Anethol und 100 mg Palladiumschwarz[6] zugesetzt und unter Stickstoff-Strom 6 Stunden lang im Sieden gehalten. Nach dem Erkalten wurde der Katalysator abfiltriert, wobei die schon orange gefärbte Lösung sofort tiefgrünlich wurde. Das Filtrat wurde im Vakuum bei Zimmertemperatur unter Stickstoff-Strom eingeengt. Hierbei schied sich eine sehr kleine Menge schwachgelbe Prismen aus, welche aus MeOH umkristallisiert wurde. Schmp. 133～134°. Sie lösen sich in MeOH mit blauer Fluorescenz und sind an der Luft ziemlich leicht veränderlich. Von dem übrigen Teil wurde keine einheitliche Substanz isoliert.

ii) 70 mg (XII)-Hydrochlorid wurden in 6 ccm EtOH gelöst, 400 mg Merkuriacetat und 2 Tropfen Eisessig zugesetzt und unter Stickstoff-Strom 4 Stunden lang auf dem Wasserbade erhitzt, wobei sich die Lösung nach etwa 5 Minuten dunkelgrün und nach 30 Minuten schwarzviolett färbte. Der hierbei ausgeschiedene Niederschlag (250 mg) wurde abfiltriert, das Filtrat im Vakuum unter vermindertem Druck im Stickstoff-Strom eingeengt, Soda-alkalisch gemacht und mit $CHCl_3$ ausgezogen. Der $CHCl_3$-Auszug (33 mg) bildet eine schwarzviolett gefärbte amorphe Masse vom Zers. Pkt. ca. 225～235°, die sich nicht weiter reinigen liess.

Zusammenfassung

1-(*o*-Brombenzyl)-isochinolin wurde neu hergestellt. Das letztere wurde durch Erhitzen mit konz. Ammoniak auf 180～190° unter Zusatz von Kupferbromür in 1-(*o*-Aminobenzyl)-isochinolin übergeführt. Nebenbei entstanden 1-Benzylisochinolin und Dibenzoindolizin. 1-(*o*-Aminobenzyl)-isochinolin wurde über sein 1,2,3,4-Tetrahydrid nach der Pschorr'schen Synthese in das Noraporphin übergeführt. Die Versuche, die durch die Pschorr'sche Synthese von 1-(*o*-Aminobenzyl)-isochinolin oder durch die Dehydrierung von Noraporphins das Dehydronoraporphin herzustellen, waren erfolglos.

(Eingegangen am 11. März 1957)

UDC 547.832.5

52. **Keizo Nomoto**: Synthesis of 4-Benzylquinoline Derivatives. I. Nitration of 4-Benzylquinoline.

(*Patent Office, Tokyo**)

Ochiai[1] found that the hydrogen atom in the 4-position of pyridine 1-oxide or quinoline 1-oxide can easily be replaced by other functional radicals, thus establishing a new method for preparing 2- or 4-substituted pyridine and quinoline compounds. He further applied this method to the synthesis of 1-benzylisoquinoline and several of its derivatives, some of which having been proved to possess a papaverine-like anesthetic activity as was expected from its skeleton.

On the other hand, Cuttler[2] and his collaborators synthesized several derivatives of α-(4-quinolyl)-α-phenylacetonitrile by condensing phenylacetonitrile with 4-chloroquinoline in the presence of sodium amide in benzene.

Consequently, a synthesis of 4-benzylquinoline and several of its derivatives was taken up. First of all, 4-chloroquinoline (I) was prepared by the Ochiai method. Compound (I) thus obtained was treated in ether with phenylacetonitrile (II) and finely pulverized sodium amide according to the Cuttler method. When condensation reaction was complete, ether was removed and the residue was dissolved in benzene. The benzene solution was shaken with conc. hydrochloric acid and α-(4-quinolyl)-α-phenylacetonitrile (III) was isolated from the acid solution by the addition of aq. ammonia. The nitrile (III) was converted

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1) E. Ochiai: J. Org. Chem., **18**, 534(1953).

2) R. A. Cuttler, A. R. Surrey, J. B. Cloke: J. Am. Chem. Soc., **71**, 3375(1949).

to the corresponding acid amide (IV) by standing overnight with conc. sulfuric acid. The acid amide freed from the acid solution was refluxed with sulfuric acid. 4-Benzylquinoline (V) was extracted from the acid solution with ether after freeing by addition of aq. ammonia. The compound (V) was also prepared by direct decyanation of (III). The purified (V) was nitrated by the ordinary procedure. Upon analysis, the nitration product was identified as 4-(*p*-nitrobenzyl)quinoline (VI). This mononitro compound was reduced to monoamino compound (VII) which in turn was diazotized. The diszonium group of the resultant (VIII) was replaced with bromine atom by the Gattermann's reaction. Thus 4-(*p*-bromobenzyl)quinoline (IX) was obtained as a pale yellow oil. Its picrate and perchlorate were prepared.

This bromo compound (IX) was also synthesized directly from *p*-bromophenylacetonitrile (X) and (I) in the presence of sodium amide. Its picrate and perchlorate were also prepared. Mixed fusion of these two bromo compounds synthesized by two different methods indicated that they are identical.

The whole course of this synthesis is represented in Chart 1.

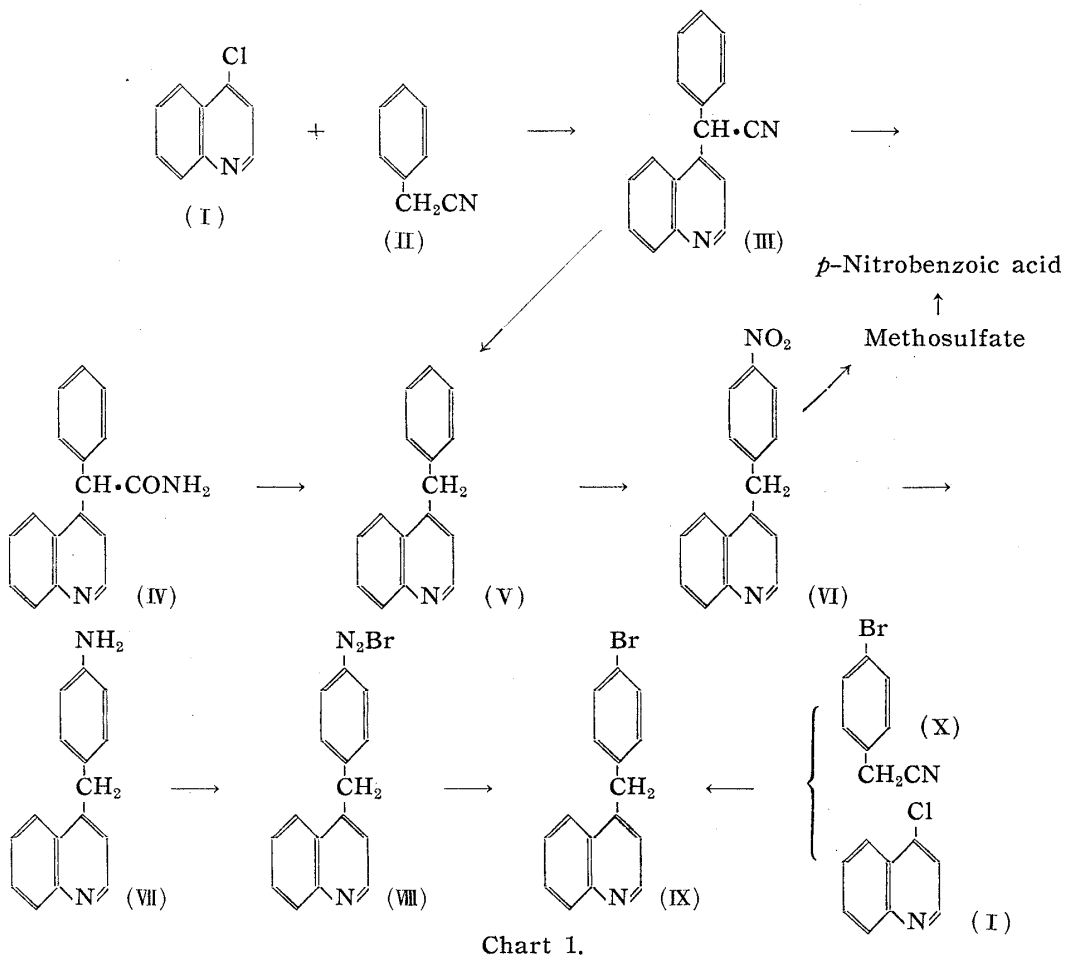

Chart 1.

The author wishes to express his appreciation to Prof. E. Ochiai of University of Tokyo for many advices and to Messrs. K. Yoshifuji and J. Saito, Directors of the Patent Office, Japanese Government, for kind encouragement.

Experimental*

α-(4-Quinolyl)-α-phenylacetonitrile (III)—A mixture of 12.5 g. (II), treated with $NaNH_2$ in Et_2O, and 10 g. of freshly distilled (I) (bp_2 112°), added in a small amount of Et_2O, was stood over-

* All m.p.s and b.p.s are uncorrected.

night, and the mixture was refluxed gently on a water bath (bath temp., ca. 40°) for about 10 hrs. When the mixture became more insoluble, the solvent was distilled off and the residue was dissolved in the same volume of benzene as the Et_2O used. The benzene solution was treated with conc. HCl and the base was extracted with $CHCl_3$ after being freed by the addition of aq. NH_4OH. The solvent was distilled off and crude (III) was obtained as a hard resinous substance. Yield, 14 g.

α-(4-Quinolyl)-α-phenylacetamide (IV) and 4-Benzylquinoline (V)–Unpurified (III), obtained above, was used as the starting material. A solution of 14 g. of (III) dissolved in 55 cc. of conc. H_2SO_4 was left to stand overnight, acetamide (IV) was liberated by pouring the strong acid solution into a mixture of pieces of ice and aq. NH_4OH. The precipitate was collected on a filter, washed with EtOH and recrystallized from BuOH to the acetamide (IV) of white crystals, m.p. 269°. Yield, 8 g. (IV) was boiled with 40 cc. of 60% H_2SO_4 for 5 hrs. and 4 g. of 4-benzylquinoline (V) was obtained as a pale yellow oil from the acid mixture by the method mentioned below. 4-Benzylquinoline was also prepared by direct decyanation of the foregoing nitrile (III) by boiling 27 g. of (III) with a mixture of 50 cc. of H_2O and 50 cc. of conc. H_2SO_4 for about 5 hrs. under reflux. After the reaction was complete, the acid mixture was poured into a mixture of crushed ice and aq. NH_4OH. An oily substance separated was taken up in Et_2O, the solvent was distilled off, and the residue was distilled in an Anshütz flask under vacuum, $b.p_{3\sim4}$ 205~210° (V), which was further distilled to give fractions of $b.p_2$ 198° and $b.p_{0.004}$ 150~153°. Thus (V) was obtained as a pale yellow oil, easily soluble in Et_2O and Me_2CO, moderately soluble in benzene. It was purified by chromatography on Al_2O_3 column with benzene. Yield, 17 g. It crystallized out after a long standing in a cold room. Sulfate: m.p. 197°, was identical with Cuttler's substance. Picrate: Rhombic crystals, m.p. 171~173°. Hydrochloride: Cubic crystals, m.p. 175~177° *Anal.* Calcd. for $C_{16}H_{13}N\cdot HCl$: C, 75.14; H, 5.51. Found: C, 74.73; H, 5.42.

Nitration of 4-Benzylquinoline (V)—4.5 g. of purified (V) was dissolved in 10 cc. of conc. H_2SO_4, cooled with ice-water to 0°, and a cold mixture of 2 cc. of HNO_3 (sp. gr., 1.38) and 2 cc. of conc. H_2SO_4 was added. After standing for about 10 mins., the mixture was warmed at 30° for 10 mins., the mixture was poured on cracked ice, and the yellow solid was separated from the mother liquor. The solid was treated several times with Et_2O, the mother liquor was made alkaline, shaken with Et_2O, and the solvent was distilled off. The residual substance was dissolved in benzene and the soln. of the nitro compound was purified by chromatography using Al_2O_3 column. Yield, 3.8 g. of m.p. 135.5°. *Anal.* Calcd. for. $C_{16}H_{12}O_2N_2$: C, 72.71; H, 4.58. Found: C, 72.71; H, 4.39.

In order to acertain the position of the nitro group, a methosulfate of the mononitro compound was prepared and oxidized with neutral $KMnO_4$ solution on a water bath, and from the oxidation product, *p*-nitrobenzoic acid was obtained. This result indicates that the nitro group had been introduced into the *para*-position of the benzyl group and the said mononitro compound is 4-(*p*-nitrobenzyl)quinoline (VI).

Reduction of 4-(*p*-Nitrobenzyl)quinoline (VI)—A mixture of 1 g. of (VI) and 4 g. of finely granulated Sn, with 17 cc. of EtOH and 5.5 cc. of conc. HCl, was warmed on a water bath for about 10 mins., EtOH was removed by distillation and 10% NaOH was added in excess. The turbid mixture was shaken several times with Et_2O, extracts were combined and distilled, affording fine white crystals. Yield, 0.5 g. The crystals, after purification by chromatography and recrystallization, melted at 130~132°. That the crystal is of amino compound can be known from the following experiment.

Preparation of 4-(*p*-Bromobenzyl)quinoline (IX) from the Reduction Product—A solution of 0.2 g. of the above-indicated crystals in 20 cc. of 40% HBr was diazotized with conc. $NaNO_2$ solution in an ice bath. After diazotization, a small amount of Gattermann's Cu powder was added to it. When evolution of N_2 gas ceased after about 0.5 hr., the product was extracted with Et_2O, washed with dil. NaOH solution, and the solvent was distilled off. Basic oily substance remaind. Picrate: m.p. 188°. The pure base was isolated from the picrate.

***p*-Bromophenylacetonitrile(X)**—(a) From *p*-Toluidine: Ten g. of *p*-toluidine was diazotized by the ordinary method and the diazonium group was then replaced by bromine atom according to the Bigelow method.[3] Yield, 5 g. The whole amount of *p*-bromotoluene thus obtained was oxidized with CrO_3 according to Lieberman and Connor method.[4] Three g. of *p*-bromobenzaldehyd (XI) was obtained, which was converted to (X) by the following Campbell-McKail method[5] (the so-called rhodanine synthesis). To a soln. of 3 g. of (XI) and 2 g. of rhodanine in 15 cc. of glacial AcOH, 4 g. of fused AcONa was added, and the resulting mixture was refluxed in an oil bath for 1.5 hrs. The condensation product, m.p. 237~238°, of the aldehyde with rhodanine was dissolved in 8% NaOH and heated on a vigorously boiling water bath until all the material dissolved. The resulting EtOH solution was cooled using a freezing mixture and an acid was precipitated by the addition

3) L. A. Bigelow: Org. Syntheses, Coll. Vol. I, 135(1948).
4) V. Lieberman, R. Connor: *Ibid.* Coll. Vol. II, 441(1948).
5) Campbell, McLail: J. Chem. Soc., **1948**, 1251.

of 10% HCl to the cold mixture. Thus, 2.5 g. of thioketo acid, m.p. 185°, was obtained, after recrystallization. Then 2.5 g. of the thioketo acid was treated with a free NH_2OH solution, prepared from 3 g. of $NH_2OH \cdot HCl$, 0.7 g. of Na, and 20 cc. of EtOH. The reulting solution was heated for about 0.5 hr., the solvent was distilled off under a reduced pressure. The residual solid mass was dissolved in 5 cc. of 5% NaOH solution, and cooled with ice after filtration. When cool, the solution was acidified with 10% HCl and an oximino acid was obtained. The whole amount of the oximino acid, after having been completely dried, was converted to the nitrile by warming in Ac_2O under reflux for 0.5 hr. After the removal of Ac_2O from the reaction mixture by distillation, it was shaken with Et_2O and H_2O. The Et_2O extract of the product was washed with Na_2CO_3 solution, dried, and Et_2O was distilled off, giving 1.5 g. of (X), $b.p_{3\sim5}$ 145～150°.

b) From *p*-Nitrotoluene : *p*-Nitrotoluene was oxidized with CrO_3 into *p*-nitrobenzaldehyde. The aldehyde group of the product was converted to $CN\text{-}CH_2$ group according to the rhodanine synthesis. *p*-Nitrophenylacetonitrile thus obtained was reduced to *p*-aminophenylacetonitrile which was then coverted to (X) by the procedure as stated in (a).

4-(*p*-Bromobenzyl)quinoline (IX)—*p*-Bromophenylacetonitrile (X) (1 g.) and 4-chloroquinoline (I) (1 g.), both of which were freshly distilled, were combined in Et_2O in the presence of $NaNH_2$ (0.7 g.), the mixture was treated in the same manner as for (III) and (IV), and 4-(*p*-bromobenzyl)quinoline (IX) was obtained as a yellow oil, $b.p_2$ 167°. It is a very weak base, its hydrochloride readily hydrolyses in the air by the presence of moisture. Attempt to obtain pure crystals of the hydrochloride failed. In order to identify this bromo compound with that obtained earlier, its picrate m.p. 188°, was prepared. No m.p. depression was shown on admixture of these picrates, thus indicating that the two bromo compounds are identical. Further, perchlorate of (IX) was prepared as cubic crystals, m.p. 151.5～152.5°, after drying over P_2O_5. *Anal.* Calcd. for $C_{16}H_{12}NBr \cdot HClO_4$: C, 48.19; H, 3.29. Found : C, 48.12; H, 3.17.

Summary

4-Benzylquionline (V) was synthesized and from its nitration product, 4-(*p*-nitrobenzyl)quinoline (VI) was isolated. It was reduced to the amino compound and substituted with bromine atom via diazonium group.' 4-(*p*-Bromobenzyl)quinoline (IX) thus obtained was identified with an authentic sample derived from 4-chloroquinoline (I) by the action of *p*-bromophenylacetonitrile (X).

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10-3

53. Kōiti Kimura and Hiroshi Hikino : Studies on the Constituents of Ephedra. I. Determination of Alkaloids in Ephedra.*

(*Faculty of Pharmacy, University of Osaka***)

The routine methods generally used for the determination of ephedrine have been acid-base titration and direct Kjehldahl steam-distillation.[1] As a special method, a colorimetric method based on the Nagai reaction was described by Feng,[2] the formation of iodoform from ephedrine was proposed as a method of estimation by Sánchez,[3] and biological methods have been used by several workers.[4] However, none of them proved adequate as a method of microdetermination.

On the other hand, ninhydrin reaction, found by Ruhemann as a color test for α-

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1) W. W. Hilty : J. Am. Pharm. Assoc., **33**, 28(1944); L. H. Welsh : *Ibid.*, **33**, 96(1944).
2) C. T. Feng : Chin. J. Physiol., **1**, 337(1928).
3) J. A. Sánchez : J. Pharm. Chin., **22**, 489(1933).
4) P. S. Pittenger : J. Am. Pharm. Assoc., **17**, 634(1928); T. S. Githens : *Ibid.*, **22**, 391(1933).