HYDROACRIDINES AND RELATED COMPOUNDS

XIII.* 2-PHENYL-7,7-DIMETHYL-5H-7,8-DIHYDROPYRANO[4,3-b]PYRIDINE: SYNTHESIS AND SOME OF ITS TRANSFORMATIONS

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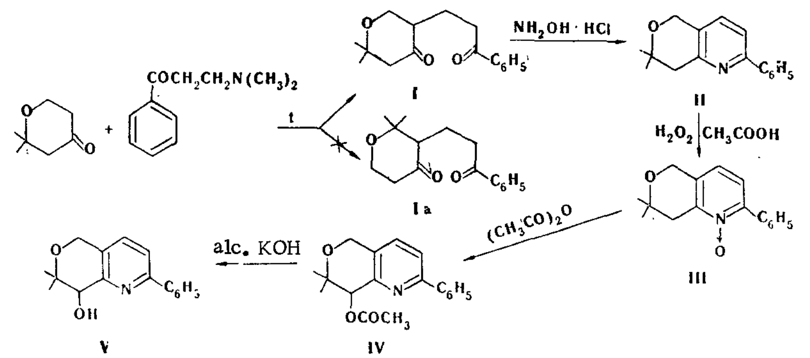
2-Phenyl-7,7-dimethyl-5H-7,8-dihydropyrano[4,3-b]pyridine and its N-oxide were synthesized. Refluxing of the latter with acetic anhydride gives 2-phenyl-7,7-dimethyl-8-hydroxy-5H-7,8-dihydropyrano[4,3-b]pyridine acetate; hydrolysis of the acetate gives the alcohol.

In order to conduct pharmacological tests, we synthesized oxahydroquinoline II from diketone I. The pyrano[4,3-b]pyridine system, upon which II is based, has received relatively little study.



Starting diketone I was obtained in good yield by refluxing β-dimethylaminopropiophenone with excess 2,2-dimethyltetrahydro-4-pyrone. The band of carbonyl absorption in the IR spectrum of the diketone has two maxima at 1715 and 1690 cm^{-1}; this is in agreement with formula I. In connection with the presence of two nonequivalent α-methylene groups in the 2,2-dimethyltetrahydro-4-pyrone molecule, one might have expected that the reaction would also have proceeded in the direction of diketone Ia. Chromatographic analysis shows that only one product – diketone I – is formed in the reaction. Oxahydroquinoline II is obtained in high yield when I is refluxed with hydroxylamine hydrochloride in n-propyl alcohol.

In addition to other signals (from the protons of the gem-methyl groups and from the aromatic protons), the NMR spectrum of II contains two singlets at 3.12 ppm (signal from the C_8 protons) and 4.92 ppm (signal from the C_5 protons); this attests to the presence of two isolated $-CH_2-$ groups. Compound II could only have been formed from a diketone with structure I.

Oxide III is formed in the oxidation of base II with hydrogen peroxide in glacial acetic acid. As in the case of other bases of this type [2], the oxidation is not complete; the steric and electronic effects of the phenyl group are apparently exerted. The IR spectrum of III contains an intense absorption band with maxima at 1310 and 1280 cm^{-1}, which is characteristic for the N-oxide group.

Refluxing of III with acetic anhydride gives acetate IV, the structure of which was confirmed by the spectral data. The IR spectrum contains intense absorption bands at 1745 and 1250 cm^{-1}, which are char-

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*See [1] for communication XII.

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acteristic for an ester group. The singlet at 3.12 ppm in the NMR spectrum vanishes, and a singlet appears at 6.12 ppm (signal of the methylidyne group attached to C_8).

Alkaline hydrolysis of the acetate proceeds extremely smoothly to give an almost quantitative yield of amino alcohol V.

EXPERIMENTAL

The IR spectra of chloroform solutions were recorded with a UR-20 spectrophotometer. The NMR spectra were obtained with a ZKR-60 spectrometer with an operating frequency of 60 MHz. Activity-II aluminum oxide was used for chromatography, and the chromatograms were developed with iodine vapors. The picrates were obtained by mixing alcohol solutions of the substance and picric acid. The hydrochlorides were obtained by passing dry hydrogen chloride through ether or benzene solutions of the substances.

2,2-Dimethyl-5-phenacylmethyltetrahydro-4-pyrone (I). A mixture of 73.1 g (0.41 mole) of β-dimethylaminopropiophenone [3] and 157 ml (1.2 mole) of 2,2-dimethyltetrahydro-4-pyrone [4] was refluxed for 1 h, after which the excess ketone was removed by distillation at reduced pressure, and the diketone was vacuum-distilled with collection of the 187-190° (3 mm) fraction. The product began to crystallize on standing to give, in 82% yield, a material with mp 63-64° (from petroleum ether) and R_f 0.20 (benzene). Found: C 73.9; H 8.0%. $C_{16}H_{20}O_3$. Calculated: C 73.8; H 7.7%.

2-Phenyl-7,7-dimethyl-5H-7,8-dihydropyrano[4,3-b]pyridine (II). A mixture of 9 g (0.036 mole) of diketone I, 10.3 g (0.14 mole) of hydroxylamine hydrochloride, and 50 ml of n-propanol was refluxed for 1 h, after which it was diluted with 300 ml of water and made alkaline with saturated potassium carbonate solution. The resulting oil was extracted with chloroform, and the solvent was evaporated to give 7 g (80%) of base II as colorless crystals with mp 99-100° (from n-propanol) and R_f 0.50 [petroleum ether–ethyl acetate (3:1)]. Found: C 80.3; H 7.6%. $C_{16}H_{17}NO$. Calculated: C 80.3; H 7.1%. The picrate was obtained as yellow-green rods with mp 185-186° (from alcohol). Found: N 12.0%. $C_{16}H_{17}NO \cdot C_6H_3N_3O_7$. Calculated: N 12.0%. The hydrochloride was obtained as colorless crystals with mp 180-181°; the product was soluble in water. Found: Cl 13.8%. $C_{16}H_{17}NO \cdot HCl$. Calculated: Cl 13.0%.

2-Phenyl-7,7-dimethyl-5H-7,8-dihydropyrano[4,3-b]pyridine N-Oxide (III). A mixture of 22.8 g (0.095 mole) of base II, 11.5 ml of 28% hydrogen peroxide, and 140 ml of glacial acetic acid was heated at 70-80° for 5 h, after which 11.5 ml of hydrogen peroxide was added, and the mixture was heated for another 5 h. The mixture was made alkaline, and the resulting oil was extracted with chloroform. The solvent was evaporated to give 22 g of a mixture of oxide III and base II. Recrystallization from heptane gave 13.3 g (55%) of oxide III with mp 156-157°. Found: C 76.3; H 6.8%. $C_{16}H_{17}NO_2$. Calculated: C 75.5; H 6.7%. The hydrochloride was obtained as colorless needles (water-soluble) with mp 167-170° [from aqueous alcohol (6:1)]. Found: Cl 11.8%. $C_{16}H_{17}NO_2 \cdot HCl$. Calculated: Cl 12.2%.

2-Phenyl-7,7-dimethyl-8-hydroxy-5H-7,8-dihydropyrano[4,3-b]pyridine Acetate (IV). A mixture of 1 g (4 mmole) of III and 5.5 ml of acetic anhydride was refluxed for 1 h, after which it was made alkaline with potassium carbonate solution and extracted with chloroform. Removal of the solvent by distillation gave 1.05 g (88%) of IV as colorless crystals with mp 124-126° (from heptane) and R_f 0.57 (chloroform). Found: C 73.6; H 6.4%. $C_{18}H_{19}NO_3$. Calculated: C 72.7; H 6.4%. The picrate was obtained as greenish crystals with mp 147-150° (from alcohol). Found: N 11.3%. $C_{18}H_{19}NO_3 \cdot C_6H_3N_3O_7$. Calculated: N 10.6%. The hydrochloride was obtained as colorless crystals (soluble in hot water) with mp 191-192° (from benzene). Found: Cl 10.9%. $C_{18}H_{19}NO_3 \cdot HCl$. Calculated: Cl 10.3%.

2-Phenyl-7,7-dimethyl-8-hydroxy-5H-7,8-dihydropyrano[4,3-b]pyridine (V). A mixture of 0.5 g (1.6 mmole) of amino ester IV and 7 ml of 20% alcoholic potassium hydroxide was refluxed for 1.5 h, after which it was diluted with 30 ml of water, and the resulting crystals were removed by filtration to give 0.4 g (95%) of colorless crystals with mp 84-86° (from heptane) and R_f 0.27 (chloroform). Found: C 75.0; H 7.2%. $C_{16}H_{17}NO_2$. Calculated: C 75.2; H 6.7%. The IR spectrum contained a band at 3495 cm^{-1} (hydroxyl group). The picrate was obtained as yellow crystals with mp 169-171° (from alcohol). Found: N 11.6%. $C_{16}H_{17}NO_2 \cdot C_6H_3N_3O_7$. Calculated: N 11.6%. The hydrochloride was obtained as colorless rods (soluble in hot water) with mp 175-177° (from benzene). Found: Cl 12.2%. $C_{16}H_{17}NO_2 \cdot HCl$. Calculated: Cl 12.2%.

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