HOMOLYTIC ALKYLATION OF QUINALDINE AND QUINOXALINE WITH 18-CROWN-6

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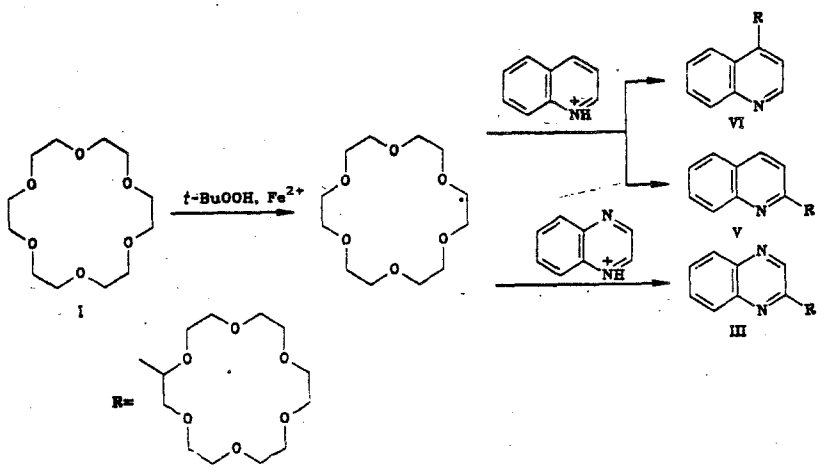
Homolytic alkylation of protonated quinoxaline with 18-crown-6, initiated by the system pivalic acid—iron(II) sulfate at 20-25°C, gives (quinoxalin-2-yl)-18-crown-6 in 85% yield. Under analogous conditions, the reaction with quinoline affords two isomers: (quinolin-4-yl)-18-crown-6 and (quinolin-2-yl)-18-crown-6, in yields of 20 and 30% respectively.

It has previously been shown that 18-crown-6 (I) reacts with protonated 2-methylquinoline in the presence of the initiating system tert-butyl hydroperoxide—iron(II) sulfate to give a quinaldine-containing crown ether [1].

It has been found that under similar conditions the crown ether (I) reacts with quinoxaline (II) protonated by sulfuric acid to also give the alkylation product (III):



The extent of reaction of the aromatic base reaches 34-40%, with 80-85% reaction of the crown ether (I). The yield of (III) was 85% on base reacted.

Examination of the regioselectivity of the homolytic alkylation showed that reaction of 18-crown-6 (I) with protonated quinoline (IV) resulted in the concurrent formation of the 2- and 4-substituted quinolines (V) and (VI).

The conversion of the base (IV) and the crown ether (I) reached 80-85%, and the yields of (V) and (VI) were 20 and 30% respectively. Although, generally speaking, attack of monoalkoxy-radicals on quinoline takes place preferentially in the 4-position [2], the bulky crown ether radical hinders the hydrogen in the 2-position to a greater extent than that in the 4-position.

EXPERIMENTAL

The products (III), (V), and (VI) were identified by PMR on a Tesla BS-497 instrument (100 MHz, $CDCl_3$, HMDS) and by elemental analysis.

The reaction of crown ether (I) with the aromatic bases (II) and (IV) was carried out in DMSO at 25°C under argon, for which purpose the aromatic base (0.01 mole), sulfuric acid (0.05 mole), iron(II) sulfate (0.005 mole), and 18-crown-6 (0.01 mole) were dissolved in 100 ml of DMSO.

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To this solution was added with stirring tert-butyl hydroperoxide (0.015 mole) over 30 min. To the solution was then added aqueous ammonia to pH 7-9, and the mixture extracted five times with chloroform. Unreacted base was removed by steam distillation.

The reaction products (III) and a mixture of (V) and (VI) were purified by column chromatography (alumina, hexane–chloroform, 3:1). The purity of isomers (V) and (VI) was established by TLC (adsorbent Silpearl, chloroform).

(Quinoxalin-2-yl)-18-crown-6 (III). PMR spectrum: 3.40-3.70 (22H, m, CH_2O), 5.30-5.40 (1H, m, OCH-Ar), 7.50-8.00 (4H, m, Ar), 8.78 ppm (1H, s, Ar).

(Quinolin-4-yl)-18-crown-6 (V). PMR spectrum: 3.40-3.71 (22H, m, CH_2O), 5.20-5.38 (1H, m, O–CH–Ar), 7.20-8.11 (5H, m, Ar), 8.82 ppm (1H, d, 2-H, Ar).

(Quinolin-2-yl)-18-crown-6 (VI). PMR spectrum: 3.42-3.71 (22H, m, CH_2O), 5.32-5.40 (1H, m, O–CH–Ar), 7.20-8.10 ppm (6H, m, Ar).

The elemental analyses of (III), (V), and (VI) were in agreement with the calculated values.

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REDUCTION OF QUINOLINECARBOXYLIC ACIDS BY RANEY ALLOY

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The heterocyclic nucleus in quinolinecarboxylic acids is reduced by Raney alloy (nickel–aluminium) in alkaline media to give 1,2,3,4-tetrahydro-2-,3-,4-,5-,6-, and 8-quinolinecarboxylic acids and 8-methyl-5-quinolinecarboxylic acid and their ethyl esters.

1,2,3,4-Tetrahydroquinolinecarboxylic acids are used in the synthesis of biologically active compounds [1, 2].

The choice of methods for the preparation of 1,2,3,4-tetrahydroquinolinecarboxylic acids is limited, and more often than not reduces to reduction of the heterocyclic ring in quinolinecarboxylic acids with tin in hydrochloric acid [3], zinc in formic acid [4], sodium in butanol [4], a mixture of formic acid and triethylammonium formate (giving the N-formyl derivatives of the acids) [4], or by catalytic hydrogenation in the presence of Adams catalyst [2, 4]. These methods have technical limitations (the use of platinum catalysts, high pressures and temperatures), and do not always give high yields, prompting a search for new modes of reduction of the heterocyclic ring.

We have found that good results are obtained by reducing 2-, 3-, 4-, 5-, 6-, and 8-quinolinecarboxylic acids and 8-methyl-5-quinolinecarboxylic acid (Ia-g) with nickel-aluminum alloy (Raney alloy). This reagent, which is usually used to reduce and hydrogenolyze heteroaromatic substituents [5], has been employed to a limited extent to convert naphthalenes into tetralins, including tetrahydronaphthoic acids [6].

Reduction of quinolines with Raney alloy has not hitherto been reported.

Treatment of the quinolinecarboxylic acids (Ia-g) with Raney alloy in 10% aqueous sodium hydroxide at 20°C proceeds readily to give high yields of the 1,2,3,4-tetrahydroquinoline-

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