HYDROXYLAMINE DERIVATIVES

IV. Synthesis of 2-Phenyl-5,6-Dihydro-8H-Pyrido[3,2-d][1,2]Oxazin-5-One and Its Derivatives*

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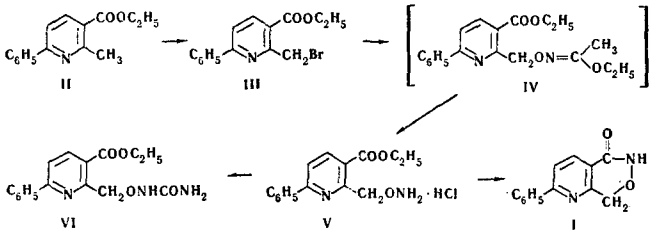
Ethyl 2-aminooxymethyl-6-phenylnicotinate hydrochloride has been synthesized by the condensation of ethyl hydroxyiminoacetate with ethyl 2-bromomethyl-6-phenylnicotinate and subsequent hydrolysis. By the cyclization of this product a new heterocyclic compound, i.e., 2-phenyl-5,6-dihydro-8H-pyrido[3,2-d][1,2]oxazin-5-one, and some of its 6-substituted derivatives have been obtained.

It is known from the literature that the six-membered analogs of cycloserine, i.e., tetrahydro-1,2-oxazin-3-one, possess definite biological activity [2]. It appeared of interest to synthesize and test substances in which this six-membered structure containing a hydroxamic ester grouping would be part of a bicyclic compound attached to pyridine.

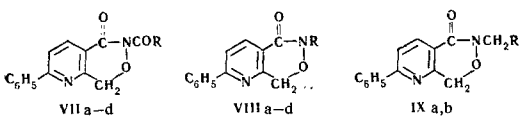
This paper describes the synthesis of the new heterocyclic compound 2-phenyl-5,6-dihydro-8H-pyrido[3,2-d][1,2]oxazin-5-one (I) and some of its derivatives.



Ethyl 2-methyl-6-phenylnicotinate (II) was synthesized by the condensation of aminocrotonic ester with benzoylacetaldehyde [3]. By bromination with bromosuccinimide, compound III was converted into ethyl 2-bromomethyl-6-phenyl-nicotinate (III) [4]. By the action of ethyl acetohydroximate [5] in the presence of sodium ethoxide, compound III yielded the corresponding derivative IV which, without isolation, on subsequent hydrolysis with an ethanolic or ethereal solution of hydrogen chloride was converted into ethyl 2-aminooxymethyl-6-phenylnicotinate hydrochloride (V). The structure of the latter was confirmed by the production of ethyl 2-ureido-oxymethyl-6-phenylnicotinate (VI), on treatment with sodium cyanate.

When heated in water, or with alkali or bicarbonate, compound V cyclized into I. Compound I is stable: it undergoes no change on being heated for 30 min with either 5% alkali or 5% hydrochloric acid. However, when it was heated with concentrated hydrochloric acid for 4 hours, substance I decomposed with the formation of 2-aminooxymethyl-6-phenylnicotinic acid hydrochloride (Va), which, on being heated in water, and also under the action of alkali and bicarbonate, was reconverted into I.

A number of 6-substituted derivatives of I have been obtained. When I was heated with acid chlorides and anhydrides in pyridine, the 6-acyl derivatives (VIIa–d) were obtained. On alkylation with alkyl halides in acetone or dimethylformamide in the presence of potassium carbonate and with halogenoalkylamines in dioxane in the presence of sodium amide, the corresponding derivatives VIIIa–d were obtained. Compound I was converted by the Mannich reaction into the 6-morpholinomethyl and 6-piperidinomethyl derivatives IXa–b.



VII a–d VIII a–d IX a,b

VIIa R = CH_3, b R = $CH_2CH(CH_3)_2$, c R = p-$C_6H_4NO_2$, r R = — piperidino;
VIIIa R = CH_3, b R = C_6H_{13}, c R = $(CH_2)_3N(CH_3)_2$, r R = $(CH_2)_2N(C_2H_5)_2$;
IXa R = — morpholino, b R = — piperidino

*For part III, see [1].

The structures of the compounds obtained were confirmed by their IR spectra, and those of compounds I and VIIIa by their PMR spectra, also. All the compounds obtained were tested for antibacterial activity.* No active substances were found.

EXPERIMENTAL

Ethyl 2-aminooxymethyl-6-phenylnicotinate hydrochloride (V). To 11 g (0.11 mole) of ethyl acetohydroximate in 200 ml of absolute ethanol was added 2.3 g (0.01 g-at.) of sodium and, after 30 min stirring, 32 g (0.10 mole) of ethyl 2-bromomethyl-6-phenylnicotinate. The mixture was stirred at 20° C for 1 hr and at 60° C for 2 hr. The sodium bromide that separated out was filtered off, the ethanol was distilled off in vaco, the residue was poured into water and extracted with ether (200–250 ml), and the ethereal solution was dried with magnesium sulfate. With ice-water cooling and stirring, an ethanolic or ethereal solution of hydrogen chloride was added to the filtered ethereal solution until the reaction was acidic (to Congo red) together with 2 ml of water. After trituration the solidifying oil was washed with ether and dried in a vacuum desiccator. Yield 20 g, mp 140–141° C (decomp, from a mixture of ethanol and ether). Found, %: C 58.0; H 5.3; N 9.4; Cl 11.5. Calculated for $C_{15}H_{16}N_2O_3 \cdot HCl$, %: C 58.4; H 5.6; N 9.1; Cl 11.5.

Ethyl 2-ureidooxymethyl-6-phenylnicotinate (VI). A mixture of 0.3 g (0.001 mole) of V and 0.07 g (0.0014 mole) of sodium cyanate in 2 ml of 50% ethanol was heated at 60° C for 10 min. The precipitate was filtered off and washed with water; mp 180–182° C (from ethanol). Found, %: C 60.8; H 5.2; N 13.4. Calculated for $C_{16}H_{17}N_3O_4$, %: C 61.0; H 5.4; N 13.3.

2-Phenyl-5,6-dihydro-8H-pyrido[3,2-d][1,2]oxazin-5-one (I). a) With stirring, 14.6 g (0.2 mole) of caustic potash in 250 ml of ethanol was added to 40 g (0.13 mole) of V in 100 ml of ethanol. The reaction mixture was boiled for 1 hr 30 min. After cooling, water was added and the precipitate was filtered off and washed with water and ethanol. Yield 20.8 g, mp 210–212° C (decomp, from ethanol). White crystalline substance soluble in pyridine, dimethyl sulfoxide, glacial acetic acid, and dimethylformamide. Found, %: C 69.0; H 4.4; N 12.1. Calculated for $C_{13}H_{10}N_2O_2$, %: C 69.0; H 4.4; N 12.3. IR spectrum, ν, cm^{-1}: 3180 (NH); 1662 (C=O); 1600 s (C=C and C=N). PMR spectrum: 5.21 ppm ($-CH_2-$).

b) Compound V was boiled in water or in a solution of bicarbonate for 30 min. The precipitate was filtered off and was washed with water and ethanol; mp 209–211° C (decomp, from ethanol). The samples obtained by methods a and b were identical (IR spectra mixed melting point).

6-Acetyl-2-phenyl-5,6-dihydro-8H-pyrido[3,2-d][1,2]-oxazin-5-one (VIIa). A mixture of 1.13 g (0.005 mole) of I in 15 ml of pyridine and 3 ml (0.03 mole) of acetic anhydride was heated at 90° C for 2 hr. The reaction mixture was poured into water, and the precipitate was filtered off, washed with water, and dried in the vacuum desiccator. Yield 1.25 g, mp 181–183° C. Soluble in chloroform, dimethylformamide, and hot ethanol. Found, %: C 67.0; H 4.6; N 10.3. Calculated for $C_{15}H_{12}N_2O_3$, %: C 67.2; H 4.5; N 10.4. IR spectrum, ν, cm^{-1}: 1725, 1695 (C=O); 1590 s (C=N and C=C).

6-Isovaleryl-2-phenyl-5,6-dihydro-8H-pyrido[3,2-d][1,2]oxazin-5-one((VIIb) was obtained in a manner similar to the preceding compound from 1.4 g (0.006 mole) of I and 0.75 g (0.006 mole) of isovaleryl chloride in pyridine. Yield 1.1 g, mp 118–120° C. Found, %: C 69.4; H 5.7; N 9.1. Calculated for $C_{18}H_{18}N_2O_3$, %: C 69.7; H 5.8; N 9.0. IR spectrum, ν, cm^{-1}: 1725, 1707 (C=O); 1592 s (C=N and C=C).

6-p-Nitrobenzoyl-2-phenyl-5,6-dihydro-8H-pyrido[3,2-d][1,2]oxazin-5-one (VIIc). A mixture of 1.1 g (0.008 mole) of p-nitrobenzoic acid and 10 ml of thionyl chloride was heated in the water bath for 2 hr, the excess thionyl chloride was distilled off, benzene was added to the residue, and this was distilled off. To the resulting p-nitrobenzoyl chloride was added 1.5 g (0.007 mole) of I and 10 ml of pyridine, and the mixture was heated for 2 hr. The reaction product was isolated in the usual way. Yield 1.7 g, mp 206–209° C, (decomp, from ethanol). Found, %: C 63.7; H 3.6; N 11.6. Calculated for $C_{20}H_{14}N_3O_3$, %: C 63.8; H 3.8; N 11.2. IR spectrum, ν, cm^{-1}: 1735 (C=O); 1591 s (C=C and C=N).

6-Isonicotinoyl-2-phenyl-5,6-dihydro-8H-pyrido[3,2-d][1,2]-oxazin-5-one (VIId) was synthesized in a manner

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similar to the preceding compound from isonicotinoyl chloride, obtained from isonicotinic acid and thionyl chloride, and I in pyridine. Yield 59%, mp 195–197° C. Found, %: C 69.0; H 4.1; N 12.4. Calculated for $C_{19}H_{13}N_3O_2$, %: C 68.9; H 4.0; N 12.7. IR spectrum, ν, cm^{-1}: 1702 broad (C=O); 1586 s (C=C and C=N).

6-Methyl-2-phenyl-5,6-dihydro-8H-pyrido[3,2-d][1,2]oxazin-5-one (VIIIa). A mixture of 0.5 g (0.002 mole) of I, 1 ml (0.016 mole) of methyl iodide, 0.5 g (0.004 mole) of dry potassium carbonate, and 25 ml of acetone was boiled for 8 hr. After the acetone had been distilled off, dry benzene was added to the residue, and then the inorganic salt was filtered off and the solution was evaporated in vacuo. Yield 0.3 g, mp 109–110° C (from benzene). The substance is soluble in ether, ethanol, and acetone. Found, %: C 70.2; H 5.1; N 11.4. Calculated for $C_{14}H_{12}N_2O_2$, %: C 70.0; H 5.0; N 11.7. PMR spectrum: 3.31 ppm (N—CH_3); 5.14 ppm (CH_2).

6-Hexyl-2-phenyl-5,6-dihydro-8H-pyrido[3,2-d][1,2]oxazin-5-one (VIIIb). A solution of 1.32 g (0.006 mole) of I in 17 ml of dimethylformamide was treated with 0.7 g (0.005 mole) of dry finely ground potassium carbonate and, after 30 min stirring at 45° C, with 0.8 g (0.006 mole) of hexyl chloride. The reaction mixture was stirred at 90–100° C for 12 hr, and, after cooling, the inorganic salts were filtered off and the solvent was driven off in vacuo. Yield 1.2 g, mp 62–63° C. The substance is soluble in ether, benzene, and ethanol. Found, %: C 73.6 H 7.0; N 9.2. Calculated for $C_{19}H_{22}N_2O_2$, %: C 73.5; H 7.1; N 9.0. IR spectrum, ν, cm^{-1}: 1656 (C=O); 1592 (C=C and C=N).

6-γ-Dimethylaminopropyl-2-phenyl-5,6-dihydro-8H-pyrido[3,2-d][1,2]oxazin-5-one (VIIIc). To 1.13 g (0.005 mole) of I in 40 ml of dry dioxane was added 0.2 g (0.005 mole) of finely ground sodium amide and then, after 40 min stirring at 70° C, 0.65 g (0.005 mole) of γ-chloropropyldimethylamine in 20 ml of absolute toluene. The mixture was stirred at 100° C for 12 hr. The sodium chloride was filtered off, the solvent was driven off in vacuo, the residue was treated with 1 ml of 10% HCl, and the mixture was filtered and evaporated in vacuo. The yield of the dihydrochloride of VIIIc was 0.7 g, mp 193–195° C (from absolute ethanol). The substance is soluble in water. Found, %: C 56.3; H 6.0; N 11.3; Cl 18.6. Calculated for $C_{18}H_{21}N_3O_2 \cdot 2HCl$, %: C 56.2; H 6.0; N 10.9; Cl 18.5. The base VIIIc was obtained from the dihydrochloride in the usual way; mp 58–60° C (from ether and hexane). Found, %: C 69.1; H 6.6; N 13.6. Calculated for $C_{18}H_{21}N_3O_2$, %: C 69.4; H 6.8; N 13.5.

6-β-Diethylaminoethyl-2-phenyl-5,6-dihydro-8H-pyrido[3,2-d][1,2]oxazin-5-one (VIIId) was obtained similarly from I and β-chloroethyldiethylamine with heating at 80° C for 8 hr. After the solvent had been distilled off in vacuo, the residue was treated with water and extracted with ether, and the ethereal solution was evaporated. The oil was dissolved in dil HCl and the solution was evaporated to dryness. The resulting hydrochloride could not be recrystallized, since on heating in organic solvents hydrogen chloride readily split off. It was dissolved in water, bicarbonate was added, and VIIId was extracted with ether. After the ether had been distilled off, the residual oil was dried in a vacuum desiccator over P_2O_5. Found, %: C 70.5; H 7.3; N 12.4. Calculated for $C_{19}H_{23}O_2N_3$, %: C 70.1; H 7.1; N 12.9.

6-Morpholinomethyl-2-phenyl-5,6-dihydro-8H-pyrido[3,2-d][1,2]oxazin-5-one (IXa). To 1.13 g (0.005 mole) of I in 25 ml of ethanol was added 1 ml of 38% formalin (0.014 mole) and 0.5 g (0.006 mole) of morpholine, and the mixture was stirred at the boil for 1 hr. The precipitate that deposited on cooling was filtered off and washed with ethanol. Yield 1.2 g, mp 147–149° C (from ethanol). Found, %: C 66.0; H 6.0; N 12.7. Calculated for $C_{18}H_{19}O_3N_3$, %: C 66.4; H 5.9; N 12.9.

2-Phenyl-6-piperidinomethyl-5,6-dihydro-8H-pyrido[3,2-d][1,2]oxazin-5-one (IXb). This was obtained in a manner similar to IXa from I, formalin, and piperidine in ethanol. Yield 70%, mp 116–118° C. Soluble in acetone and benzene. Found, %: C 70.4; H 6.4; N 12.8. Calculated for $C_{19}H_{21}N_3O_2$, %: C 70.6; H 6.5; N 13.0. IR spectrum, ν, cm^{-1}: 1663 (C=O); 1593 s (C=C and C=N).

The IR spectra were taken on a UR-10 instrument using mulls in paraffin oil (NaCl prism). The PMR spectra were recorded on a JNM 4H-100 instrument in pyridine solution (compound I and in $CDCl_3$ (compound VIIIa) on the δ scale relative to tetramethylsilane.

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