed report about this matter will be published separately.

Unsymmetrical imidazole-4,5-dicarboxamide derivatives (**5**) were synthesized from **3** as follows: the monoamide **3** was treated with an excess amount of thionyl chloride in benzene containing trace amounts of dimethylformamide at 80°, and the cyclic dimerization product (**9**) was isolated as crystals after filtration. A purification of **9** was carried out by stirring the crude product in THF at 60°. The impurities in **9** were dissolved in THF. The structure of **9** was confirmed by spectral data and elemental analyses. The ms spectrum exhibits molecular ion corresponding to the molecular weight of the cyclic dimerization product. The ir spectrum shows a peak due to the 1-acylimidazole moiety (1730 cm^{-1}) [5]. In the nmr spectrum the signal of the imidazole ring proton of **9** was observed at lower field by 0.8-0.9 ppm compared with that of **3**.

On the other hand, an attempt to prepare **9** by direct treatment of **6** with the corresponding amine was unsuccessful. This reaction produced only the symmetrical diamide (**10**) [1e].



9a, R_2 = H, R_3 = $CH_2CH(CH_3)_2$
b, R_2 = H, R_3 = CH_2Ph



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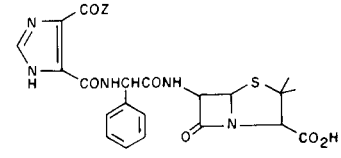
The novel diimidazopyrazine derivative thus prepared (**9**) was heated with an excess of appropriate amine in dichloromethane under reflux. After concentration of the reaction mixture and recrystallization, the corresponding unsymmetrical diamide (**5**) was obtained in good yield. In this case the reaction with aniline or diethylamine has been successfully carried out.

Furthermore, this reaction is applicable to amines having a carboxy group such as ampicillin. The reaction with **9a** was carried out in dichloromethane by adding triethylamine to dissolve ampicillin. The obtained novel penicillin (**11**) has shown lower antibacterial activity than those of the 5-carboxy derivative (**12**) and 5-ethoxycarbonyl derivative (**13**), which the author has been prepared previously [2].



11, Z = $NHCH_2CH(CH_3)_2$
12, Z = OH
13, Z = OC_2H_5

The studies for physiological activities of other compounds prepared here are in progress.

EXPERIMENTAL

Infrared spectra were measured on a Shimadzu IR-430 spectrophotometer or Digilab STS-15E spectrophotometer (ft-ir). Proton nuclear magnetic resonance spectra were measured on a Varian EM-390 (90 MHz) spectrometer using TMS or DSS as an internal reference. Mass spectra were measured on a JEOL DX-300 mass spectrometer.

4(5)-Carboxy-5(4)-ethoxycarbonylimidazole (**2**).

A suspension of **7** (6.24 g, 20 mmoles) in ethanol (150 ml) was stirred under reflux for 17 hours. An insoluble solid was collected by filtration and recrystallized from ethanol (1 *l*) to give 2.73 g of **2**. The filtrate of the reaction mixture was concentrated and chilled to give an additional 0.84 g for a total yield of 49%, ir (Nujol): ν max 1725 cm^{-1} (-$COOC_2H_5$); nmr (DMSO): δ 1.31 (t, 3H, -CH_3), 4.29 (q, 2H, -CH_2-), 7.83 (s, 1H, imidazole C_2-H); fd-ms: $[M + H]^+$ at m/z 185 $[2M + H]^+$ at m/z 369 (mol wt, 184).

Anal. Calcd. for $C_7H_8N_2O_4$: C, 45.65; H, 4.38; N, 15.21. Found: C, 46.04; H, 4.47; N, 15.36.

4(5)-Carboxy-5(4)-isobutylaminocarbonylimidazole (**3a**).

To a solution of isobutylamine (6.6 g, 90 mmoles) and triethylamine (22 ml) in dichloromethane (200 ml), **7** (9.4 g, 30 mmoles) was added and the mixture was stirred for 5 hours at 40°. After concentration, a residue was dissolved in water (150 ml) and washed with ethyl acetate. The water solution was adjusted to *p*H 2 with 2*N* hydrochloric acid. After cooling, a precipitate was collected by filtration and dried under vacuum. The crude solid thus obtained was stirred in THF at 50°. After insoluble material was removed by filtration, the solution was concentrated and ether was added. After cooling, a precipitate was filtered, washed with petroleum ether and dried to give 9.2 g (73%) of **3a**; nmr (DMSO): δ 0.90 (d, 6H,-CH(CH_3)$_2$), 1.93 (m, 1H, -C*H*), 3.18 (dd, 2H, -CH_2-CH), 8.03 (s, 1H, imidazole C_2-H), 9.33 (br t, 1H, -CONH-); fd-ms: $[M + H]^+$ at m/z 212 (mol wt, 211).

Anal. Calcd. for $C_9H_{13}N_3O_3$: C, 51.17; H, 6.22; N, 19.90. Found: C, 51.12; H, 6.45; N, 19.72.

In a similar manner, **7** was allowed to react with benzylamine, diethylamine or L-phenylalanine methyl ester hydrochloride to give the following compounds **3b-d**, respectively.

4(5)-Benzylaminocarbonyl-5(4)-carboxyimidazole (**3b**).

This compound was obtained in a yield of 68%; nmr (DMSO): δ 4.53 (d, 2H, -C*H*$_2$-Ph), 7.10-7.50 (m, 5H, -Ph), 8.03 (s, 1H, imidazole C$_2$-H), 9.90 (br t, 1H, -CONH-); fd-ms: [M]$^+$ at m/z 245 (mol wt, 245).

Anal. Calcd. for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.14. Found: C, 58.50; H, 4.51; N, 17.16.

4(5)-Carboxy-5(4)-diethylaminocarbonylimidazole (**3c**).

This compound was obtained in a yield of 12%; nmr (DMSO): δ 1.22 (t, 6H, -CH_2CH_3), 3.90 (q, 4H, -C*H*$_2$CH$_3$), 7.90 (s, 1H, imidazole C$_2$-H).

Anal. Calcd. for $C_9H_{13}N_3O_3$: C, 51.17; H, 6.20; N, 19.90. Found: C, 51.31; H, 6.52; N, 19.77.

L-α-[4(5)-Carboxyimidazole-5(4)-carboxamido]-β-phenylpropionic Acid Methyl Ester (**3d**).

This compound was obtained in a yield of 43%; nmr (DMSO): δ 3.25 (d, 2H, -C*H*$_2$-Ph), 3.70 (s, 3H, -$COOCH_3$), 4.85 (m, 1H, -NH-C*H*-CO$_2$-), 7.30 (br s, 5H, Ph), 8.02 (s, 1H, imidazole C$_2$-H), 10.07 (br d, 1H, -CONH-).

Anal. Calcd. for $C_{15}H_{15}N_3O_5$: C, 56.78; H, 4.77; N, 13.24. Found: C, 56.65; H, 4.89; N, 13.16.

β-[4(5)-Carboxyimidazole-5(4)-carboxamido]ethanesulfonic Acid Sodium Salt (**3e**).

To a suspension of taurine (3.75 g, 30 mmoles) in water (70 ml), 13.5% sodium hydroxide was added to dissolve it and *p*H was adjusted to 8.9. To this solution, **7** (6.99 g, 22.4 mmoles) was added in limited amounts with stirring and cooling, maintaining the *p*H at 6.0-7.5 by adding 13.5% sodium hydroxide. After stirring for 1 hour under ice-cooling, the *p*H of the mixture was adjusted to 3.0 with 6% hydrochloric acid. After a precipitate was removed by filtration, the filtrate was stored in a refrigerator for 3 days. A precipitated solid was collected by filtration and dried under vacuum to give 3.79 g (27%) of **3e**; nmr (deuterium oxide): δ 3.27 (t, 2H, -C*H*$_2$-SO_3-), 3.83 (t, 2H, -NH-C*H*$_2$-), 7.80 (s, 1H, imidazole C$_2$-H).

Anal. Calcd. for $C_7H_8N_3O_6SNa\cdot1.3H_2O$: C, 27.24; H, 3.47; N, 13.62; Na, 7.45. Found: C, 27.50; H, 3.95; N, 13.44; Na, 7.60.

4(5)-(2,4-Dichlorobenzylaminocarbonyl)-5(4)-ethoxycarbonylimidazole (**4a**).

To a solution of 2,4-dichlorobenzylamine (4.4 g, 25 mmoles) in dichloromethane (100 ml), **8a** (1.66 g, 5 mmoles) was added and the reaction mixture was stirred for 4 hours under reflux. After cooling, an insoluble solid was collected by filtration and recrystallized from dichloromethane and ether to give 1.88 g of **4a**. In addition, the filtrate of the reaction mixture was washed with 1*N* hydrochloric acid and water and dried (magnesium sulfate). After concentration, a residual solid was recrystallized from the same solvents to give an additional 1.15 g for a total yield of 89%; ir (potassium bromide): ν max 1690 (-$COOC_2H_5$), 1659 cm^{-1} (-CONH-); nmr (DMSO): δ 1.32 (t, 3H, -CH_3), 4.30 (q, 2H, -OCH_2-), 4.58 (d, 2H, -NHC*H*$_2$-), 7.30-7.69 (m, 3H, -Ph-2, 4Cl), 7.81 (s, 1H, imidazole-C$_2$-H), 10.07 (br s, 1H, -CONH-); fd-ms: [M + H]$^+$ at m/z 342 (mol wt, 341).

Anal. Calcd. for $C_{14}H_{13}Cl_2N_3O_3$: C, 49.13; H, 3.84; N, 12.28. Found: C, 49.04; H, 3.67; N, 12.22.

4(5)-Benzoyloxyaminocarbonyl-5(4)-methoxycarbonylimidazole (**4b**).

To a solution of *O*-benzylhydroxylamine hydrochloride (3.19 g, 20 mmoles) and triethylamine (3 ml, 22 mmoles) in dichloromethane (100 ml), **8b** (1.52 g, 5 mmoles) was added and the mixture was stirred for 4 hours under reflux. After cooling, an insoluble solid was collected by filtration and recrystallized from THF and ether to give 1.96 g (71%) of **4b**; ir (potassium bromide): ν max 1694 (-$COOCH_3$), 1670 cm^{-1} (-CONHO-); nmr (DMSO): δ 3.78 (s, 3H, -CH_3), 4.90 (s, 2H, -OCH_2-), 7.37 (m, 5H, -Ph), 7.92 (s, 1H, imidazole C$_2$-H).

Anal. Calcd. for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.93; H, 4.84; N, 15.19.

1,6-Diisobutylaminocarbonyl-5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1′,5′-*d*]-pyrazine (**9a**).

To a suspension of **3a** (12.7 g, 60 mmoles) in dry benzene (280 ml) containing DMF (4 ml), thionyl chloride (60 ml) was added and the mixture was stirred at 80° for 6 hours. After cooling, an insoluble solid was collected by filtration. The crude product thus obtained was suspended in THF (400 ml) and stirred at 60° for 30 minutes. The insoluble solid was collected by filtration and dried under vacuum to give 3.03 g (26%) of analytically pure **9a**; ir (Nujol): ν max 1730 cm^{-1} (carbonyl imidazolide); nmr (DMSO): δ 0.96 (d, 12H, -CH(C*H*$_3$)$_2$), 1.88 (m, 2H, -C*H*(CH$_3$)$_2$), 3.13 (dd, 4H, -NHC*H*$_2$-), 8.63 (br t, 2H, -CONH-), 8.88 (s, 2H, imidazole C$_2$-H); fab-ms: [M + H]$^+$ at m/z 387 (mol wt, 386).

Anal. Calcd. for $C_{18}H_{22}N_6O_4$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.91; H, 6.01; N, 21.57.

1,6-Dibenzylaminocarbonyl-5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1′,5′-*d*]-pyrazine (**9b**).

In a similar manner, **9b** was obtained from **3b** in a 35% yield; ir (Nujol): ν max 1730 cm^{-1} (carbonyl imidazolide); nmr (DMSO): δ 4.52 (d, 4H, -NHC*H*$_2$-), 7.27-7.39 (m, 10H, -Ph), 8.97 (s, 2H, imidazole C$_2$-H), 9.25 (br t, 2H, -CONH-); fd-ms: [M]$^+$ at m/z 454 (mol wt, 454).

In spite of attempts for purification, this compound was not obtained in an analytically pure form and analyses (C, H, N) were within ±1.5%.

4(5)-Isobutylaminocarbonyl-5(4)-phenylaminocarbonylimidazole (**5a**).

To a solution of aniline (2.3 g, 25 mmoles) in dichloromethane (100 ml), **9a** (1.93 g, 5 mmoles) was added and the mixture was stirred for 4 hours under reflux. After removal of an insoluble solid by filtration, the filtrate was concentrated *in vacuo* and a residue was dissolved in ethyl acetate (150 ml). The solution was washed with 1*N* hydrochloric acid, 2% sodium bicarbonate and water and dried (magnesium sulfate). After evaporation, a residual solid was recrystallized from ethyl acetate and petroleum ether to give 2.03 g (71%) of **5a**; nmr (DMSO): δ 0.93 (d, 6H, -CH(C*H*$_3$)$_2$), 1.92 (m, 1H, -C*H*(CH$_3$)$_2$), 3.18 (d, d, 2H, -NHC*H*$_2$CH), 6.93-7.78 (m, 5H, -Ph), 7.87 (s, 1H, imidazole C$_2$-H), 8.92 (br s, 1H, -CONH-); fd-ms: [M]$^+$ at m/z 286 (mol wt, 286).

Anal. Calcd. for $C_{15}H_{18}N_4O_2$: C, 62.92; H, 6.34; N, 19.57. Found: C, 63.17; H, 6.40; N, 19.43.

4(5)-(2,4-Dichlorobenzylaminocarbonyl)-5(4)-isobutylaminocarbonylimidazole (**5b**).

In a similar manner, 2,4-dichlorobenzylamine was allowed to react with **9a** to give **5b** in an 87% yield; nmr (DMSO): δ 0.89 (d, 6H, -CH(C*H*$_3$)$_2$), 1.80 (m, 1H, -C*H*(CH$_3$)$_2$), 3.13 (dd, 2H, -NHC*H*$_2$CH), 4.53 (d, 2H, -NHC*H*$_2$-Ph), 7.25-7.67 (m, 3H, -Ph-2, 4Cl), 7. 83 (s, 1H, imidazole C$_2$-H), 8.56 (br s, 1H, -CONH-), 9.16 (br s, 1H, -CONH-); fd-ms: [M + H]$^+$ at m/z 369 (mol wt, 368).

Anal. Calcd. for $C_{16}H_{18}Cl_2N_4O_2$: C, 52.04; H, 4.92; N, 15.18. Found: C, 52.10; H, 4.73; N, 15.23.

4(5)-Benzylaminocarbonyl-5(4)-diethylaminocarbonylimidazole (**5c**).

In a similar manner, diethylamine was allowed to react with **9b** to give **5c** in a 50% yield; nmr (DMSO): δ 1.12 (t, 6H, -CH_3), 3.53 (q, 4H, -C*H*$_2$CH$_3$), 4.49 (d, 2H, -C*H*$_2$Ph), 7.31 (m, 5H, -Ph), 7.80 (s, 1H, imidazole C$_2$-H), 9.93 (br s, 1H, -CONH-); fab-ms: [M + H]$^+$ at 301 (mol wt, 300).

Anal. Calcd. for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.85; H, 7.09; N, 18.46.

(2*S*,5*R*,6*R*)-3,3-Dimethyl-6[(*R*)-2-[4(5)-isobutylaminocarbonylimidazole-5(4)-carboxamido]-2-phenylacetamido]-7-oxo-4-thia-1-azabicyclo[3,2,0]-heptane-2-carboxylic Acid (**11**).

To an ice-cooled suspension of anhydrous ampicillin (0.84 g, 2.4 mmoles) in dichloromethane (20 ml), triethylamine (0.42 ml) was added and the mixture was stirred for 30 minutes under ice-cooling. To this solution, **9a** (0.386 g, 1 mmole) was added and stirred overnight at room temperature. After removal of an insoluble solid by filtration, the filtrate was concentrated *in vacuo*. A residue was dissolved in water (25 ml) and

covered with ethyl acetate (30 ml). The *p*H of the water phase was brought to 2 with 2*N* hydrochloric acid. The organic layer was separated and the water layer was extracted by ethyl acetate (30 ml). The combined extracts were washed with water, dried (magnesium sulfate) and evaporated. A residual solid was recrystallized from ethyl acetate and petroleum ether to give 0.22 g (20%) of **11**; ir (Nujol): 1770 cm^{-1} (β-lactam); nmr (DMSO): δ 0.90 (d, 6H, -CH(C*H*$_3$)$_2$), 1.42, 1.57 (two s, each 3H, penicillin C_3-CH_3), 1.86 (m, 1H, -C*H*(CH$_3$)$_2$), 3.11 (dd, 2H, -NHC*H*$_2$CH), 4.16 (s, 1H, penicillin C_2-H), 5.26-5.58 (m, 2H, penicillin C_5-H and C_6-H), 5.87 (d, 1H, -PhC*H*-CO-), 7.02-7.57 (m, 5H, -Ph), 7.79 (s, 1H, imidazole C_2-H), 8.42, 8.66, 9.18 (three br s, each 1H, -CONH-); fab-ms: $[M + H]^+$ at m/z 543 (mol wt, 542).

Anal. Calcd. for $C_{25}H_{30}N_6SO_6 \cdot 0.8H_2O$: C, 53.90; H, 5.73; N, 15.09; S, 5.75. Found: C, 54.08; H, 5.61; N, 14.70; S, 5.64.

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REFERENCES AND NOTES

[1a] A. C. Cuckler, L. R. Chapin, C. M. Malanga, E. F. Rogers, H. J. Becker, R. L. Clark, W. J. Leanza, A. A. Pessolano, T. Y. Shen and L. H. Sarett, *Proc. Soc. Exptl. Biol. Med.*, **98**, 167 (1958); [b] L. Bauer, C. N. V. Nambury and D. Dhawan, *J. Heterocyclic Chem.*, **1**, 275 (1964); [c] J. Nematollahi, W. Guess and J. Autian, *J. Med. Chem.*, **9**, 660 (1966); [d] J. J. Baldwin and F. C. Novello, German Offen. 2,322,561 (1973); *Chem. Abstr.*, **80**, 27253y (1974); [e] K. Takahashi, N. Iguma, N. Kato and K. Mitsuhashi, *Nippon Kogaku Kaishi,* 2244 (1975); [f] J. R. Nulu and J. Nematollahi, *J. Med. Chem.*, **12**, 804 (1969); [g] S. Kasina and J. Nematollahi, *Synthesis,* 163 (1975); [h] E. Belgodere, R. Bossio, V. Parrini and R. Pepino, *Arzneim-Forsch.*, **30**, 1051 (1980); [i] E. Belgodere, R. Bossio, V. Parrini and R. Pepino, *J. Heterocyclic Chem.*, **19**, 561 (1982).

[2] N. Yasuda, H. Iwagami, E. Nakanishi, T. Nakamiya, Y. Sasaki and T. Murata, *J. Antibiot.*, **36**, 242 (1983).

[3] The ir spectra of these compounds were investigated by ft-ir.

[4] This compound was prepared by the method reported in ref [1g].

[5] The ir spectrum of 1-acetylimidazole (commercially available) exhibits ν CO at 1730 cm^{-1}.