BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 1254—1256 (1972)

Oxazolidone Derivatives of Hydroxyamino Acids. VII.[1] Syntheses and Properties of DL-*trans*-3-Benzoyl-5-methyl-2-oxo-oxazolidine-4-carboxylic Acid and Its Derivatives.

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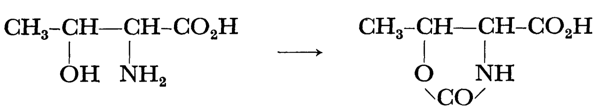
(Received September 18, 1971)

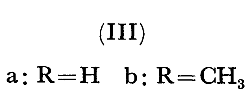
Threonine (I) was cyclized by the reaction with phosgene to give an oxazolidonecarboxylic acid (II).[2] It was thought to be of interest to study the reaction of phosgene with *N*-benzoylthreonine. The reaction of II with benzoyl chloride as well as the formation of *trans*-*N*-benzoylmethyloxazolidonecarboxylic acid (IVa) by direct cyclization of *N*-benzoyl-DL-threonine (IIIa) with phosgene in alkaline solution were unsuccessful. According to the method given previously,[1] IIIa was treated with phosgene in benzene in the presence of *N*,*N*-dimethylaniline. The expected *O*-chlorocarbonyl compound (Va) was obtained. Cyclization of this intermediate Va to IVa was not achieved and an azlactone VI was obtained.



$$\underset{\text{OH}\ \ \text{NH}_2}{CH_3\text{-}CH\text{—}CH\text{-}CO_2H} \longrightarrow \underset{\underset{\diagdown CO \diagup}{\text{O}\ \ \ \text{NH}}}{CH_3\text{-}CH\text{—}CH\text{-}CO_2H}$$

(I) (II)

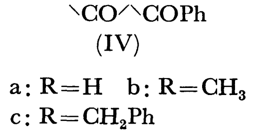
In a similar way, methyl *N*-benzoyl-DL-threoninate (IIIb) was treated with phosgene to give *O*-chlorocar-



$$\underset{\text{OH}\ \ \text{NHCOPh}}{CH_3\text{-}CH\text{—}CH\text{-}CO_2R}$$

(III)

a: R=H b: $R=CH_3$
c: $R=CH_2Ph$



$$\underset{\underset{\diagdown CO \diagup\diagdown COPh}{\text{O}\ \ \ \text{N}}}{CH_3\text{-}CH\text{—}CH\text{-}CO_2R}$$

(IV)

a: R=H b: $R=CH_3$
c: $R=CH_2Ph$

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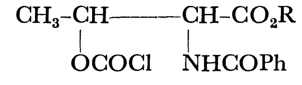
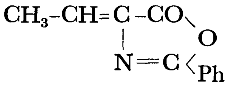
[1] Part VI: T. Inui, S. Tanaka, and M. Takino, This Bulletin, **43**, 1582 (1970).

[2] T. Kaneko and T. Inui, *Nippon Kagaku Zasshi*, **82**, 1075 (1961); T. Inui and T. Kaneko, *ibid.*, **82**, 1078 (1961).



$CH_3\text{-}\underset{\underset{OCOCl}{|}}{CH}\text{———}\underset{\underset{NHCOPh}{|}}{CH}\text{-}CO_2R$

(V)



$CH_3\text{-}CH{=}\underset{\underset{N=C\langle_{Ph}}{|}}{C}\text{-}CO\diagdown O$

(VI)

a: R=H b: R=CH_3
c: R=CH_2Ph

bonyl derivative Vb. Compound Vb was cyclized to methyl DL-*trans*-3-benzoyl-5-methyl-2-oxo-oxazolidine-4-carboxylate (IVb) when refluxed in xylene for 1—2 hr. When IVb was hydrolyzed in alkaline medium, elimination of the benzoyl group took place and DL-*trans*-5-methyl-2-oxo-oxazolidine-4-carboxylic acid (II) was obtained in the place of IVa. From this finding, the selective cleavage of threonine peptides is suggested.[3]

Benzyl *N*-benzoyl-DL-threoninate (IIIc) was converted with phosgene into the corresponding oxazolidone ester IVc through its *O*-chlorocarbonyl intermediate Vc. Catalytic hydrogenation of IVc with 5% palladium on carbon gave an acidic IVa. Treatment of IVa with thionyl chloride in benzene gave acid chloride (VII) which was converted into methyl ester IVb. VII was treated with aniline to give its an ilide. It is expected that this result will be useful for the synthesis of peptides containing modified threonine residues.

Experimental[4]

Reaction of N-*Benzoyl*-DL-*threonine (IIIa) with Phosgene. a) In Alkaline Solution*: To a solution of IIIa[5] (5.5 g, 0.025 mol) in 10% aqueous potassium hydroxide solution (60 m*l*, 0.107 mol) was added a solution of phosgene (3.0 g, 0.030 mol) in toluene (10 m*l*) at 0°C for 35 min and the reaction mixture was stirred at 0°C for 2 hr. After the organic layer had been removed, IIIa was recovered on acidification of the aqueous layer with concentrated hydrochloric acid. Yield, 3.9 g (recovery 71%), mp 146—147°C. A mixed melting point with an authentic sample showed no depression. The IR spectra were also identical with those of an authentic sample.

b) In Benzene Solution: Phosgene was passed through a suspension of IIIa (4.5 g, 0.02 mol) and *N*,*N*-dimethylaniline (1.0 g, 0.008 mol) in benzene (70 m*l*) at 5—8°C for 30 min. The reaction mixture was stirred for 4 hr below 20°C. Carbon dioxide (or nitrogen) was passed through the solution to remove excess phosgene. The benzene solution was washed with dilute hydrochloric acid and water. The dried solution was evaporated *in vacuo* to give Va. Yield, 3.9 g (67%), mp 125—126°C (decomp.) after recrystallization from ethyl acetate - petroleum ether (50—90°C).

Found: C, 50.94; H, 4.43; N, 5.02; Cl, 12.21%. Calcd for $C_{12}H_{12}O_5NCl$: C, 50.45; H, 4.23; N, 4.96; Cl, 12.41%.

N-*Benzoyl-2-aminocrotonic Acid Azlactone (VI)*. A solution of Va (0.3 g, 0.001 mol) in xylene (3 m*l*) was refluxed for 1.3 hr and evaporated *in vacuo* to give VI. Yield, 0.15 g (76%). It gave a negative Beilstein's test. Its IR spectra were identical with those of an authentic sample.[6]

Methyl N-*Benzoyl*-O-*chlorocarbonyl*-DL-*threoninate (Vb)*. In a similar way to that for the preparation of Va, phosgene was passed through a suspension of IIIb[7] (4.7 g, 0.02 mol) and *N*,*N*-dimethylaniline (2.4 g, 0.02 mol) in benzene (70 m*l*) at 5—8°C for 30 min. Vb was obtained as crystals from the reaction mixture. Yield, 4.9 g (83%), mp 81—82°C after recrystallization from benzene - petroleum ether (50—90°C).

Found: C, 52.35; H, 4.67; N, 4.97; Cl, 12.34%. Calcd for $C_{13}H_{14}O_5NCl$: C, 52.09; H, 4.71; N, 4.70; Cl, 11.84%.

Methyl DL-trans-*3-Benzoyl-5-methyl-2-oxo-oxazolidine-4-carboxylate (IVb)*. A solution of Vb (6.0 g, 0.02 mol) in xylene (60 m*l*) was refluxed for 1.5 hr. The solution was evaporated *in vacuo* to give IVb as crystals. Yield, 4.0 g (75%), mp 115—117°C and 116—117°C after recrystallization from ethyl acetate - petroleum ether (50—90°C). IR (Nujol mull): 1800, 1780 (C=O in the oxazolidone ring), 1750 (C=O in the ester group), 1680 cm^{-1} (C=O in the benzoyl group).

Found: C, 59.36; H, 5.03; N, 5.16%. Calcd for $C_{13}H_{13}O_5N$: C, 59.31; H, 4.98; N, 5.32%.

Hydrolysis of IVb with hydrochloric acid (1: 1, v/v) gave DL-threonine. The properties of this sample were identical with those of an authentic sample.

DL-trans-*5-Methyl-2-oxo-oxazolidine-4-carboxylic Acid (II)*. To a suspension of IVb (1.3 g, 0.005 mol) in methanol (5 m*l*) was added 1 N methanolic potassium hydroxide solution (6.0 m*l*, 0.006 mol) and the reaction mixture was kept for 3.5 hr at room temperature. After diluting with water, the separated oil was extracted with ethyl acetate. Methyl benzoate was isolated from the extract as a sweet-smelling oil. Yield, 0.5 g (70%). Its IR spectra were identical with those of an authentic sample.

The aqueous layer separated from ethyl acetate extract was acidified with concentrated hydrochloric acid and evaporated *in vacuo* to dryness. The residue was extracted three times with hot ethyl acetate, and the evaporation of the combined extracts gave II. Yield, 0.5 g (70%), mp 126—127°C after recrystallization from ethyl acetate; lit,[2] mp 127—128°C. A mixed melting point with an authentic sample showed no depression.

Benzyl N-*Benzoyl*-O-*chlorocarbonyl*-DL-*threoninate (Vc)*. In a similar way to that for the preparation of Va, phosgene was passed through a suspension of IIIc[8] (12.5 g, 0.04 mol) and *N*,*N*-dimethylaniline (4.8 g, 0.04 mol) in benzene (140 m*l*) at 5°C for 30 min. Vc was obtained as crystals from the reaction mixture. Yield, 12.4 g (83%), mp 82—83°C after recrystallization from benzene - petroleum ether (50—90°C).

Found: C, 60.96; H, 4.92; N, 3.43; Cl, 9.23%. Calcd for $C_{19}H_{18}O_5NCl$: C, 60.72; H, 4.83; N, 3.73; Cl, 9.43%.

Benzyl DL-trans-*3-Benzoyl-5-methyl-2-oxo-oxazolidine-4-carboxylate (IVc)*. A solution of Vc (10.0 g, 0.026 mol) in xylene (100 m*l*) was refluxed for 2 hr. IVc was obtained from the solution. Yield, 7.1 g (76%), mp 69—70°C after recrystallization from benzene - petroleum ether (50—90°C). IR (Nujol mull): 1800 (C=O in the oxazolidone ring), 1755 (C=O in the ester group), 1680 cm^{-1} (C=O in the benzoyl group).

Found: C, 69.67; H, 5.34; N, 3.62; sol., 9.53%. Calcd for $C_{19}H_{17}O_5N\cdot 1/6C_6H_6$: C, 69.83; H, 5.33; N, 3.70; sol., 10.32%.

Drying over phosphorus pentoxide *in vacuo* raised the melting point to 79—80°C.

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3) T. Kaneko and T. Inui, This Bulletin, **36**, 1541 (1963); T. Kaneko, S. Kusumoto, T. Inui, and T. Shiba, *ibid.*, **41**, 2155 (1968).

4) All melting points are uncorrected.

5) H. D. West and H. E. Carter, *J. Biol. Chem.*, **119**, 109 (1937).

6) H. E. Carter, P. Handler, and D. B. Melville, *ibid.*, **128**, 359 (1939).

7) K. Pfister, C. A. Robinson, A. C. Shabica, and M. Tishler, *J. Amer. Chem. Soc.*, **70**, 2297 (1948); **71**, 1101 (1949).

8) T. Inui, *Science Reports Osaka Univ.*, **18**, 19 (1969).

DL-trans-*3-Benzoyl-5-methyl-2-oxo-oxazolidine-4-carboxylic Acid (IVa).* A suspension of IVc (5.7 g, 0.016 mol) and 5% palladium on carbon (0.7 g) in a mixture of methanol (150 m*l*) and water (50 m*l*) was shaken for 2.5 hr in an atmosphere of hydrogen. After the catalyst had been removed, the filtrate was evaporated *in vacuo* to provide an oil which was crystallized by seeding. Yield, 6.5 g (86%), mp 151—153°C and 154—155°C after recrystallization from water. IR (Nujol mull): 1805 (C=O in the oxazolidone ring), 1730 (C=O in the carboxyl group), 1675 cm^{-1} (C=O in the benzoyl group).

Found: C, 57.90; H, 4.47; N, 5.58%. Calcd for $C_{12}H_{11}O_5N$: C, 57.83; H, 4.45; N, 5.62%.

DL-trans-*3-Benzoyl-5-methyl-2-oxo-oxazolidine-4-carboxylic Chloride (VII).* A suspension of IVa (1.5 g, 0.006 mol) in a mixture of thionyl chloride (3 m*l*) and benzene (10 m*l*) was warmed on a water bath for 2.5 hr. The resulting solution was evaporated *in vacuo* to give crystals. Yield, 1.6 g (100%), mp 67—70°C. IR (Nujol mull): 1810, 1795 (C=O in the oxazolidone ring and the acid chloride group), 1690 cm^{-1} (C=O in the benzoyl group).

Treatment of VII with methanol gave IVb in good yield, mp 113—115°C. Its IR spectra were identical with those of the product obtained from Vb by the cyclization process.

Treatment of VII with aniline in benzene gave DL-*trans*-3-benzoyl-5-methyl-2-oxo-oxazolidine-4-carboxanilide in a yield of 70%, mp 122—123°C after recrystallization from dioxane-petroleum ether (50—90°C).

Found: C, 63.28; H, 6.34; N, 6.37%. Calcd for $C_{18}H_{16}O_4N_2 \cdot 1.5C_4H_8O_2$: C, 63.14; H, 6.18; N, 6.14%.