Reactions with 2H-Pyrido[2,3-e]-1,3-oxazine-2,4(3H)-dione

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The recently described pyrido(oxazine is lends itself to a number of reactions of preparative value. Representative examples of such reactions are shown below and described in the experimental part. All compounds prepared (II—IV) are new. Their structures follow from the syntheses, from analyses, and from the fact that they all, except the carbonates IV, give a red ferric chloride reaction.

Experimental. N-Butyl-N’-(3-hydroxypicolyl)urea (II). I (1.00 g) and butylamine (5.0 ml) are mixed and heated under reflux (30 min). The resulting clear solution is evaporated to dryness from a water bath (95°), at last under 1 mm. The paste residue is dissolved in methanol (12 ml). Water (4 ml) is added and the hot solution brought to pH 5—6 by addition of 3 N hydrochloric acid (2.5—3.0 ml). The solution is cooled, whereby crystals of II separate. The white crystals are isolated by filtration, washed with water (5 ml) and dried (1 h, 50°, 1 mm). The yield is 1.20 g (85%) of II, m.p. 102—103° (Hersberg app., corr.). [Found: C 55.6; H 6.3; N 17.7. Calc. for C₁₅H₁₉N₃O₃ (237.3): C 55.7; H 6.4; N 17.7.]

The product gives a red ferric chloride reaction in aqueous-ethanolic solution.

N-Phenyl-N’-(3-hydroxypicolyl)urea (III). I (1.00 g) is heated (100°) with aniline (5.0 ml) for a few minutes to give a clear solution. The solution is kept at 120° (30 min). After cooling, ether (40 ml) is added. The resulting white crystals of III are isolated by filtration, washed with ether, and dried (15 h, 90°, 1 mm). The yield is 1.49 g (95%) of III, m.p. 191°. [Found: C 60.7; H 4.2; N 16.2. Calc. for C₁₅H₁₁N₃O₂ (257.2): C 60.7; H 4.3; N 16.3.]

The product gives a red ferric chloride reaction in ethanolic solution.

3-(3,4-Dichlorophenylcarbamoyloxy)picolinamide (IV). I (2.00 g, 0.0122 mole) and 3,4-dichloroaniline (2.00 g, 0.0123 mole) are mixed and kept at 140° for 75 min. The resulting crystalline mass is crystallized from dimethylformamide (100 ml) with carbon black. The wet crystals are washed with dimethylformamide (two 15 ml portions) and dried (90 min, 80°, 1 mm). The yield is 3.64 g (92%) of IV, m.p. 237—238°. [Found: C 48.2; H 3.0; Cl 21.8; N 12.6. Calc. for C₁₅H₁₁N₃O₂ (326.1): C 47.3; H 2.8; Cl 21.7; N 12.9.]

The product gives no ferric chloride reaction.

N-Dimethylamino-N’-(3-hydroxypicolyl)urea (V). I (1.00 g) and dimethylhydrazine (5.0 ml) are mixed and heated under reflux (45 min). The resulting clear solution is evaporated to dryness from a water bath (80°) under 10 mm. The paste residue is dissolved in hot methanol (2 ml). Ether (200 ml) is added in one portion. The almost clear solution is filtered through a sintered glass disk (G 4), whereby a small amount of a brownish-yellow, cloudy precipitate is removed. The filtrate is evaporated with stirring to 20—30 ml, whereby white crystals of V separate. The crystals are

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isolated by filtration and dried overnight (20°, 1 mm). The yield is 0.88 g (64 %) of V. [Found: C 48.3; H 5.5; N 24.9. Calc. for C₁₇H₁₃N₂O₃ (224.2): C 48.2; H 5.4; N 25.0].

The products obtained in the above synthesis do not always behave in the same way, when heated in a tube. They may soften and melt completely at temperatures between 115° and 152°, depending upon the particular product, as well as upon the rate of heating. The yields obtained in the synthesis are also not reproducible, being either around 65 % or around 85 %. However, all products are always analytically pure, give a red ferric chloride reaction, and have identical infrared absorption spectra in a chloroform solution. It has not been investigated, whether the different products obtained in the crystalline state are polymorphic or isomeric (e.g. tautomeric).

3-Hydroxypropylocarboxamic acid methyl ester (VI). I (1.00 g) is added to a solution of sodium methoxide in methanol (from sodium (0.15 g) and methanol (5 ml)) and the mixture heated under reflux (5 min). The reaction mixture is cooled and acetic acid (0.37 ml) and then water (10 ml) added. The resulting suspension of white crystals is stirred for half an hour. The crystals are isolated by filtration, washed with water (10 ml) and then dried (2 h, 50°, 1 mm). The yield is 1.07 g (89 %) of VI. [Found: C 48.8; H 4.2; N 14.7; OCH₃ 15.1. Calc. for C₁₇H₁₉N₂O₃ (196.2): C 49.0; H 4.1; N 14.3; one OCH₃ 15.8]. The product gives a red ferric chloride reaction.

The above analyses indicate, that the product contains about 4 % of pyridoxazine as an impurity. Thin-layer chromatography also shows the presence of pyridoxazine. We believe that the pyridoxazine was not present in the wet crystals, but has been formed during drying.

When heated in a tube the product melts around 170° and resolidifies around 220° (formation of I). 1.00 g of the product was heated in an open tube to 190 – 210° for 7 min. During this time it first gave off methanol and then solidified. The resulting brown solid was crystallized from acetic acid (12 ml) with carbon black to give 0.64 g (76 %) of I, m.p. 265 – 270° with decomposition. [Found: C 51.3; H 2.7; N 16.9. Calc. for C₇H₄N₂O₃ (164.1): C 51.2; H 2.5; N 17.1].

Studies on Orchidaceae Alkaloids

V.* A New Alkaloid from Phalaenopsis amabilis Bl.

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A new alkaloid phalaenopsisin (I) has been isolated from Phalaenopsis amabilis Bl., m.p. 99° – 101°, elementary formula C₁₇H₁₅N₂O₃, MW 361 which was verified by its mass spectrum. Prominent peaks in the mass spectrum are m/e 361 (M⁺), 330, 288, 124 (base peak), 83, and a metastable ion at m/e 230 corresponding to a breakdown of m/e 361 to m/e 288.

The hydrochloride of I (C₇H₆N₂ClO₃) had m.p. 155° – 156°. The UV absorption of the base has maxima at 264, 255, 254, 248, and 243 μm, the IR spectrum shows a strong band at 1735 cm⁻¹, but no NH band.

The molecule contains one O—CH₃ but no N—CH₃ or C—CH₃. The hydrochloride of I shows the following distinct bands in the NMR spectrum (DMSO d₆): τ = 2.55 5H singlet, τ = 4.3 1H singlet (N⁺—H), τ = 5.72 2H triplet (J = 6 cps), τ = 6.24 3H singlet, τ = 6.84 2H singlet, τ = 6.86 and 7.33 2H A—B (J = 16 cps).

The data suggest that the alkaloid is an ester containing a mono-substituted benzene nucleus. All elementary analyses gave the correct values. The LD₅₀ of the hydrochloride of I in mice (intravenous) is 75 mg/kg. A full report on the isolation and structure of I will be published later.

The mass spectra were measured by Dr Ryhage and the NMR spectrum of the hydrochloride by Dr. Melera, Varian AG, Zürich, on a HA 100 spectrometer. The work has been supported by grants from the Swedish Natural Science Research Council.

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