93. Eiji Ochiai and Junzaburo Takeuchi : Polarization of Aromatic Heterocyclic Compounds. LXXXIII.¹⁾ Nitration of 2,4-Dimethylquinoline (Addendum).

(Pharmaceutical Institute, Medical Faculty, University of Tokyo)

Nitration of 2,4-dimethylquinoline can be found in the works of Roberts and Turner²⁾ who treated the said compound with sulfuric and nitric acids in a cold state (0° to 5°) and obtained a mononitro compound of m.p. 118–119°. From the fact that they obtained 8-chloro-2,4-dimethylquinoline by the reduction and subsequent diazotation of the mononitro compound, they concluded that the original compound obtained had been 8-nitro-2,4-dimethylquinoline. In their work (Report XXXIII)³⁾, Ochiai and Shimizu obtained two kinds of mononitro compounds of m.p. 147°, and 160–162°, respectively, in 3 : 1 ratio by treating 2,4-dimethylquinoline with conc. sulfuric acid and potassium nitrate, on a boiling water bath. These compounds were determined as 8-nitro- and 6-nitro-2,4-dimethylquinolines, respectively, by their coincidence with these compounds synthesized by Beyer's method from *o*- and *p*-nitraniline. It was assumed, therefore, that the mononitro compound obtained by Roberts and Turner must have been a mixture, or a molecular compound, of these two nitro compounds. Without the knowledge of these works of Ochiai and Shimizu, Price, et al.,⁴⁾ reexamined the experiments of Roberts and Turner, and determined that the mononitro compound obtained by the latter was an eutectic mixture (2 : 1) of 8-nitro- and 6-nitro-2,4-dimethylquinoline. Later, Vaughan⁵⁾ obtained a mononitro compound of m.p. 109.9–110.1° from the mother liquor of these two mononitro compounds and assumed it to be 5-nitro-2,4-dimethylquinoline.

The present authors followed the nitration of Roberts and Turner on 2,4-dimethylquinoline and obtained 8-nitro- and 6-nitro compounds, as well as platelet crystals of a mononitro compound of m.p. 110–111° from their mother liquor, which was determined, as assumed by Vaughan, to be 5-nitro-2,4-dimethylquinoline.

Mononitro compound of m.p. 110–111° gives a picrate of m.p. 184°, and gives colorless prisms of monoamino-2,4-dimethylquinoline of m.p. 80–82.5° by reduction. The latter gives a picrate of plate crystals, m.p. 248° (decomp.), and a monoacetyl compound of m.p. 177.5–179.5°. The latter was identical with 5-acetylamino-2,4-dimethylquinoline synthesized by method described later, so that the original nitro compound was determined as 5-nitro-2,4-dimethylquinoline.

It follows, therefore, that the nitration of 2,4-dimethylquinoline by sulfuric and nitric acids gives, chiefly, 8-nitro compound with a by-product of 6-nitro and a very small amount of 5-nitro compounds.

Synthesis of 5-Amino-2,4-dimethylquinoline :

Experimentation on quinoline cyclization from 6-bromo-3-nitraniline by both Beyer's and Combe's methods ended in recovery of the original material. Nitration of 8-chloro-2,4-dimethylquinoline was then attempted by following the conditions given by Roberts and Turner, and a mononitro compound, as described by them, was obtained as pale

1) LXXXII. This Journal, **70**, 384 [1950].

2) Roberts & Turner : J. Chem. Soc., **129**, 1837 [1927].

3) Ochiai & Shimizu : J. Pharm. Soc., Japan, **63**, 398 [1943].

4) Price, Velzen & Guthrie : J. Org. Chem., **12**, 203 [1947].

5) Vaughan : J. Am. Chem. Soc., **70**, 2294; Chem. Abstracts, **42**, 6821.

yellow prisms, m.p. 108–109.5°. Dichloro-2,4-dimethylquinoline obtained by the reduction, diazotation and by Gatterman's method of the latter was identical with 5,8-dichloro-2,4-dimethylquinoline synthesized by Beyer's method from 2,5-dichloraniline. This reestablished the results obtained by Roberts and Turner, and determined the original nitro compound to be 5-nitro-8-chloro-2,4-dimethylquinoline. It followed, therefore, that the reduction of this compound to 5-amino-8-chloro-2,4-dimethylquinoline and dechlorination of the latter with $\text{Pd} \cdot \text{CaCO}_3$ gave 5-amino-2,4-dimethylquinoline, prisms, m.p. 80–82.5°. This compound gives an acetate of needles, m.p. 176–178.5°.

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Experimental

Nitration of 2,4-Dimethylquinoline—2,4-Dimethylquinoline (5.0g.) was dissolved in conc. H_2SO_4 (25 g.) under cooling by ice, and a mixture of fuming HNO_3 (4.75 g.) and conc. H_2SO_4 (9.5 g.) was added in drops while keeping the temperature around 5°C. After leaving it standing for 2 hrs. the solution was poured into ice water, alkalized with Na_2CO_3 and the precipitate here obtained was filtered, dried, and recrystallized from EtOH to yellowish white needles, m.p. 117–121°. Yield, 4.3 g. After collecting the same crystals from the mother liquor by concentration, this was evaporated to dryness and the residue crystallized repeatedly from MeOH. Platelet crystals of m.p. 110–111° (picrate, m.p. 184°) was obtained. Yield, 0.1 g.

The crystals of m.p. 117–121° that separated from the EtOH solution were collected, dissolved in benzene and passed through an alumina column of 17 mm. $\times$ 31 cm. Development of the column by benzene gave crystals of m.p. 140–146° (yield, 3.5 g.), and of m.p. 137–154° (yield, 1.2 g.). The former recrystallized from MeOH to white, fine needles, m.p. 147°, and the latter from acetone to pale yellow needles, m.p. 160–162°. The proportion of the yield was approximately 3 : 1 : 0.1 for crystals of m.p. 147°, 160–162° and 110–111°, respectively.

Analysis of substance with m.p. 110–111° : Calculated for $\text{C}_{11}\text{H}_{10}\text{O}_2\text{N}_2$: C, 65.31; H, 5.00; N, 13.87. Found : C, 65.75; H, 4.86; N, 13.73.

The mixed fusion of the substance with m.p. 147° with 8-nitro-2,4-dimethylquinoline synthesized by Beyer's method from *o*-nitraniline gave no depression of the melting point.

The substance with m.p. 160–162° also gave no depression of the melting point when fused with 6-nitro-2,4-dimethylquinoline synthesized from *p*-nitraniline.

5-Amino-8-chloro-2,4-dimethylquinoline—A mixture of 5-nitro-8-chloro-2,4-dimethylquinoline, m.p. 108.5–109.5°, obtained by the nitration of 8-chloro-2,4-dimethylquinoline according to Roberts and Turner (0.2 g.), 1.5 % FeCl_3 solution (1.0 cc.), iron powder (0.2 g.) and MeOH (3 cc.) was warmed for 1.5 hrs. over a water bath, 1 drop of NH_3 added and filtered. The solvent was distilled off from the filtrate, and residual, yellow crystals were recrystallized from benzene to pale yellow prisms, m.p. 171–2.5°. Yield, 0.12 g. Cl-reaction, positive.

Anal. Calculated for $\text{C}_{11}\text{H}_{11}\text{N}_2\text{Cl}$: C, 63.60; H, 5.36; N, 13.56. Found : C, 63.46; H, 5.44; N, 14.73.

5-Acetylamino-2,4-dimethylquinoline— $\text{PdO} \cdot \text{CaCO}_3$ (0.05 g.) and MeOH (5 cc.), with the addition of a small amount of Pd-coal, were shaken in a H_2 stream to allow complete absorption of hydrogen. To this was added 5-nitro-8-chloro-2,4-dimethylquinoline (0.1 g.) dissolved in MeOH (5 cc.), 5 % methanolic KOH (0.75 cc.) added, and shaken in a hydrogen stream. After about 40 minutes, the calculated amount of hydrogen (38 cc.) was absorbed. The catalyst was then filtered off, CO_2 saturated in the filtrate, the solvent distilled off, and the residue was extracted with benzene. Slight evaporation of this benzene solution precipitated out yellowish-white, fine needles, m.p. 74–81°. Acetic anhydride

(0.2 cc.) was immediately added, boiled for a short time, diluted with water, and extracted with AcOEt after being alkalized with ammonia. Crystalline residue obtained by the distillation of the solvent was recrystallized from benzene to pale, yellowish-white, fine needles, m.p. 176–178.5°. Cl-reaction, negative.

Anal. Calculated for $C_{13}H_{14}ON_2$: C, 72.85; H, 6.59; N, 13.07. Found: C, 72.67; H, 6.16; N, 13.35.

Reduction of Nitro-2,4-dimethylquinoline of m.p. 110–111°—A mixture of 0.1 g. of the mononitro compound, 1.5 % $FeCl_3$ solution (0.3 cc.) and iron powder (0.1 g.) was warmed over a boiling water bath for 1.5 hrs., 1 drop of dil. NH_4OH added, and extracted with hot MeOH. By distillation of the solvent, tarry residue was obtained which later solidified. This was divided into two portions, and the first was distilled under reduced pressure.

The distillate of b.p.₆ 130° (bath temperature) was recrystallized from benzene to colorless prisms, m.p. 80–82.5°.

Anal. Calculated for $C_{11}H_{12}N_2$: C, 76.67; H, 7.02; N, 16.28. Found: C, 75.56; H, 6.80; N, 15.54.

Picrate: Dark brown needles or plates from MeOH, m.p. 248° (decomp.).

Anal. Calculated for $C_{11}H_{12}N_2 \cdot C_6H_3O_7N_3$: C, 50.43; H, 4.01. Found: C, 51.77; H, 3.56.

• Acetate: Fine needles, m.p. 177.5–179.5°, from benzene.

Anal. Calculated for $C_{13}H_{14}ON_2$: C, 72.85; H, 6.59; N, 13.07. Found: C, 72.68; H, 6.13; N, 12.83.

No depression of the melting point occurred when this was fused with 5-acetylamino-2,4-dimethylquinoline.

Summary

Three isomers are obtained on nitration of 2,4-dimethylquinoline. The hitherto uncertain isomer was identified as 5-nitro-2,4-dimethylquinoline. The following new compounds were prepared: 5- and 6-amino-2,4-dimethylquinoline, 5-acetylamino-2,4-dimethylquinoline and 5-amino-8-chloro-2,4-dimethylquinoline. (Received March 23, 1950)

94. Eiji Ochiai und Yoshiro Kobayashi: Synthese von Derivaten der Cinchona-Alkaloiden. XIX¹⁾ Synthese von 2'-substituiertem Dihydrochinin.

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Vor kurzem haben Ochiai, Okamoto und Kobayashi²⁾ durch Erhitzen des ar.-Mono-*N*-oxydes von Chinin bzw. Dihydrochinin mit Säureanhydrid auf 120–130° das entsprechende 2'-Hydroxyderivat hergestellt, und Ochiai und Okamoto³⁾ haben aus dem 2'-Hydroxychinin über 2'-Chlorderivat in 2'-Butoxychinin abgeleitet.

Da das 2'-Butoxychinin eine lokalanästhetische Wirkung zeigte, haben wir diese Untersuchung fortgesetzt und analoger Weise nach unten angegebener Reaktionsreihe 2'-Butoxy- und Methoxy-derivat von Dihydrochinin dargestellt.

Die Darstellung von 2'-Hydroxydihydrochinin wurde durch Herabsetzung der Reaktionstemperatur auf 105° und durch Verlängerung der Reaktionszeit verbessert. Die Ausbeute

1) XVIII Mitteilung: Diese Zeitschr., **70**, 381 [1950].

2) Diese Zeitschr., **68**, 109 [1948].

3) Diese Zeitschr., **68**, 112 [1948].