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Pyridyl Ketones by Addition of Pyridyllithium to Carboxylic Acids. A New Synthesis of α-(2-Piperidyl)-2-aryl-4-quinolinemethanols (1)

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Sir:

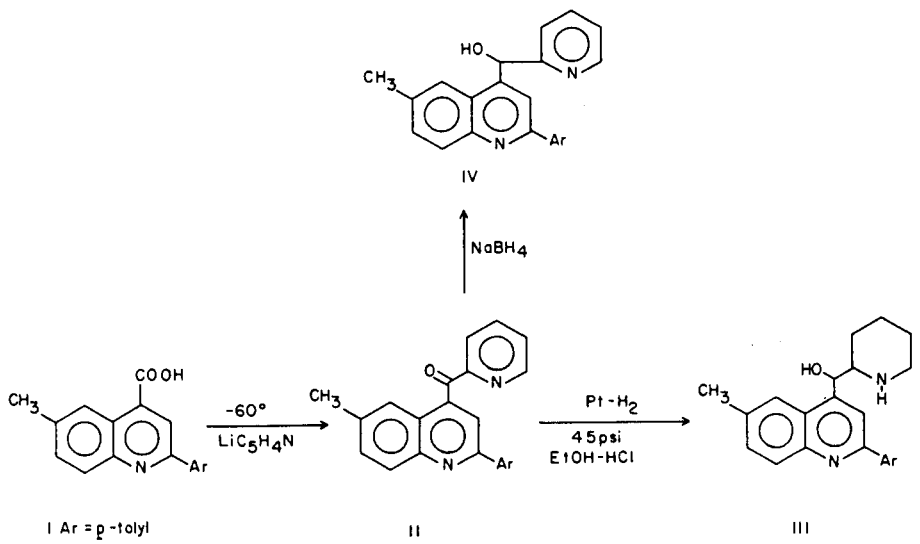
Resurgence of the malaria problem led us to synthesize a number of the title compounds, a type which had previously been made by a cumbersome 6-step synthesis from the corresponding quinoline-4-carboxylic acids (2). We now report a new and more convenient 2-step synthesis by which we have made fifteen α-(2-piperidyl)-2-aryl-quinolinemethanols in the 6-methyl, 8-methyl, 6,8-dimethyl and 8-trifluoromethyl series (*cf.* III). Also, by a variant in the second step, we have made twenty α-(2-pyridyl) analogs of type IV which represent a new class of potential synthetic medicinals, but which appear to be inactive toward malaria (1b).

In the example illustrated below the first step involves conversion of 2-*p*-tolylquinoline-4-carboxylic acid (I) by 2-pyridyllithium into 2-pyridyl ketone II. This reaction represents the first pyridyl ketone synthesis by addition of α-pyridyllithium to a carboxylic acid. The second step in the synthesis is controlled reduction of II. Catalytic hydrogenation specifically reduces the carbonyl and pyridyl groups and gives α-piperidylquinolinemethanol III; whereas, sodium borohydride reduces only the carbonyl group of II and gives the α-(2-pyridyl)quinolinemethanol IV. These reactions should find wide application in the alkaloid and synthetic medicinal fields.

Addition of 2 moles of α-pyridyllithium (3) at -60° to acid I followed by hydrolysis gave pyridyl ketone II; 60%; m.p. 142-143° (4,5). The structure is supported by: ν max (KBr), 1670 cm^{-1} (C=O); λ max (EtOH), 268, 344 mμ (2-arylquinoline type); nmr (deuteriochloroform), 1H signal at 1.3 τ characteristic of pyridine α-hydrogens.

Hydrogenation with platinum oxide of ketone II at 45 psi in ethanol containing 2 moles of hydrochloric acid, reduced the carbonyl and pyridyl groups, but not the quinoline nucleus. Only one of the two possible diastereoisomeric α-(2-piperidyl)quinolinemethanols III was isolated; 56%; m.p. 214-216° (4); λ max (EtOH), 267, 330, 339 mμ, ν max (KBr), *ca.* 3300 cm^{-1}; 2550-2750 cm^{-1}; nmr (deuteriochloroform), no signal at 1.3 τ, 1H doublet at 4.6 τ assignable to carbinol α-H, broad 3H and 6H multiplets at 6.5 and 8.4 τ, assigned to α-piperidyl and to β- and γ-piperidyl protons, respectively. The structure III was verified by infrared identity and mmp with a sample synthesized from I by the old route (2).

Reduction of only the carbonyl group of the 2-pyridyl ketone II by sodium borohydride afforded α-(2-pyridyl)-quinolinemethanol IV; 90%: m.p. 176-177.5° (4); ν max (KBr), 3200 cm^{-1}; λ max (EtOH), 268, 329, 339 mμ; nmr (deuteriochloroform), 1.4 τ, 4.5 τ (1H signals).



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(1a) Supported by the Walter Reed Army Institute of Research, Contract No. DA-49-193-MD-2955. (b) Antimalarial testing is in progress.

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(4) All new compounds gave correct elemental analyses.

(5) Addition of methyllithium to I gives the corresponding methyl ketone (80%) [*cf.* C. Tegner, *Acta. Chem. Scand.*, 6, 782 (1952)] and bromination gave the α-bromo ketone. These reactions were substituted for the conversion of I to the acid chloride, the hazardous large scale diazomethylation, and hydrobromination, which were formerly used in the synthesis of α-dialkylaminomethyl-2-aryl-4-quinolinemethanols (2d).

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