NOTES

Studies of Pyridotropolones. VIII.[1] Synthesis of 7-Isopropyl-6-quinolinols

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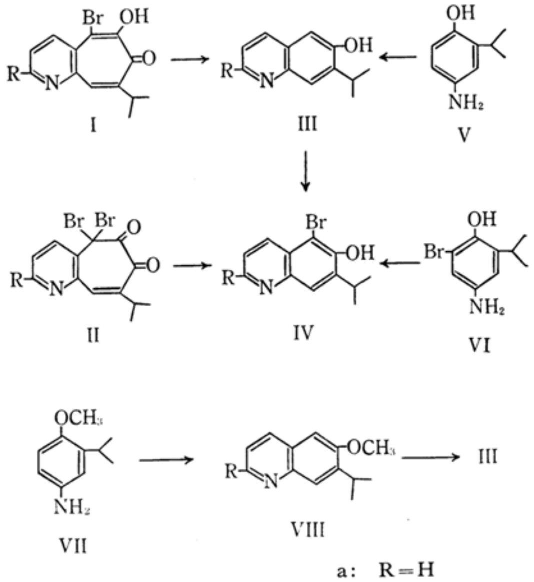
In order to make a final confirmation of the structure of the quinolinols obtained by the alkaline rearrangement of 5-bromo- and 5, 5-dibromo-8-isopropyl-pyrido[3, 2-*d*]tropolone (I and II),[2] 7-isopropyl-6-quinolinol and its 2-methyl homolog (III and IV) were synthesized unambiguously by two methods. The details of the research will be reported herein.

The Skraup and Doebner-Miller reaction of 4-amino-2-isopropylphenol (V)[3] under usual conditions did not afford any quinolinol derivative, but 7-isopropyl-6-quinolinol (IIIa) was obtained by a Skraup reaction using α-bromoacrolein,[4] and its 2-methyl homolog (IIIb) was formed by a Doebner-Miller reaction using α-bromocrotonaldehyde.[5]

A Skraup reaction with α-bromoacrolein in 85% phosphoric acid was carried with 4-amino-6-bromo-2-isopropylphenol (VI) prepared by the reduction of 6-bromo-2-isopropyl-4-nitrophenol[6]; 5-bromo-7-isopropyl-6-quinolinol (IVa) was thus obtained in a 49% yield. However, the Doebner-Miller reaction of the aminophenol was unsuccessful, yielding only a tarry material. The reason for this failure being considered to be the instability of the aminophenol used, the corresponding anisol, 4 - amino - 2 - isopropylanisol[7] (VII), was next subjected to the reaction. VII with α-bromoacrolein in 85% phosphoric acid yielded 7-isopropyl-6-methoxyquinoline (VIIIa) in a 80% yield. The methyl homolog of VIIIa was obtained by a Doebner-Miller reaction (in a 44% yield), by Tamura's modification[8] (in a 71% yield) and by using α-bromocrotonaldehyde (in a 68% yield). The two methoxyquinolines, VIIIa and VIIIb, afforded the corresponding quinolinols, IIIa and IIIb, upon being heated with hydroiodic acid. Of the two possible directions of the cyclization in the Skraup and Doebner-Miller quinoline synthesis of 4-amino-2-isopropyl-phenol or -anisol, only one was observed, that leading to 7-isopropyl-6-quinolinol; no indication was found of the formation of a 5-isopropyl counterpart. This was probably due to the steric hindrance of the isopropyl group. The 7-isopropyl-6-quinolinols (III and IV) thus synthesized were found to be identical with the corresponding rearrangement products of brominated 8-isopropyl-pyrido[3, 2-*d*]tropolones (I and II)[2] by a mixed melting point test and by a comparison of the UV and IR spectra.



a: $R=H$
b: $R=CH_3$

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Experimental

7-Isopropyl-6-quinolinol (IIIa). 1) To a mixture of V (0.3 g) in 85% phosphoric acid (1.1 m*l*) heated at 120°C, α-bromoacrolein (0.18 m*l*) was added drop by drop, the mixture was then kept at the same temperature for 10 min. After cooling, a small amount of water was added, and the mixture was neutralized with aqueous ammonia. The precipitate was dissolved in acetone and treated with activated charcol. The solvent was removed, and the residue was recrystallized from diluted methanol to give IIIa (0.28 g, yield 75%).

2) The heating of VIIIa (0.8 g) in hydroiodic acid (1.5 m*l*) gave IIIa (0.32 g, yield 41%).

7-Isopropyl-2-methyl-6-quinolinol (IIIb). 1) Treating V (1.5 g) in 85% phosphoric acid (10 m*l*) with α-bromocrotonaldehyde,⁵⁾ as described above, gave IIIb (0.22 g, yield 10%).

2) The heating of VIIIb (0.45 g) in hydroiodic acid (1 m*l*) gave IIIb (0.14 g, yield 34%).

4-Amino-6-bromo-2-isopropylphenol (VI).*[2] Into a solution of 6-bromo-2-isopropyl-4-nitrophenol (2 g) in benzene (80 m*l*), activated iron⁹⁾ prepared from iron powder (20 g) was added in small portions while the mixture was being heated on a water bath. After the mixture had then been refluxed for 1.5 hr, water (0.4 m*l*) was added, drop by drop, and the mixture was heated under reflux for an additional 2 hr. The iron powder was then removed and the benzene was distilled off to leave a brown solid. Recrystallization from dilute methanol gave pale brown needles, mp 101.5—102°C (1.6 g, yield 94%).

5-Bromo-7-isopropyl-6-quinolinol (IVa). VI (0.69 g) in 85% phosphoric acid (2 m*l*) was treated with α-bromoacrolein (0.28 m*l*), as has been described above, to give IVa (0.4 g, yield 49%).

7-Isopropyl-6-methoxyquinoline (VIIIa).*[2] VII (1.6 g) in 85% phosphoric acid (10 m*l*) was treated with α-bromoacrolein (0.9 m*l*) by a method described above to give a colorless oil, bp 152—153°C/6 mmHg (0.85 g, yield 80%). Picrate, yellow micro needles, mp 210—211°C.

7-Isopropyl-2-methyl-6-methoxyquinoline (VIIIb).*[2] 1) A mixture of VII (1.5 g), para-aldehyde (1.8 g), and concentrated hydrochloric acid (4.5 m*l*) was heated at 120°C for 40 min. After cooling, a small amount of water was added, and the mixture was neutralized with aqueous ammonia and then extracted with ether. The solvent was removed, and the residue was distilled in vacuo to give a pale yellow oil, bp 138—139°C/4 mmHg (0.5 g, yield 26%). Picrate, yellow micro hexagonal plates, mp 229—230°C.

2) VII (1.65 g) was treated in a manner similar to that described by Tamura *et al.*⁸⁾ to give VIIIb (1.63 g, yield 71%).

3) VII (1.65 g) in 85% phosphoric acid (4 m*l*) was treated with α-bromocrotonaldehyde⁵⁾ (1.88 g) by a method similar to that described above to give VIIIb (1.46 g, yield 68%).

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*[2] Satisfactory analyses have been obtained for all the new compounds described in this paper.

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