

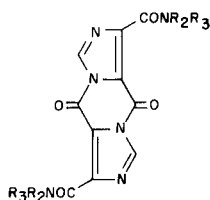
condary amine such as diethylamine resulted in a low yield. Moreover, the attempts to prepare monoanilide of **1** were unsuccessful. These differences are ascribed to the steric effect and in the case of the reaction with aniline, the less nucleophilicity of the N of aniline is also an influential factor.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

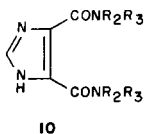
Unsymmetrical imidazole-4,5-dicarboxamide derivatives (**5**) were synthesized from **3** as follows: the monoamide **3** was treated with an excess amount of thionyl chloride in benzene containing trace amounts of dimethylformamide at 80° , and the cyclic dimerization product (**9**) was isolated as 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, $R_2 = \text{H}$, $R_3 = \text{CH}_2\text{CH}(\text{CH}_3)_2$

b, $R_2 = \text{H}$, $R_3 = \text{CH}_2\text{Ph}$

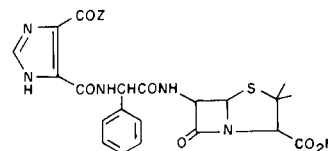


10

The novel diimidazopyrazine derivative thus prepared (**9**) was heated with an excess of appropriate amine in dichloromethane under reflux. After concentration of the re-

action 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, $Z = \text{NHCH}_2\text{CH}(\text{CH}_3)_2$

12, $Z = \text{OH}$

13, $Z = \text{OC}_2\text{H}_5$

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} ($-\text{COOC}_2\text{H}_5$); nmr (DMSO): δ 1.31 (t, 3H, $-\text{CH}_3$), 4.29 (q, 2H, $-\text{CH}_2-$), 7.83 (s, 1H, imidazole $\text{C}_2\text{-H}$); fd-ms: $[\text{M} + \text{H}]^+$ at m/z 185 $[2\text{M} + \text{H}]^+$ at m/z 369 (mol wt, 184).

Anal. Calcd. for $\text{C}_7\text{H}_8\text{N}_2\text{O}_4$: 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 pH 2 with 2N 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, $-\text{CH}(\text{CH}_3)_2$), 1.93 (m, 1H, $-\text{CH}$), 3.18 (dd, 2H, $-\text{CH}_2-\text{CH}$), 8.03 (s, 1H, imidazole $\text{C}_2\text{-H}$), 9.33 (br t, 1H, $-\text{CONH}-$); fd-ms: $[\text{M} + \text{H}]^+$ at m/z 212 (mol wt, 211).

Anal. Calcd. for $\text{C}_9\text{H}_{13}\text{N}_3\text{O}_3$: 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, $-\text{CH}_2\text{-Ph}$), 7.10-7.50 (m, 5H, $-\text{Ph}$), 8.03 (s, 1H, imidazole $\text{C}_2\text{-H}$), 9.90 (br t, 1H, $-\text{CONH-}$); fd-ms: $[\text{M}]^+$ at m/z 245 (mol wt, 245).

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_3$: 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, $-\text{CH}_2\text{CH}_3$), 3.90 (q, 4H, $-\text{CH}_2\text{CH}_3$), 7.90 (s, 1H, imidazole $\text{C}_2\text{-H}$).

Anal. Calcd. for $\text{C}_9\text{H}_{13}\text{N}_3\text{O}_3$: 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, $-\text{CH}_2\text{-Ph}$), 3.70 (s, 3H, $-\text{COOCH}_3$), 4.85 (m, 1H, $-\text{NH-CH-CO}_2$), 7.30 (br s, 5H, $-\text{Ph}$), 8.02 (s, 1H, imidazole $\text{C}_2\text{-H}$), 10.07 (br d, 1H, $-\text{CONH-}$).

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_5$: 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 pH 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 pH at 6.0-7.5 by adding 13.5% sodium hydroxide. After stirring for 1 hour under ice-cooling, the pH 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, $-\text{CH}_2\text{-SO}_3$), 3.83 (t, 2H, $-\text{NH-CH}_2$), 7.80 (s, 1H, imidazole $\text{C}_2\text{-H}$).

Anal. Calcd. for $\text{C}_7\text{H}_8\text{N}_3\text{O}_6\text{SNa} \cdot 1.3\text{H}_2\text{O}$: 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 1N 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 ($-\text{COOC}_2\text{H}_5$), 1659 cm^{-1} ($-\text{CONH-}$); nmr (DMSO): δ 1.32 (t, 3H, $-\text{CH}_3$), 4.30 (q, 2H, $-\text{OCH}_2$), 4.58 (d, 2H, $-\text{NHCH}_2$), 7.30-7.69 (m, 3H, $-\text{Ph-2, 4Cl}$), 7.81 (s, 1H, imidazole- $\text{C}_2\text{-H}$), 10.07 (br s, 1H, $-\text{CONH-}$); fd-ms: $[\text{M} + \text{H}]^+$ at m/z 342 (mol wt, 341).

Anal. Calcd. for $\text{C}_{14}\text{H}_{13}\text{Cl}_2\text{N}_3\text{O}_3$: 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 ($-\text{COOCH}_3$), 1670 cm^{-1} ($-\text{CONHO-}$); nmr (DMSO): δ 3.78 (s, 3H, $-\text{CH}_3$), 4.90 (s, 2H, $-\text{OCH}_2$), 7.37 (m, 5H, $-\text{Ph}$), 7.92 (s, 1H, imidazole $\text{C}_2\text{-H}$).

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_4$: 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-5H,10H-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 imidazolid); nmr (DMSO): δ 0.96 (d, 12H, $-\text{CH}(\text{CH}_3)_2$), 1.88 (m, 2H, $-\text{CH}(\text{CH}_3)_2$), 3.13 (dd, 4H, $-\text{NHCH}_2$), 8.63 (br t, 2H, $-\text{CONH-}$), 8.88 (s, 2H, imidazole $\text{C}_2\text{-H}$); fab-ms: $[\text{M} + \text{H}]^+$ at m/z 387 (mol wt, 386).

Anal. Calcd. for $\text{C}_{18}\text{H}_{22}\text{N}_6\text{O}_4$: 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-5H,10H-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 imidazolid); nmr (DMSO): δ 4.52 (d, 4H, $-\text{NHCH}_2$), 7.27-7.39 (m, 10H, $-\text{Ph}$), 8.97 (s, 2H, imidazole $\text{C}_2\text{-H}$), 9.25 (br t, 2H, $-\text{CONH-}$); fd-ms: $[\text{M}]^+$ 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 $\pm 1.5\%$.

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 1N 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, $-\text{CH}(\text{CH}_3)_2$), 1.92 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 3.18 (d, 2H, $-\text{NHCH}_2\text{CH}$), 6.93-7.78 (m, 5H, $-\text{Ph}$), 7.87 (s, 1H, imidazole $\text{C}_2\text{-H}$), 8.92 (br s, 1H, $-\text{CONH-}$); fd-ms: $[\text{M}]^+$ at m/z 286 (mol wt, 286).

Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_2$: 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, $-\text{CH}(\text{CH}_3)_2$), 1.80 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 3.13 (dd, 2H, $-\text{NHCH}_2\text{CH}$), 4.53 (d, 2H, $-\text{NHCH}_2\text{-Ph}$), 7.25-7.67 (m, 3H, $-\text{Ph-2, 4Cl}$), 7.83 (s, 1H, imidazole $\text{C}_2\text{-H}$), 8.56 (br s, 1H, $-\text{CONH-}$), 9.16 (br s, 1H, $-\text{CONH-}$); fd-ms: $[\text{M} + \text{H}]^+$ at m/z 369 (mol wt, 368).

Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{Cl}_2\text{N}_4\text{O}_2$: 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, $-\text{CH}_3$), 3.53 (q, 4H, $-\text{CH}_2\text{CH}_3$), 4.49 (d, 2H, $-\text{CH}_2\text{Ph}$), 7.31 (m, 5H, $-\text{Ph}$), 7.80 (s, 1H, imidazole $\text{C}_2\text{-H}$), 9.93 (br s, 1H, $-\text{CONH-}$); fab-ms: $[\text{M} + \text{H}]^+$ at 301 (mol wt, 300).

Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_4\text{O}_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.85; H, 7.09; N, 18.46.

(2S,5R,6R)-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

REFERENCES AND NOTES

covered with ethyl acetate (30 ml). The pH 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, $-\text{CH}(\text{CH}_3)_2$), 1.42, 1.57 (two s, each 3H, penicillin C_5 - CH_3), 1.86 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 3.11 (dd, 2H, $-\text{NHCH}_2\text{CH}$), 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, $-\text{PhCH-CO-}$), 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, $-\text{CONH-}$); fab-ms: $[\text{M} + \text{H}]^+$ at m/z 543 (mol wt, 542).

Anal. Calcd. for $\text{C}_{28}\text{H}_{30}\text{N}_6\text{SO}_6 \cdot 0.8\text{H}_2\text{O}$: 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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- [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} .