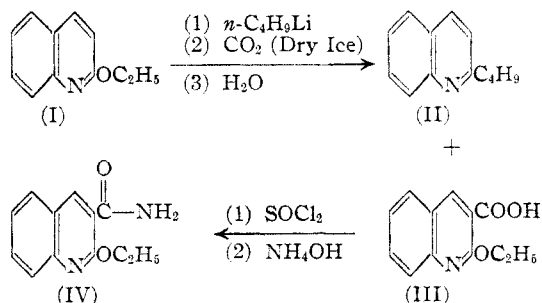


[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

## The Metalation of 2-Ethoxyquinoline

BY HENRY GILMAN AND JOHN A. BEEL

The reaction of 2-ethoxyquinoline (I)<sup>1</sup> with *n*-butyllithium<sup>2</sup> in ether at room temperature followed by carbonation resulted in a 57.9% yield of 2-*n*-butylquinoline (II) and a 7.1% yield of 2-ethoxyquinoline-3-carboxylic acid (III) as shown in the equations



That the metalation had taken place in the 3-position was proved by analysis and the melting point of III<sup>3</sup> and conversion of III to the carboxamide,<sup>4</sup> which was identified by mixed melting point with an authentic specimen of 2-ethoxyquinoline-3-carboxamide (IV).<sup>5</sup> The 2-*n*-butylquinoline was identified by the melting point of the picrate and a mixed melting point determination with an authentic specimen of the picrate.

The particularly strong *ortho*-orienting effect<sup>6</sup> of the alkoxy grouping is demonstrated in this metalation as no nuclear metalation of quinoline by reactive organometallic compounds has been observed in other 2-substituted derivatives<sup>7</sup> with the possible exception of 2-chloroquinoline.<sup>8</sup> In quinoline itself, the relative electron densities in various parts of the molecule<sup>9</sup> would lead one to expect that metalation, if initiated by an electrophilic attack by the metal ion,<sup>10</sup> would occur at the 8- or 3-position; the 8-mercuration of quinoline<sup>11</sup> may be mentioned in this connection. The nucleophilic view of metalation,<sup>12</sup> on the other hand, would predict attack at the 2- or 4-position. Actually, neither of these expectations is realized, since the facility of the addition of RLi to the azomethine linkage of quinoline takes precedence over any tendency toward

metalation. This is evidenced by the formation of 2-*n*-butylquinoline in 89% yield<sup>7a</sup> from quinoline and *n*-butyllithium at  $-75^\circ$  (bath temperature).

The ethoxy grouping in the 2-position of quinoline apparently deactivates the azomethine linkage, for under conditions which would yield almost the theoretical amount of 2-*n*-butylquinoline from quinoline and *n*-butyllithium, a 14.9% recovery of 2-ethoxyquinoline was obtained. The formation of the 2-*n*-butylquinoline from 2-ethoxyquinoline could result either from a preliminary addition to the azomethine linkage followed by elimination of lithium ethoxide or ethanol, or by a direct cleavage of the ethoxy grouping.

## Experimental

**2-Ethoxyquinoline and *n*-Butyllithium.**—A solution of 0.19 mole of *n*-butyllithium<sup>2</sup> in 253 ml. of ether was added slowly at room temperature to 32.2 g. (0.19 mole) of 2-ethoxyquinoline.<sup>1</sup> Twenty minutes after the addition the refluxing stopped, and a Color Test I<sup>13</sup> was negative. The mixture was carbonated by pouring into a slush of ether and Dry Ice. Hydrolysis was effected by adding water, and a precipitate of lithium bicarbonate was removed by filtration. Acidification of the aqueous layer yielded 2.42 g. (6.5%) of an acid which melted at  $120\text{--}130^\circ$ . Solution in sodium hydroxide and reprecipitation by hydrochloric acid yielded a compound which melted at  $132\text{--}133^\circ$ . This is the melting point of 2-ethoxyquinoline-3-carboxylic acid.<sup>3</sup>

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{11}\text{NO}_3$ : N, 6.45; neut. equiv., 217.2. Found: N, 6.38; neut. equiv., 218.0.

The ether layer was dried over sodium sulfate; the ether was removed by distillation, and the residue was distilled in a still of sixteen theoretical plates at a vacuum of 0.1 mm. This resulted in 4.8 g. (14.9% recovery) of 2-ethoxyquinoline ( $n_D^{20}$  1.5882) and 17.0 g. (49.4%) of 2-*n*-butylquinoline, identified by melting point of its picrate ( $163^\circ$ ) and mixed melting point of the picrate with an authentic specimen.<sup>8</sup> The recovery of 2-ethoxyquinoline increased the yields of 2-ethoxyquinoline-3-carboxylic acid and 2-*n*-butylquinoline to 7.1% and 57.9%, respectively. The last fraction ( $n_D^{20}$  1.5462) formed a crystalline precipitate on standing. This was filtered and washed with petroleum ether (b. p.  $60\text{--}70^\circ$ ). The melting point of this unidentified material was  $95^\circ$ .

**Preparation of 2-Ethoxyquinoline-3-carboxamide.**—A small amount of the acid was treated with thionyl chloride and then with concentrated ammonium hydroxide to form the carboxamide (m. p.  $155\text{--}157^\circ$ ). A mixed melting point with this material and a sample of 2-ethoxyquinoline-3-carboxamide<sup>4,5</sup> melted at  $156\text{--}157^\circ$ .

## Summary

1. 2-Ethoxyquinoline has been metalated in the 3-position in 7.1% yield by *n*-butyllithium at room temperature.

2. This reaction also results in a 57.9% yield of 2-*n*-butylquinoline.

3. A brief discussion of the orientation of the metalation has been presented.

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