PYRIDO[2,3-g]QUINOLINES

I.* sym-OCTAHYDRO-4,9-DIOXOPYRIDO[2,3-g]QUINOLINE

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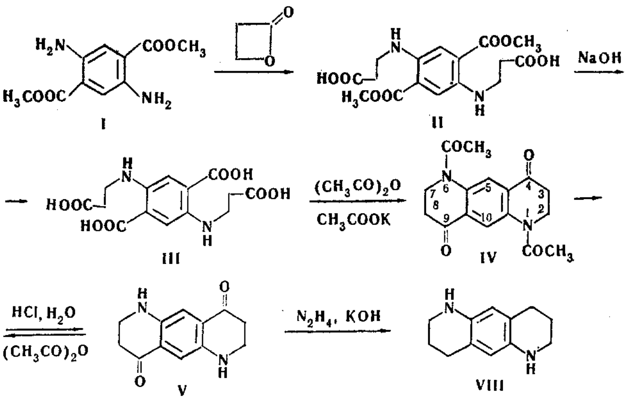
The heretofore unknown sym-octahydro-4,9-dioxopyrido[2,3-g]quinoline was synthesized by carboxyethylation of dimethyl 2,5-diaminoterephthalate with β-propiolactone with subsequent hydrolysis of the resulting 2,5-bis(β-carboxyethylamino)terephthalic acid ester and cyclization of 2,5-bis(β-carboxyethylamino)terephthalic acid. The structure of the product was confirmed by the UV and IR spectra and also by reduction to the known sym-octahydropyrido[2,3-g]quinoline.

Linear pyrido[g]quinolines are little-studied compounds. This is particularly the case for derivatives of pyrido[2,3-g]quinoline, which are of interest in the search for biologically active compounds as a result of their structural proximity to compounds of the benzo[g]quinoline series [1]. The literature contains limited information, regarding only the 2,7-isomers, on oxo derivatives of pyrido[2,3-g]quinoline [2-5]. An unsuccessful attempt to obtain the 4,9-dioxo isomer has also been described [6]. We have proposed a new route for the synthesis of pyrido[2,3-g]quinoline derivatives:



Carboxyethylation of I with propiolactone leads to a quantitative yield of II. Tetracarboxylic acid III is obtained by alkaline hydrolysis of II. Compound III was cyclized by reaction with acetic anhydride and potassium acetate, as proposed for the synthesis of hydrogenated quinolones [8, 9]. The 1,6-diacetyl-sym-octahydro-4,9-dioxopyrido[2,3-g]quinoline (IV) obtained was deacetylated in acidic medium to form V. Diketones IV and V were characterized by their carbonyl derivatives – the dioxime of IV (VI) and the dihydrazone of V (VII). To confirm its structure, V was reduced via the Wolff–Kishner reduction to sym-octahydropyrido[2,3-g]quinoline (VIII), which is identical to the substance previously obtained [5] by reduction with lithium aluminum hydride of an analog of V with a different (2,7) orientation of the oxo groups.

The IR spectrum of IV contains bands at 1762 and 1663 cm^{-1} which correspond to ν_{CO} of the ketone and acetyl groups, respectively.

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*See [7] for preliminary communication.

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The IR spectrum of V has a band at 3362 cm^{-1} (NH) in addition to a band at 1672 cm^{-1} (CO). The NH band at 3363 cm^{-1} remains in the spectrum of VIII, while the carbonyl absorption band vanishes.

The UV spectrum of V has two maxima at 259 nm (log ε 4.46) and 520 nm (3.56), and the latter band is markedly shifted to the long-wave region as compared with monoketones [10].

EXPERIMENTAL

The IR spectra in mineral oil were obtained with a UR-20 spectrophotometer, while the UV spectra in ethanol were obtained with an EPS-3 spectrometer.

Dimethyl 2,5-Bis(β-carboxyethylamino)terephthalate (II). β-Propiolactone [15.9 g (0.22 mole)] was added to a solution of 22.4 g (0.1 mole) of dimethyl 2,5-diaminoterephthalate [11] in 260 ml of dry acetone, and the mixture was refluxed for 3 h. The acetone was removed to dryness, and the solid residue was washed with alcohol to give 35 g (95%) of red-orange crystals of II with mp 215-216° (decomp., from aqueous ethanol followed by acetic acid). Found %: C 52.0; H 5.6; N 7.5. $C_{16}H_{20}N_2O_8$. Calculated %: C 52.2; H 5.5; N 7.6.

2,5-Bis(β-carboxyethylamino)terephthalate (III). A mixture of 36.8 g (0.1 mole) of II, 14 g (0.35 mole) of NaOH, and 150 ml of water was heated with stirring to the boiling point, and the resulting solution was filtered and acidified with 20% sulfuric acid to pH 2. The crystalline precipitate that formed on cooling of the mixture was separated and washed with water to give 32 g (94%) of light crystals with a greyish tinge and mp 344-346° (decomp., from water). Found %: C 49.7; H 4.8; N 8.5. $C_{14}H_{16}N_2O_8$. Calculated %: C 49.4; H 4.7; N 8.2.

1,6-Diacetyl-sym-octahydro-4,9-dioxopyrido[2,3-g]quinoline (IV). A. A mixture of 34 g (0.1 mole) of III and 300 ml of acetic anhydride containing 39.2 g (0.4 mole) of fused potassium acetate was heated for 2 h at 100° (vigorous CO_2 evolution was observed). The temperature was then gradually raised to 130°, and the mixture was heated at this temperature for about 15 min until complete cessation of CO_2 evolution. The acetic anhydride was removed in vacuo until the residue was dry. Water (100 ml) and 5 ml of 40% NaOH were added to the solid residue, and the precipitate that formed on standing was filtered and washed with water to give 8.1 g (24%) of a yellowish substance. After two recrystallizations from benzene and one crystallization from ethyl acetate–ethanol (1 : 1), colorless crystals with mp 236-238° were obtained. Found %: N 8.3. $C_{16}H_{16}N_2O_4 \cdot 2H_2O$. Calculated %: N 8.3.

B. A mixture of 0.22 g of V and 0.3 g of potassium acetate in 3 ml of acetic anhydride was refluxed for 10 min. The crystals that formed on cooling of the mixture were filtered and washed with water to give a product with mp 236-238° (ethyl acetate–ethanol); a mixture of a sample of this product with a sample of IV obtained by method A did not give a melting-point depression.

Dioxime of IV (VI). A mixture of 0.6 g (0.002 mole) of IV and 0.6 g (0.0082 mole) of hydroxylamine hydrochloride in 20 ml of pyridine was refluxed for 2 h. Slightly yellow crystals with mp > 360° (from acetic acid) precipitated when the mixture was cooled. Found %: N 17.3. $C_{16}H_{18}N_4O_4$. Calculated %: N 17.0.

sym-Octahydro-4,9-dioxopyrido[2,3-g]quinoline (V). A mixture of 3 g (0.01 mole) of III, 10 ml of concentrated hydrochloric acid, and 5 ml of acetic acid, and 5 ml of water was heated at 100° until all of III dissolved (~30 min). The solution was evaporated to dryness in vacuo, 10% NaOH was added to the residue until an alkaline reaction was obtained, and the resulting dark-violet precipitate was filtered and washed with water. The product was purified by extraction in a Soxhlet apparatus with benzene–methanol (5 : 1) to give dark-cherry-red crystals with a metallic luster and mp 280° (decomp., from benzene) that were soluble in alcohol and acetone, moderately soluble in benzene, and slightly soluble in water. Found %: C 66.6; H 5.5; N 13.1. $C_{12}H_{12}N_2O_2$. Calculated %: C 66.7; H 5.6; N 13.0.

Dihydrazone of V (VII). Hydrazine hydrate [1 g (0.02 mole)] was added to a solution of 0.065 g (0.003 mole) of V in 15 ml of alcohol, and the solution was refluxed for 1.5 h and allowed to stand at room temperature for 12 h. The resulting crystals were washed with methanol to give 0.07 g (97%) of ruby-red crystals with mp 251-252° (decomp., from methanol). Found %: C 59.3; H 6.5; N 34.8. $C_{12}H_{16}N_6$. Calculated %: C 59.0; H 6.6; N 34.4.

sym-Octahydropyrido[2,3-g]quinoline (VIII). A mixture of 0.325 g (0.0015 mole) of V, 0.8 g (0.016 mole) of hydrazine hydrate, and 0.8 g of KOH in 10 ml of ethylene glycol was heated for 3 h at 180°. The mixture was then evaporated to dryness, and the solid residue was washed with water to give colorless crystals with mp 160-162° (from benzene), which is in agreement with the literature data [5]. Found %: N 15.0. $C_{12}H_{16}N_2$. Calculated %: N 14.9.

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