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4-Amino-2-oxazolidinones

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Thermal cyclization of β-haloalkylidenebisbenzylcarbamates (III) and subsequent hydrogenolysis of the intermediate 4-carbobenzoxyamino-2-oxazolidinones (IV) afford 4-amino-2-oxazolidinones (V). Some of the chemical properties of the aminooxazolidinones are also described.

Cycloserine (Oxamycin) a naturally occuring antibiotic is an aminoisooxazolidinone derivative (I) (1). In the present paper the synthesis of the isomer 4-amino-2-oxazolidinone (II) and other 2-oxazolidinones bearing amino and alkoxyl functional groups in the 4 position is described.

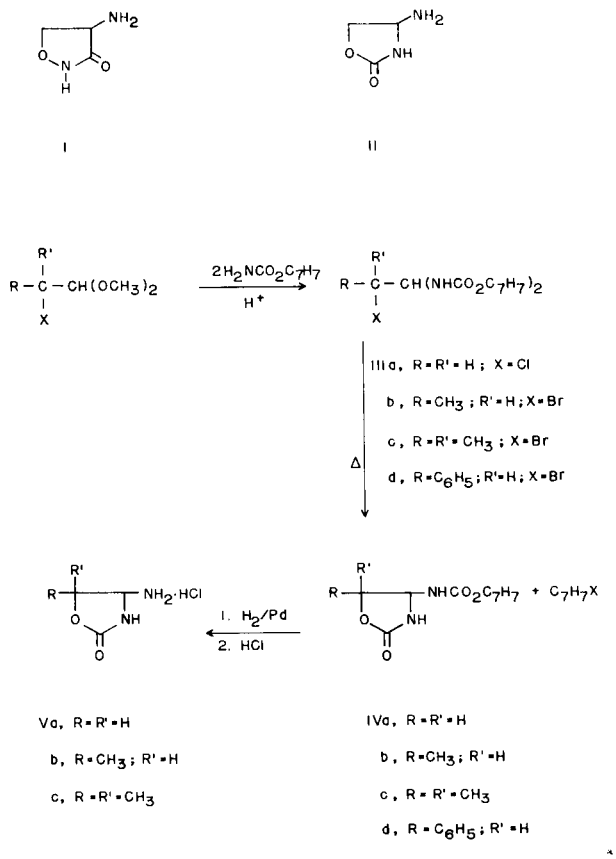
The 4-amino-2-oxazolidinones were prepared by using one general procedure. β-Haloacetals were condensed with benzylcarbamate in boiling benzene and in the presence of β-naphthalenesulfonic acid, to give β-haloalkylidenebisbenzylcarbamates (III). The bisadducts cyclized on heating in an inert solvent to the corresponding 4-carbobenzoxyamino-2-oxazolidinones (IV) (2). The carbobenzoxyamino-oxazolidinones thus obtained, showed two characteristic carbonyl absorptions at 1725 cm^{-1} (carbamate) and 1765 cm^{-1} (oxazolidinone). The carbobenzoxy protecting groups were then removed by catalytic hydrogenolysis in glacial acetic acid and the 4-amino-2-oxazolidinones were isolated as their hydrochlorides (V). The 4-amino-2-oxazolidinones were further characterized as their *N*-benzoyl and *N*-phenylacetyl derivatives. These derivatives also showed two characteristic carbonyl absorptions at 1680 cm^{-1} (amide) and 1765 cm^{-1} (oxazolidinone).

N-Carbobenzoxy-*l*-serine azide was reported to undergo, on heating, rearrangement and cyclization to the optically active 4-carbobenzoxyamino-2-oxazolidinone (3,4).

In addition to 4-amino-2-oxazolidinone itself, 5-methyl and 5,5-dimethyl-4-amino-2-oxazolidinones were also prepared by the above procedure. β-Bromo-β-phenylethylidenebisbenzylcarbamate (IIId) and β-bromo-β-phenylethylidenebisethylcarbamate cyclized on heating to the corresponding 4-carbalkoxy-5-phenyl-2-oxazolidinone. The former compound (IVd) has one endocyclic and one exocyclic *O*-benzyl bonds and afforded, therefore, on catalytic hydrogenolysis, β-phenylethylamine. The 4-carbethoxyamino-5-phenyl-2-oxazolidinone lost ethylcarbamate when heated in toluene solution, in the presence of β-naphthalenesulfonic acid, to give 5-phenyl-2(3)-oxazolidone. This 5-phenyl-2-oxazolidone afforded ω-aminoacetophenone on acid hydrolysis.

The amino group in 4-amino-2-oxazolidinone hydrochloride (Va) was found to exchange, in boiling alcohol solutions for alkoxy groups. Thus, 4-methoxy, 4-ethoxy and 4-benzyloxy-2-oxazolidinones were prepared. The 4-alkoxy-2-oxazolidinones showed only one carbonyl absorption at 1760 cm^{-1}.

The free 4-amino-2-oxazolidinones were unstable, they gradually lost ammonia in solution to give crystalline water soluble products which were insoluble in the ordinary organic solvents.



EXPERIMENTAL

β-Chloroethylidenebisbenzylcarbamate (IIIa).

A solution of dimethyl chloroacetal (13 g.), benzylcarbamate (30.2 g.), glacial acetic acid (12 g.), and β-naphthalenesulfonic acid (1 g.) in benzene (200 ml.) was refluxed for 5 hours and the water formed was removed by azeotropic distillation. Ethyl acetate (200 ml.) was added and the combined benzene-ethyl acetate solution was washed with a saturated bicarbonate solution and water and dried over anhydrous sodium sulfate. The product obtained, after removal of the organic solvent *in vacuo*, was crystallized from methanol. The yield was 19.0 g. (51%), m.p. 140°.

Anal. Calcd. for $C_{18}H_{19}ClN_2O_4$: N, 7.72; Cl, 9.77. Found: N, 7.42; Cl, 9.99.

4-Carbobenzoxyamino-2-oxazolidinone (IVa).

A solution of β-chloroethylidenebisbenzylcarbamate (10 g.) in *p*-cymene (300 ml.) was refluxed for 9 hours. The solution was then cooled to room temperature and hexane (300 ml.) added. After standing overnight in the refrigerator the product was filtered off and crystallized twice from benzene. The yield was 3.6 g. (61%), m.p. 126°.

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.19; H, 5.18; N, 11.70.

4-Amino-2-oxazolidinone Hydrochloride (Va).

4-Carbobenzoxyamino-2-oxazolidinone (1 g.) was catalytically hydrogenated in glacial acetic acid (20 ml.) under 4 atmospheres pressure and in the presence of 5% palladized charcoal (0.2 g.). After 5 hours the solution was filtered from the catalyst and saturated with dry hydrogen chloride. The hydrochloride, thus obtained, was precipitated with dry ether (100 ml.), filtered and washed with dry ether. The hydrochloride melted at 153-154° after crystallization from absolute ethanol and dry ether, yield 0.55 g. (95%).

Anal. Calcd. for $C_3H_7ClN_2O_2$: N, 20.22; Cl, 25.59. Found: N, 19.99; Cl, 25.68.

4-Benzamido-2-oxazolidinone.

This compound was prepared from 4-amino-2-oxazolidinone hydrochloride and benzoyl chloride by the Schotten-Baumann procedure (aqueous bicarbonate). The product melted at 198° after crystallization from ethyl acetate-hexane, yield 62%.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.58. Found: C, 58.46; H, 4.95; N, 13.61.

4-Phenylacetamido-2-oxazolidinone.

This compound was prepared from 4-amino-2-oxazolidinone hydrochloride and phenylacetyl chloride by the Schotten-Baumann procedure (aqueous bicarbonate). The product melted at 188° after crystallization from ethyl acetate, yield 71%.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.85; H, 5.43; N, 12.41.

4-Methoxy-2-oxazolidinone.

A solution of 4-amido-2-oxazolidinone hydrochloride (0.4 g.) in absolute methanol (30 ml.) was refluxed for 5 hours. The excess methanol was then evaporated and the residue crystallized from benzene-methylcyclohexane. The yield was 0.2 g. (59%), m.p. 65°.

Anal. Calcd. for $C_4H_7NO_3$: C, 41.02; H, 6.03; N, 11.96. Found: C, 41.18; H, 5.89; N, 11.99.

4-Ethoxy-2-oxazolidinone.

A solution of 4-amino-2-oxazolidinone (0.22 g.) in absolute ethanol (15 ml.) was refluxed as described above. The product melted at 45° after crystallization from benzene-hexane, yield 0.12 g. (57%).

Anal. Calcd. for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.98; H, 6.69; N, 10.85.

4-Benzyloxy-2-oxazolidinone.

A solution of 4-amino-2-oxazolidinone (5 g.) in benzyl alcohol (50 ml.) was heated at 100° for 2 hours. The excess benzyl alcohol was removed *in vacuo* (0.1 mm.) and the residue was crystallized from carbontetrachloride-hexane. The yield was 3 g. (42%), m.p. 103°.

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 61.53; H, 5.54; N, 7.27.

β-Bromopropylidenebisbenzylcarbamate (IIIb).

A solution of α-bromopropionaldehyde dimethyl acetal (10 g.), benzylcarbamate (165 g.), glacial acetic acid (6.5 g.) and β-naphthalenesulfonic acid (0.5 g.) in benzene (100 ml.) was refluxed for 2.5 hours as described above for the preparation of β-chloroethylidenebisbenzylcarbamate. The solid residue was crystallized from ethanol. The yield was 16.5 g. (72%), m.p. 164°.

Anal. Calcd. for $C_{19}H_{21}BrN_2O_4$: N, 6.65; Br, 18.97. Found: N, 6.93; Br, 19.06.

4-Carbobenzoxyamino-5-methyl-2-oxazolidinone (IVb).

A solution of β-bromopropylidenebisbenzylcarbamate (5 g.) in *ortho*-xylene (150 ml.) was refluxed for 3 hours. The solution was cooled to room temperature and hexane (150 ml.) was added. After standing overnight in the refrigerator, the solid product was filtered off and crystallized from benzene. The yield was 1.9 g. (65%); m.p. 106°.

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.35; H, 5.51; N, 11.07.

4-Amino-5-methyl-2-oxazolidinone hydrochloride (Vb).

A solution of 4-carbobenzoxyamino-5-methyl-2-oxazolidinone (0.7 g.) in glacial acetic acid (10 ml.) was catalytically hydrogenated as described above for the preparation of 4-amino-2-oxazolidinone. The hydrochloride melted at 155° after crystallization from absolute ethanol and dry ether, yield 0.4 g. (95%).

Anal. Calcd. for $C_4H_9ClN_2O_2$: N, 18.45; Cl, 23.21. Found: N, 18.21; Cl, 23.31.

4-Benzamido-5-methyl-2-oxazolidinone.

This compound was prepared from 4-amino-5-methyl-2-oxazolidinone hydrochloride and benzoyl chloride by the Schotten-Baumann procedure (aqueous bicarbonate). The product melted at 192° after crystallization from ethyl acetate-hexane, yield 65%.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.96; H, 5.30; N, 12.45.

4-Phenylacetamido-5-methyl-2-oxazolidinone.

This compound was prepared from 4-amino-5-methyl-2-oxazolidinone and phenylacetyl chloride by the Schotten-Baumann procedure (aqueous bicarbonate). The product melted at 136° after crystallization from ethyl acetate-hexane, yield 62%.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.31; H, 6.00; N, 11.67.

β-Bromoisobutylidenebisbenzylcarbamate (IIIc).

A solution of α-bromoisobutyraldehyde dimethyl acetal (20 g.), benzylcarbamate (30 g.), glacial acetic acid (12 g.) and β-naphthalenesulfonic acid (1 g.) in dry benzene (200 ml.) was refluxed for 7 hours as described above for the preparation of β-chloroethylidenebisbenzylcarbamate. The solid residue was crystallized from methanol. The yield was 27 g. (61%), m.p. 119°.

Anal. Calcd. for $C_{20}H_{23}BrN_2O_4$: N, 6.44; Br, 18.36. Found: N, 6.59; Br, 18.66.

4-Carbobenzoxyamino-5,5-dimethyl-2-oxazolidinone (IVc).

A solution of β-bromoisobutylidenebisbenzylcarbamate (10 g.) in formamide (50 ml.) was heated in an oil bath (130°) for 7 hours. The reaction mixture was poured into water (250 ml.) and extracted with ethyl acetate. The ethyl acetate solution was then washed with 10% hydrochloric acid and dried over anhydrous sodium sulfate. After the removal of the solvent the oily residue was triturated with toluene and was left overnight in the refrigerator. The solid product, thus obtained, was crystallized from toluene. The yield was 1.8 g. (30%); m.p. 135°.

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.21; H, 6.14; N, 10.45.

4-Amino-5,5-Dimethyl-2-oxazolidinone hydrochloride (Vc).

A solution of 4-carbobenzoxyamino-5,5-dimethyl-2-oxazolidinone (1.2 g.) in glacial acetic acid (12 ml.) was catalytically hydrogenated as described above for the preparation of 4-amino-2-oxazolidinone. The hydrochloride obtained melted at 260°, yield 0.7 g. (94%).

Anal. Calcd. for $C_5H_{11}ClN_2O_2$: N, 16.81; Cl, 21.31. Found: N, 16.62; Cl, 21.42.

4-Benzamido-5,5-dimethyl-2-oxazolidinone.

This compound was prepared from 4-amino-5,5-dimethyl-2-oxazolidinone and benzoyl chloride by the Schotten-Baumann procedure (aqueous bicarbonate). The product melted at 245° after crystallization from ethyl acetate, yield 40%.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.42; H, 6.14; N, 11.70.

β-Bromo-β-phenylethylidenebisbenzylcarbamate (IIId).

A mixture of α-bromophenylacetaldehyde dimethyl acetal (10 g.), benzylcarbamate (12.4 g.) and concentrated hydrochloric acid (0.5 ml.) was left for 3 days at room temperature. The solid product, thus obtained, was triturated with 2-propanol, filtered and crystallized from ethyl acetate-hexane. The yield was 6.3 g. (32%), m.p. 150°.

Anal. Calcd. for $C_{24}H_{23}BrN_2O_4$: N, 5.81; Br, 16.51. Found: N, 5.75; Br, 16.74.

4-Carbobenzoxyamino-5-phenyl-2-oxazolidinone (IVd).

A solution of β-bromo-β-phenylethylidenebisbenzylcarbamate (2 g.) in *ortho*-xylene (60 ml.) was refluxed for 4 hours. The solution was cooled to room temperature and hexane (100 ml.) added. After standing overnight in the refrigerator the solid product was filtered and crystallized from ethyl acetate-hexane. The yield was 1 g. (77%), m.p. 180°.

Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.21; H, 5.25; N, 9.00.

β-Bromo-β-phenylethylidenebisethylcarbamate.

A mixture of α-bromophenylacetaldehyde dimethyl acetal (5 g.) ethylcarbamate (3.6 g.) and concentrated hydrochloric acid (0.5 ml.) was left at room temperature for three days. The solid product was triturated with cyclohexane, filtered and crystallized from chyclohexane-hexane. The yield was 6 g. (81%), m.p. 136°.

Anal. Calcd. for $C_{14}H_{19}BrN_2O_4$: N, 7.82; Br, 22.22. Found: N, 7.86; Br, 21.81.

4-Carbethoxyamino-5-phenyl-2-oxazolidinone.

A solution of β-bromo-β-phenylethylidenebisethylcarbamate (1 g.) *ortho*-xylene (30 ml.) was refluxed for 4 hours. The solution was then cooled to room temperature and left overnight in the refrigerator. The solid product was filtered and crystallized from ethyl acetate-hexane. The yield was 0.51 g. (80%), m.p. 178°.

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.63; H, 5.67; N, 11.29.

5-Phenyl-2(3)-oxazolidone.

A solution of 4-carbethoxyamino-5-phenyl-2-oxazolidinone (2.5 g.) in toluene (50 ml.) containing β-naphthalenesulfonic acid (0.5 g.) was refluxed for 10 minutes. The mixture was cooled to room temperature and ethyl acetate (50 ml.) was added to dissolve the solid precipitate. The combined ethyl acetate-toluene solution was washed with aqueous bicarbonate solution dried over anhydrous sodium sulfate and evaporated to dryness. The white solid was crystallized from a small volume of ethyl acetate. The yield was 1.3 g. (79%), m.p. 223-224°.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.96; H, 4.28; N, 8.76.

Acid hydrolysis of 5-phenyl-2(3)-oxazolidone.

A solution of the oxazolidone (0.5 g.) in 6 *N* hydrochloric acid (30 ml.) was refluxed for 3 hours. The solution was then evaporated to dryness and the residue was benzoylated with benzoyl chloride by the Schotten-Baumann procedure. The product melted at 124° and was identical through mixed melting point and infrared spectra with ω-benzamidoacetophenone.

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