HYDROXYLAMINE DERIVATIVES

VI.* CYCLIC HYDROXYLAMINE DERIVATIVES

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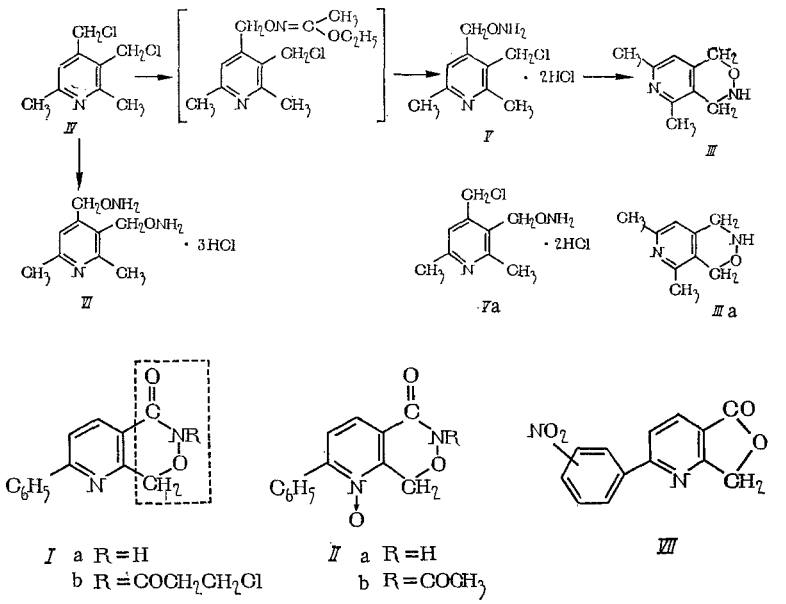
We previously synthesized 2-phenyl-6H,8H-pyrido(3,2-d)-1,2-oxazine-5-one (Ia) which contains the $-CH_2ONHCO-$ grouping characteristic for cycloserine in the ring. In continuing our search for tuberculostatic substances in this series we have synthesized several derivatives of (Ia), viz., (Ib) and (IIa, b) as well as a substance which can be assigned the 5,7-dimethyl-1H,3H,4H-pyrido(4,3-d)-1,2-oxazine (III) or the isomeric (IIIa) structure on the basis of spectral data. The synthesis of this substance was accomplished proceeding from 2,6-dimethyl-3,4-bis(α-chloromethyl)pyridine (IV) via the scheme:



The starting (IV) [2] was obtained by condensation of ethyl acetylpyruvate with aminocrotonic ester [3] with subsequent reduction with lithium aluminum hydride of the 2,6-dimethyl-3,4-dicarbethoxypyridine formed to 2,6-dimethyl-3,4-bis(α-hydroxymethyl)pyridine [4] and replacement of the hydroxy groups of chlorine. Condensation of (IV) with ethyl oximidoacetate in equimolecular ratios at room temperature with subsequent treatment of the condensation product with hydrogen chloride in ether gave the dihydrochloride of the corresponding monoaminoxymethyl-substituted pyridine (V) or (Va). The reaction of (IV) with two moles of ethyl oximidoacetate on heating proceeds with the replacement of both chloro groups by the ethyl oximidoacetate residue, and, in this case, treatment of the reaction product with hydrogen chloride gave the trihydrochloride of 2,6-dimethyl-3,4-bis(α-aminoxymethyl)pyridine (VI).

*See Communication V [1].

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The dihydrochloride is stable but the corresponding base could not be obtained from it in pure form. Its cyclization by both alcoholic alkali as well as butylamine gave a difficult-to-separate mixture of substances. A cyclization product was isolated from the mixture in only 7% yield after the dihydrochloride was refluxed with aqueous potassium hydroxide for 7 h.

The dihydrochloride may be one of the two possible isomers (V) or (Va), and, in accordance with this, their cyclization should lead to isomers (III) or (IIIa). We presently do not have sufficient data to decide which of these isomers we have obtained.

The following signals are present in the PMR spectrum of the dicyclic compound: two singlets at 2.28 and 2.43 ppm corresponding to the protons of the two methyl groups on the aromatic ring, two singlets at 4.06 and 4.76 ppm corresponding to the protons of the two CH_2 groups, and a singlet at 6.71 ppm for the proton of the pyridine ring. An intensive band at 3200 cm^{-1}, associated with the NH valence vibrations, is observed in the IR spectrum of this compound.

In continuing our studies of the properties of the previously synthesized (Ia), we have obtained the N-oxides both from it and its 6-acetyl derivative. The 6-acetyl derivative (IIb) was obtained from (IIa) by reaction with acetic anhydride. 2-Phenyl-6(β-chloropropionyl)-6H,8H-pyrido(3,2-d)-1,2-oxazine-5-one (Ib) was synthesized by reaction of (Ia) with β-chloropropionyl chloride. Attempts to condense (Ib) with morpholine and piperidine were unsuccessful, and only a quantitative yield of pyridoxazinone (Ia) was obtained as a result of these reactions in absolute benzene at room temperature. A nitro compound which, from the data of elementary analysis and the IR spectrum, is apparently the lactone (VII), was obtained by nitration of (Ia) and its 6-acetyl derivative with a nitrating mixture at room temperature or with nitric acid at −15°C. An absorption band characteristic for the lactone carbonyl is observed in the IR spectrum at 1760 cm^{-1}, and characteristic bands for the phenyl nitro group are observed at 1530 cm^{-1} and 1350 cm^{-1}. The great similarity between the spectrum of the compound obtained and that of 6-nitrophthalide [5] (1760, 1520, and 1340 cm^{-1}) may serve as a confirmation of structure (VII).

The compounds obtained as well as the previously synthesized derivatives of (Ia) were investigated for their tuberculostatic activity. The results indicated that all compounds have slight activity (at 125-100 μg/ml) in a culture medium without serum as well as in the presence of 10% normal horse serum. An exception to this was 2-phenyl-6-hexyl-6H,8H-pyrido(3,2-d)-1,2-oxazine-5-one, which, in a medium without serum, suppressed the growth of the Academia strain in doses of 16 μg/ml, i.e., it is somewhat more active than the other compounds. However, this compound is of no practical value since its activity drops sharply to 250 μg/ml in a medium with serum.

EXPERIMENTAL

2,6-Dimethyl-3,5-bis(α-chloromethyl)pyridine Hydrochloride (IV·HCl). A mixture of 4.2 g 2,6-dimethyl-3,4-bis(α-hydroxymethyl)pyridine and 10 ml of thionyl chloride was refluxed for 4 h. After cooling, ether was added to the solution and the precipitate was filtered to give 5.6 g (94%) of (IV·HCl) with mp 221°. Found %: C 44.78; H 5.12; Cl 43.94; N 5.51. C_9H_{11}·HCl. Calculated %: C 44.93; H 5.03; Cl 44.20; N 5.82.

2,6-Dimethyl-3,4-bis(α-chloromethyl)pyridine (IV). This compound was obtained from the above hydrochloride by reaction with sodium carbonate with repeated extraction of the reaction mixture with ether. The ether extract was dried over potassium carbonate and solvent was removed to give 55% of (IV), a liquid with strong irritating and vesicant activity.

2,6-Dimethyl-3(4)-chloromethyl-4(3)-aminoxymethylpyridine (V) or (Va). Ethyl oximidoacetate (10.3 g) was added to 2.3 g of sodium in 70 ml of absolute alcohol, the mixture was stirred for 30 min, 20.4 g of (II) was added, and the mixture was stirred for 1 h at room temperature. The precipitate was filtered. The alcoholic solution was heated and filtered through a layer of carbon. After cooling, 20 ml of 10% hydrogen chloride in ether was added to the filtrate. The oil which separated hardened during trituration to give 6.8 g (25%) of product with mp 163° (decomposition, from alcohol−ether). Found %: C 39.41; H 5.40; Cl 38.49 (including 25.67 ionic Cl); N 10.47. $C_9H_{13}ClN_2O$·2HCl. Calculated %: C 39.51; H 5.59; Cl 38.88 (including 25.92 ionic Cl); N 10.24.

2,6-Dimethyl-3,4-bis(α-aminoxymethyl)pyridine Trihydrochloride (VI). Ethyl oximidoacetate (10.3 g) and 10.2 g of (IV) were added to 2.3 g of sodium in 70 ml of absolute alcohol. The reaction mixture was heated, and the hot reaction solution was filtered through carbon. On cooling, 25 ml of 10% hydrogen chloride in ether was added to the filtrate to give 5.7 g (37%) of (VI) with mp 187° (decomposition). Found %: C 35.50; H 5.60; Cl 35.00; N 13.93. $C_9H_{15}N_3O_2$·3HCl. Calculated %: C 35.22; H 5.92; Cl 34.69; N 14.09.

5,7-Dimethyl-1H,3H,4H-pyrido(4,3-d)-1,2-oxazine (III) or Its Isomer (IIIa). A mixture of 5.5 g of (V) or (Va) and 3.4 g of potassium hydroxide in 100 ml of alcohol was refluxed for 7 h. The precipitate was filtered, the alcohol was evaporated to dryness, and the residue was repeatedly extracted with ether. The ether solution was dried with potassium carbonate, the ether was evaporated, and the residue was pressed on a porous plate to give 0.3 g (7%) of (III) or (IIIa) with mp 146-148° (from alcohol–petroleum ether). Found %: C 65.97; H 6.97; N 16.88. $C_9H_{12}N_2O$. Calculated %: C 65.83; H 7.36; N 17.06.

N-Oxy-2-phenyl-6H,8H-pyrido(3,2-d)-1,2-oxazine-5-one (IIa). Hydrogen peroxide (3 ml of 30%) was added to 2.26 g (Ia) in 30 ml of glacial acetic acid. The reaction solution was heated at 80-85° for 3 h. After cooling, 2 ml of 30% hydrogen peroxide was added to the solution, the mixture was heated for 5 h at the same temperature, and the solution was then evaporated in vacuo. Water was added to the residue, and the mixture was made alkaline with concentrated potassium carbonate. The precipitate was filtered and washed with water to give 2.3 g (95%) of (IIa) with mp 204-206° (decomposition, from alcohol). Found %: C 64.38; H 4.18; N 11.83. $C_{13}H_{10}N_2O_3$. Calculated %: C 64.45; H 4.16; N 11.56. IR spectrum (ν cm^{-1}): 3210 (NH); 1675 (C = O). (IIa) was similarly obtained from 2-phenyl-6-acetyl-6H,8H-pyrido(3,2-d)-1,2-oxazine-5-one.

N-oxy-2-phenyl-6-acetyl-6H,8H-pyrido(3,2-d)-1,2-oxazine-5-one. (IIb). This compound was obtained from (IIa) by refluxing with acetic anhydride for 15 min. After evaporation in vacuo, a dilute solution of sodium bicarbonate was added to the residue. The mixture was extracted with chloroform, the chloroform was removed, and the semisolid residue was recrystallized from ethyl acetate–petroleum ether (2 : 1) to give a product with mp 127-129°. Found %: C 63.65; H 4.34; N 9.64. $C_{15}H_{12}N_2O_4$. Calculated %: C 63.37; H 4.25; N 9.89.

2-Phenyl-6-(β-chloropropionyl)-6H,8H-pyrido(3,2-d)-1,2-oxazine-5-one (Ib). A mixture of 1.13 g of (Ia) in 10 ml of dioxane and 0.63 g of β-chloropropionyl chloride was refluxed for 5 h. The reaction mixture was poured into water, and the residue was filtered and washed with water to give 0.9 g (57%) of (Ib) with mp 138-140° (from butanol). Found %: C 60.43; H 4.31; Cl 10.81; N 8.93. $C_{16}H_{13}ClN_2O_3$. Calculated %: C 60.67; H 4.14; Cl 11.20; N 8.84. IR spectrum (ν cm^{-1}): 1710, 1730 (C = O); 1595 (C = C) and (C = N). NH-groups absorption was absent.

Nitration of 2-Phenyl-6H,8H-pyrido(3,2-d)-1,2-oxazine-5-one. A. (Ia) (0.56 g) was added to a mixture of 2 ml of sulfuric acid and 2 ml of nitric acid (sp. gr. 1.52), during which dissolving of the solid and heating were observed. Ice water was added to the mixture; the precipitate was filtered and washed with water, sodium bicarbonate solution, and once again with water and alcohol to give 0.4 g (62.5%) of (VII) with mp 175-176° (from alcohol). Found %: C 60.63; H 2.92; N 10.60. $C_{13}H_8N_2O_4$. Calculated %: C 60.94; H 3.15; N 10.93.

B. (Ia) (1.13 g) was added to 10 ml of nitric acid (sp. gr. 1.5) at −15° and the mixture was stirred for 15 min. (VII) (1 g, 78.1%) with mp 175-176° was isolated by the method described above. This compound was obtained under similar conditions from 2-phenyl-6-acetyl-6H,8H-pyrido(3,2-d)-1,2-oxazine-5-one.

The IR spectra were obtained with an IR-10 spectrometer in mineral oil, while the PMR spectra were obtained with a GNM-4H-100 spectrometer in deuterochloroform (δ scale) with hexamethyldisiloxane as internal standard.*

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