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Oxazolidone Derivatives of Hydroxyamino Acid. VI.[1] Reactions of Phosgene on *N*-Acylserine Esters

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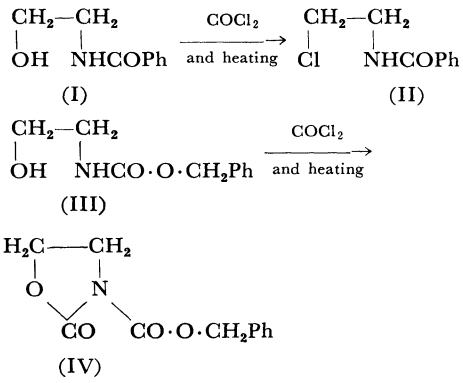
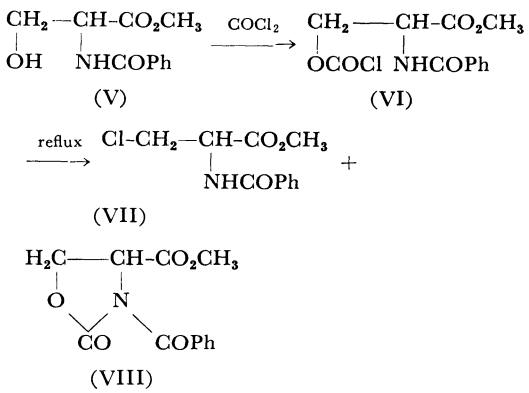
Treatment of *N*-(β-hydroxyethyl)-benzamide (I), *i.e.* *N*-benzoyl derivative of β-hydroxyethylamine, with phosgene and subsequent heating afforded *N*-(β-chloroethyl)-benzamide (II) through the corresponding *O*-chlorocarbonyl derivative. However, under the same condition, benzyl *N*-(β-hydroxyethyl)-carbamate (III) yielded only 3-benzyloxy-



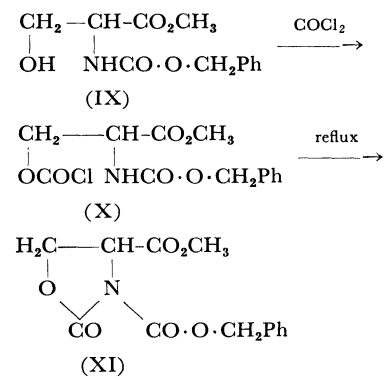
carbonyl(cbz)-2-oxo-oxazolidine (IV).[2] The present paper is concerned with the reactions of phosgene with *N*-benzoyl- and *N*-cbz-derivatives of methyl L-serinate (V and IX), having structures similar to those of I and III respectively.

Bergel reported that the reaction of benzyl *N*-cbz-DL-serinate with phosgene in benzene gave benzyl *N*-cbz-*O*-chlorocarbonyl-DL-serinate.[3] In the present study, methyl *N*-benzoyl-L-serinate (V), obtained from methyl L-serinate and benzoyl chloride, was converted with phosgene to the *O*-chlorocarbonyl derivative (VI). Reflux of VI in xylene provided a crystalline product, which was shown to be a mixture of methyl L-2-benzamido-3-chloropropionate (VII) and methyl 3-benzoyl-L-2-oxo-oxazolidine-4-carboxylate (VIII) by means of thin-layer chromatography with silica gel G (TLC). Separation of VII from VIII was achieved by using a column with silica gel, and by eluting it with a mixture of chloroform and ethyl acetate (9 : 1, v/v). The structures of compounds, VII and VIII, were



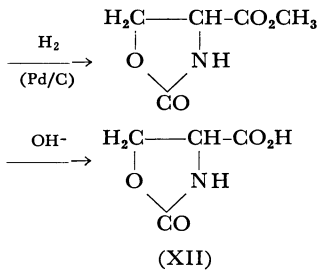
confirmed by their infrared spectra and nuclear magnetic resonance (NMR) spectra.

In a similar manner, the oily methyl *N*-cbz-L-serinate (IX) was converted with phosgene to the corresponding *O*-chlorocarbonyl compound (X). In this case, methyl 3-cbz-L-2-oxo-oxazolidine-4-carboxylate (XI) was obtained as the sole product by heating X in xylene. The structure of XI was also confirmed by elemental analysis and by a study of its



NMR spectra. Catalytic hydrogenation and subsequent hydrolysis of XI gave L-2-oxo-oxazolidine-4-carboxylic acid (XII). The properties tested on XII were identical with those of the authentic sample[4,5].

1) Part V: T. Inui, Y. Ohta, T. Ujike, H. Katsura and T. Kaneko, This Bulletin, **41**, 2148 (1968).
2) D. Ben-Ishai, *J. Amer. Chem. Soc.*, **78**, 4962 (1956).
3) F. Bergel and R. Wade, *J. Chem. Soc.*, **1959**, 941.
4) T. Kaneko, I. Takeuchi and T. Inui, This Bulletin, **41**, 974 (1968).
5) T. Saito, *ibid.*, **37**, 624 (1964).



(XII)

Experimental*1

Methyl *N*-Benzoyl-L-serinate (V). To a cold solution of methyl L-serinate hydrochloride (15.6 g, 0.1 mol) in water (225 m*l*), sodium hydrogen carbonate (25.2 g, 0.3 mol) and benzoyl chloride (16.0 m*l*, 0.13 mol) were added in succession. The reaction mixture was stirred for 2—3 hr at room temperature, and the resulting clear solution was extracted twice with ethyl acetate. Evaporation of the dried extract provided V as crystals. Yield, 18.0 g (81%), mp 85—86°C after recrystallization from benzene, $[\alpha]_D^{20}$ +16.0° (*c* 1.25, 95% ethanol); lit,[6] mp 84—86°C, $[\alpha]_D^{26}$ +17.7° (*c* 1, 95% ethanol).

Found: C, 59.27; H, 5.95; N, 6.34%. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27%.

Methyl *N*-Benzoyl-*O*-chlorocarbonyl-L-serinate (VI). Phosgene was passed through a solution of V (13.4 g, 0.06 mol) and *N*,*N*-dimethylaniline (7.3 g, 0.06 mol) in benzene (240 m*l*) at 5—10°C for 20 min, and the mixture was stirred for 2—3 hr below 20°C. Nitrogen was passed through the solution to remove the excess phosgene. The benzene solution was washed with dilute hydrochloric acid. The dried solution was evaporated *in vacuo* to give VI. Yield, 15.1 g (88%), mp 95—96°C (decomp.) after recrystallization from benzene.

Found: C, 50.28; H, 3.86; N, 4.85%. Calcd for $C_{12}H_{12}NO_5Cl$: C, 50.46; H, 4.23; N, 4.90%.

Treatment of a solution of VI in benzene with an etheral solution of aniline gave methyl *N*-benzoyl-*O*-(*N*-phenylcarbamoyl)-L-serinate; mp 134°C, $[\alpha]_D^{20}$ −24.1° (*c* 2.36, *N*,*N*-dimethylformamide).

Found: C, 63.16; H, 5.22; N, 7.76%. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18%.

Methyl L-2-Benzamido-3-chloropropionate (VII) and Methyl 3-Benzoyl-L-2-oxo-oxazolidine-4-carboxylate (VIII). A solution of VI (2.86 g, 0.01 mol) in xylene (60 m*l*) was refluxed for 4.5 hr. The solution was evaporated *in vacuo* to give an oil which was solidified by seeding (wt, 2.44 g). It gave a strong positive Beilstein's test and exhibited two spots on TLC. The product in a minimum amount of chloroform was adsorbed on a column (diameter 1.6 cm) of silica gel (50 g) and eluted with a mixture of chloroform and ethyl acetate (9: 1, v/v). Aliquots of the effluent fractions were subjected to TLC.

The fractions, exhibiting a single spot (R_f∼0.50)*2 on TLC, were combined and evaporated *in vacuo* to give VII as crystals. Yield, 0.62 g (25.6%) mp 112—114°C. Recrystallization from petroleum ether raised the melting point to 114—116°C, $[\alpha]_D^{20}$ −12.9° (*c* 1.67, 95% ethanol); lit,[6] mp 114—115.5°C,$[\alpha]_D^{23}$ −14° (*c* 1, 95% ethanol).

IR (Nujol mull): 3280, 1635, 1540 (–CONH– in the amide group), 1735 cm^{-1} (C=O in the ester group).

NMR (Deuterochloroform solution, 60 MHz): 3.84 (singlet, CH_3– peak in the ester group), 4.03 (doublet, *J*=3.2 Hz, $-CH_2-$ peak in the Cl–CH_2–CH group), 5.16 (quintet, >CH peak in the $-CH_2-CH-NH-$ group), 6.85—7.20 (broad, NH peak), 7.25—7.90 ppm (multiplet, C_6H_5– peak).

Found: C, 54.46; H, 4.70; N, 5.50%. Calcd for $C_{11}H_{12}NO_3Cl$: C, 54.67; H, 5.00; N, 5.80%.

The other fractions exhibiting a single spot (R_f∼0.25)*2 on TLC, were also combined and evaporated *in vacuo* to obtain VIII as prisms. Yield, 0.25 g (10.0%), mp 123—124°C. For analysis, it was recrystallized from benzene-petroleum ether (2: 1), mp 124.0—124.5°C, $[\alpha]_D^{21}$ −10.6° (*c* 2.08, methanol).

IR (Nujol mull): 1790 (C=O in the oxazolidone ring), 1750, 1730 (C=O in the ester group), 1680 cm^{-1} (C=O in the benzoyl group).

NMR (Deuterochloroform solution, 60 MHz): 3.80 (singlet, CH_3– peak in the ester group), 4.17—5.15 (multiplet, $-CH_2-CH$ peak in the oxazolidone ring), 7.35—7.75 ppm (multiplet, C_6H_5– peak).

Found: C, 57.58; H, 4.40; N, 5.89%. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62%.

Methyl *N*-Cbz-L-serinate (IX). Applying the method for the preparation of dimethyl *N*,*N*′-biscbz-L-cystinate by Zervas[7], a solution of methyl L-serinate hydrochloride (3.1 g, 0.02 mol) in a mixture of 30% aqueous potassium hydrogen carbonate solution (30 m*l*) and chloroform (30 m*l*) was treated with cbz-chloride (4.0 m*l*) at 5°C for 1 hr. The chloroform layer was treated with pyridine (1.0 m*l*) at 5°C for 10 hr and then washed successively with dilute sulfric acid, water and dilute aqueous potassium hydrogen carbonate solution. Evaporation of the dried solution gave IX as syrup. Yield, 4.3 g (85%).

Methyl *N*-Cbz-*O*-chlorocarbonyl-L-serinate (X). In a way similar to that described for the preparation of VI, phosgene was passed through a solution of IX (5.0 g, 0.02 mol) and *N*,*N*-dimethylaniline (2.4 g, 0.02 mol) in benzene (80 m*l*) for 20 min at 5—10°C. From the reaction mixture, X was obtained as white crystals. Yield, 5.1 g (82%), mp 65—67°C.

Found: C, 49.98; H, 4.33; N, 3.85%. Calcd for $C_{13}H_{14}NO_6Cl$: C, 49.46; H, 4.47; N, 4.44%.

Methyl *N*-cbz-*O*-(*N*-phenylcarbamoyl)-L-serinate was obtained by treatment of aniline on X, mp 127—128°C and 128—129°C after recrystallization from benzene, $[\alpha]_D^{20}$ −23.6° (*c* 1.25, *N*,*N*-dimethylformamide).

Found: C, 61.08; H, 5.39; N, 7.40%. Calcd for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52%.

Methyl 3-Cbz-L-2-oxo-oxazolidine-4-carboxylate (XI). A solution of X (2.5 g, 0.008 mol) in xylene (50 m*l*) was refluxed for 5 hr. The solution was evaporated *in vacuo* to leave crystals exhibiting a single spot (R_f∼0.45)*2 on TLC. Yield, 1.6 g (72%), mp 63—64°C and 64—65°C after recrystallization from ether, $[\alpha]_D^{20}$ −80.1° (*c* 3.39, methanol).

IR (Nujol mull): 1810 (C=O in the oxazolidone ring), 1745 (C=O in the ester group), 1730 cm^{-1} (C=O in the cbz group).

*1 All melting points are uncorrected.

6) E. M. Fry, *J. Org. Chem.*, **15**, 438 (1950).

*2 The R_f values refer to TLC with the chloroform-ethyl acetate (9: 1, v/v) as solvent system.

7) L. Zervas and L. Photaki, *J. Amer. Chem. Soc.*, **84**, 3887 (1962).

NMR (Deuterochloroform solution, 60 MHz): 3.73 (singlet, CH_3– peak in the ester group), 4.14—4.94 (multiplet, $-CH_2-\underset{|}{C}H-$ peak in the oxazolidone ring), 5.30 (slightly split singlet, $-CH_2-$ peak in the cbz group) 7.35 ppm (singlet, C_6H_5- peak).

Found: C, 56.01; H, 4.62; N, 5.12%. Calcd for $C_{13}H_{13}NO_6$: C, 55.92; H, 4.69; N, 5.02%.

L-2-Oxo-oxazolidine-4-carboxylic Acid (XII). A stream of hydrogen was passed through a solution of XI (4.2 g, 0.015 mol) in a mixture of methanol (50 m*l*) and water (10 m*l*) for 3 hr in the presence of 10% palladium on carbon (1.0 g). After the catalysts had been removed by filtration, the filtrate was evaporated *in vacuo* to provide an oil (wt, 1.4 g). Into a solution of the oil in methanol (35 m*l*), 1 N potassium hydroxide (9.5 m*l*, 0.0095 mol) was added and the mixture was stirred for 1.5 hr at room temperature. The solvent was evaporated *in vacuo* to a small volume, and the residual solution was diluted with water. The aqueous solution was extracted with ethyl acetate and acidified with 1 N hydrochloric acid (10 m*l*). The acidic solution was evaporated *in vacuo* to dryness and the residue was extracted three times with hot ethyl acetate. The dried extract was evaporated *in vacuo* to give XII as crystals. Yield, 1.0 g (51%), mp 114—117°C and 118—119°C after recrystallization from ethyl acetate-petroleum ether, $[\alpha]_D^{20}$ −18.2° (*c* 2.23, water); lit,[4] mp 118.5—120°C, $[\alpha]_D^{22.5}$ −17.7° (*c* 3.44, water).

The mixed melting point with an authentic sample was not depressed. The results obtained by means of infrared spectra were also identical with those of an authentic sample.

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