[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Further Study of the Synthesis of 4-Hydroxyquinolines from β-Anilinopropionic and Butyric Acids

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In an earlier communication[1] the results of a preliminary study of the cyclization of β-anilinopropionic acids to 4-keto-1,2,3,4-tetrahydroquinoline derivatives, as first noted by Clemo and Perkin,[2] were reported. In view of the ready availability of such acids by addition of aromatic amines to ethyl acrylate or acrylonitrile this scheme offers attractive possibilities for the synthesis of 4-hydroxy- and 4-chloroquinolines which have recently assumed importance as intermediates for the manufacture of the 4-aminoquinoline series of drugs. While β-(*p*-methoxyanilino)-propionic acid, after tosylation, underwent ring closure when treated with phosphorus oxychloride to yield a substance giving the correct analytical figures for a 4-ketotetrahydroquinoline the failure of this compound, after removal of the tosyl group, to undergo either dehydrogenation to a 4-hydroxyquinoline, or disproportionation to a quinoline and a tetrahydroquinoline caused doubt to be expressed as to whether it actually possessed the structure assigned to it.

The investigation of these substances has been continued and positive evidence that the Clemo and Perkin compounds are indeed 4-keto-1,2,3,4-tetrahydroquinolines has been secured. In addition, the original goal of dehydrogenation to 4-hydroxyqinolines has now been achieved.

At the outset, in order to establish conclusively that the compounds at hand possess the assumed structure, an alternate synthesis for such keto tetrahydroquinolines was sought. The interesting "aldol bases" originally described by Miller and Plöchl[3] from the reaction of an aromatic amine with acetaldehyde served admirably for this purpose. The investigations of Jones and his coworkers[4] have established with reasonable certainty that these substances possess structures of the type of II. As such they gave diacyl- and N-nitrosoacyl-derivatives. That the bicyclic structure (II) is an extremely labile one was indicated by the preparation of oximes which can only come from an open structure of the type of I. Recently the validity of structures such as II has been questioned by Jacques[5] who has produced some evidence favoring the existence of the substances as represented by I exclusively.

In the present work the series of quinoline derivatives proceeding from 4-hydroxy-6-chloro-1,2,3,4-tetrahydroquinaldine (II) has been chosen for study because of the favorable effect to be expected from the chlorine substituent on the physical properties of the compounds and because the formation of isomers in the ring closure experiments would be avoided. II was readily prepared from *p*-chloroaniline (III) and acetaldehyde essentially according to Jones, *et al.*,[4a] and more conveniently from III and crotonic aldehyde. The substance possessed the expected properties. It readily formed a diacetate (IV), and on treatment with hydrochloric acid it disproportionated with dehydration to a mixture of 6-chloroquinaldine and 6-chlorotetrahydroquinaldine. A number of attempts at selective hydrolysis of the acetoxy group in the diacetate, IV, resulted in cleavage of the N-acetyl group also. However on benzoylation of II with benzoyl chloride in absolute ethanol at low temperature, the 1-benzoyl derivative (V) resulted. Oxidation of V with chromic oxide gave 1-benzoyl-4-keto-6-chloro-1,2,3,4-tetrahydroquinaldine (VI) which readily gave an oxime. Further, it was demonstrated that no radical change had occurred during the oxidation of V to VI by reduction of VI to V with aluminum isopropoxide. In addition reduction of VI by the Wolff–Kishner hydrazine method gave 1-benzoyl-6-chlorotetrahydroquinaldine (VIII) which was identical with the substance prepared by benzoylation of the tetrahydroquinaldine formed by disproportionation of II. Removal of the benzoyl group from VI by acid hydrolysis gave 4-keto-6-chloro-1,2,3,4-tetrahydroquinaldine (VII).

From the opposite direction VII was prepared by a series of reactions analogous to those leading to the Clemo and Perkin compounds. The addition of aniline to crotonic acid to yield β-anilinobutyric acid has been described as a photochemical reaction taking place in the presence of ultraviolet light by Stoermer and Robert.[6] We now find that irradiation is unnecessary and that excellent yields of β-(*p*-chloroanilino)-butyric acid (IX) are obtained merely by warming the reactants together. Apparently the crotonic acid serves as the catalyst for the addition. Tosylation of the acid IX gave the N-tosyl derivative (X), which on treatment with phosphorus oxychloride underwent ring closure to the tosylketotetrahydroquinaldine (XI). Hydrolytic removal of the tosyl group from XI gave 4-keto-6-chloro-1,2,3,4-tetrahydroquinaldine (VII) which was identical in all respects with the compound prepared from the aldol base II. Finally in order to remove any remaining doubt concerning the structure of VII, it was found possible to dehydrogenate the latter in 90% yield by

(1) Elderfield, *et al.*, THIS JOURNAL, **68**, 1259 (1946).

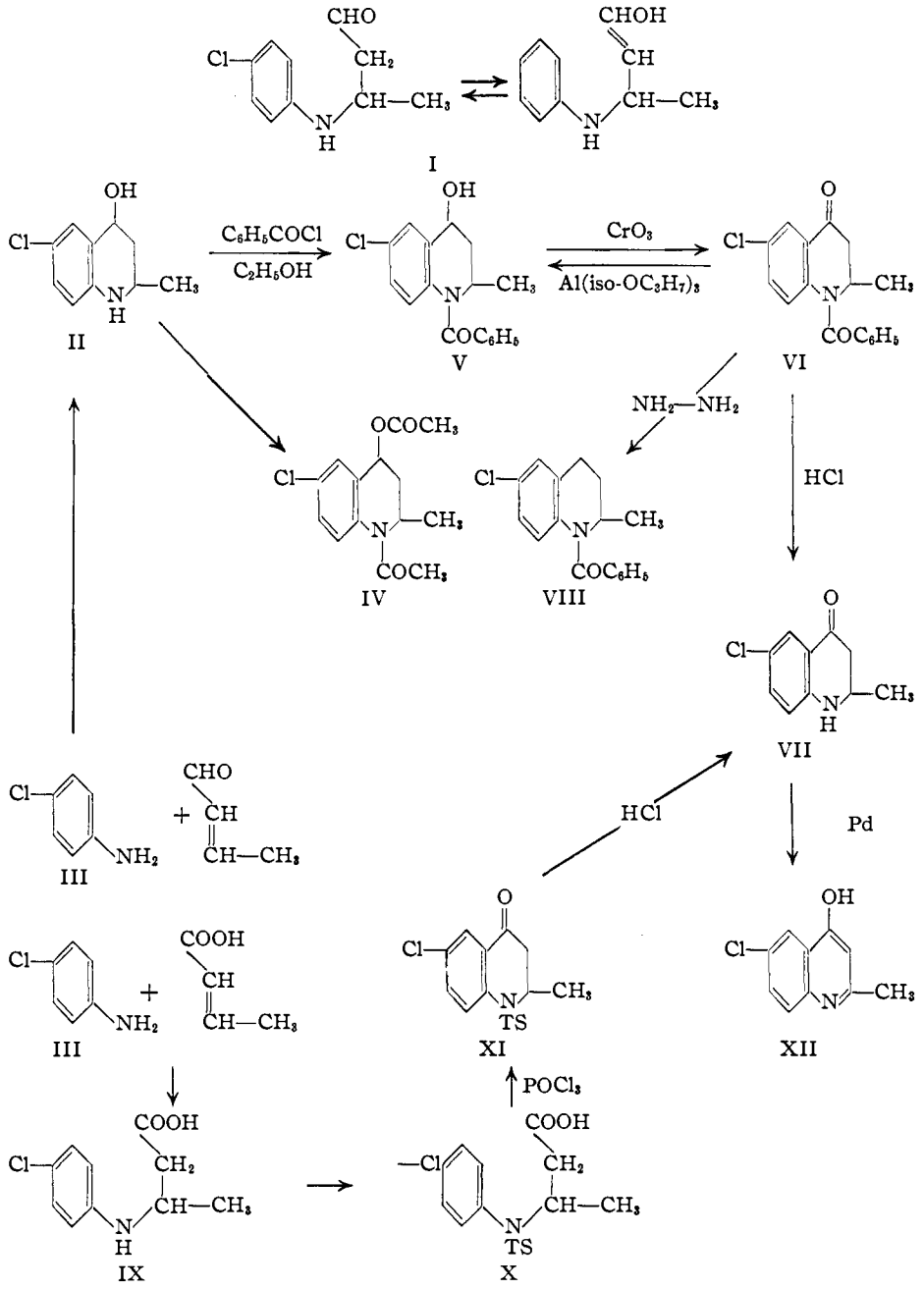
(2) Clemo and Perkin, *J. Chem. Soc.*, **125**, 1608 (1924); **127**, 2297 (1925); Backeberg, *ibid.*, 618 (1933); *cf.* Diesbach and Kramer, *Helv. Chim. Acta*, **28**, 1399 (1945).

(3) Miller and Plöchl, *Ber.*, **29**, 1462 (1896).

(4) (a) Jones and White, *J. Chem. Soc.*, **97**, 633 (1910); (b) Edwards, Garrod and Jones, *ibid.*, **101**, 1376 (1912).

(5) Jacques, *Ann. chim.*, [11] **20**, 322 (1945).

(6) Stoermer and Robert, *Ber.*, **55**, 1030 (1922).

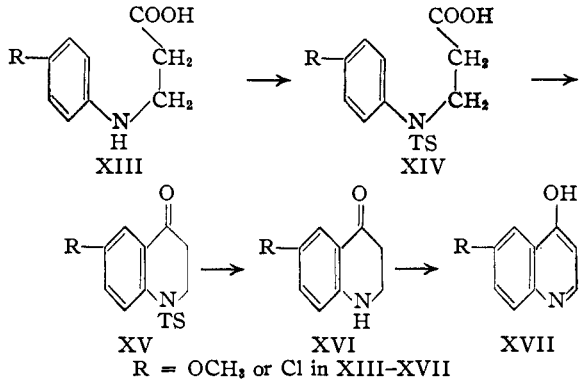


heating it with maleic acid in the presence of palladium on charcoal, a method first used for the dehydrogenation of nitrogen heterocycles in the synthesis of harmin by Akabori and Saito.[7] The resulting 4-hydroxy-6-chloroquinaldine (XII) was identified by mixing melting points with a known sample prepared by the Conrad–Limpach method and by conversion to the corresponding 4-chloro-derivative.

We therefore conclude that in the quinaldine series, all doubt has been removed as to the nature of the products of ring closure of tosylated β-anilinobutyric acids and that these possess structures of the type of XI. As a corollary of the above observations, the views of Jacques regarding the structure of II do not appear tenable.

With a background of the above experience, the original Clemo and Perkin compounds were reinvestigated as shown by XIII–XVII using two series in which R = OCH_3 and R = Cl. Throughout the series, the yields of all compounds have been materially increased over those given in our earlier paper.[1] The dehydrogenation of XVI proceeded in quantitative yield to give the hydroxy quinolines which were converted to the 4-chloro

(7) Akabori and Saito, *Ber.*, **63**, 2245 (1930).



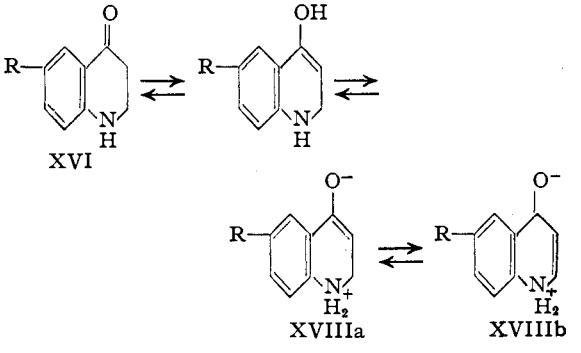
R = OCH_3 or Cl in XIII–XVII

derivatives by standard methods. Both the 4-hydroxyquinolines and the 4-chloroquinolines prepared from them were identified with known samples prepared by standard methods.

During the course of this work certain other observations have been made which are not without interest. The presence of the N-tosyl group appears to be a necessary condition for ring closure of either the β-anilinobutyric or propionic acids with phosphorus oxychloride. Attempts at ring closure of the N-acetyl and N-benzoyl derivatives resulted in substantially quantitative recovery of the starting materials either as such or as the corresponding anilides which resulted from cleavage of the anilino acids.

For the dehydrogenation of the ketotetrahydroquinaldine (VII) a *p*H of 9–10 was necessary. On the other hand with the ketotetrahydroquinolines at a *p*H of 7 the dehydrogenation proceeded smoothly. The reason for this difference apparently may be traced to the presence of the methyl group in the former series.

All of the ketotetrahydroquinolines which we have encountered possess a characteristic canary yellow color. We ascribe this to the existence of these substances at least partially as zwitterions of the type of XVIIIa and XVIIIb in which a quinoid chromophore is found in one of the tautomers.



Experimental[8,9]

Condensation of *p*-Chloroaniline and Acetaldehyde. 4-Hydroxy-6-chloro-1,2,3,4-tetrahydroquinaldine II.—*p*-Chloraniline (11 g.) was condensed with 12.5 g. (16 ml.) of freshly distilled acetaldehyde in a mixture of 950 ml. of water and 35 ml. of hydrochloric acid (sp. gr. 1.19) at 10–15° essentially according to Edwards, Garrod and Jones.[4b] The yield of crude II, m. p. 160–163° (dec.), was 9 g. (53%). After two recrystallizations from benzene 6.5 g. of material, m. p. 169–170° (dec.), was obtained. The substance forms small colorless needles. It is stable to aqueous and alcoholic alkali, but decomposes slowly in cold dilute acid.

Anal. Calcd. for $C_{10}H_{12}ClNO$: C, 60.7; H, 6.1. Found: C, 61.1; H, 6.2.

The same substance was prepared more advantageously by adding 7 g. of redistilled crotonic aldehyde to a solution of 12 g. of *p*-chloroaniline in one liter of 5% hydrochloric acid during fifteen minutes at 10–15°. After standing overnight at room temperature and filtration from a small amount of amorphous material, the solution was made basic with sodium hydroxide solution and extracted with 20 ml. of ether–hexane (1:1) at 5–10°. The curdy precipitate which separated at the interface was collected and washed twice with hexane. After recrystallization from benzene this gave 7.6 g. of material, m. p. 169–170°.

1-Acetyl-4-acetoxy-6-chloro-1,2,3,4-tetrahydroquinaldine. IV.—A solution of 2 g. of the above compound was refluxed with 10 ml. of acetic anhydride containing 0.1 g. of sodium acetate for two hours. After dilution with 100 ml. of water and decomposition of the acetic anhydride with sodium carbonate, the pale yellow solid which separated after several hours was filtered and recrystallized first from 50% aqueous ethanol (charcoal) and finally from 95% ethanol. The yield of material, m. p. 116–117°, was 2 g.

Anal. Calcd. for $C_{14}H_{16}ClNO_3$: C, 59.7; H, 5.7; N, 5.0; sapon. equiv., 281.7. Found: C, 59.6; H, 5.9; N, 5.2; sapon. equiv., 284.

All attempts at selective hydrolysis of the acetoxy group in this substance resulted also in removal of the N-acetyl group.

1-Benzoyl-4-hydroxy-6-chloro-1,2,3,4-tetrahydroquinaldine, V.—One milliliter of benzoyl chloride was added to a solution of 1 g. of II in 20 ml. of absolute ethanol at 0°. After standing in the refrigerator for three hours a second ml. of benzoyl chloride was added and the mixture was allowed to stand overnight at 2°. After removal of the solvent, the remaining thick yellow oil was washed with three 10-ml. portions of hexane and then triturated with ice and 20 ml. of 5% hydrochloric acid. The gray brown precipitate which formed was collected and recrystallized from benzene yielding 1 g. of material, m. p. 183–184°.

Anal. Calcd. for $C_{17}H_{16}ClNO_2$: C, 67.7; H, 5.3; N, 4.6. Found: C, 67.5; H, 4.7; N, 4.6.

1-Benzoyl-4-keto-6-chloro-1,2,3,4-tetrahydroquinaldine, VI.—To a solution of 1 g. of the above benzoyl compound (V) in 20 ml. of glacial acetic acid at 50° was added during the course of five minutes a solution of 1 g. of chromium trioxide in a mixture of 1 ml. of acetic acid and 0.5 ml. of water. After standing fifteen minutes at room temperature, the mixture was poured into 250 ml. of water. After shaking for five minutes the curdy pale yellow precipitate was recrystallized from dilute ethanol to yield 0.9 g. of white crystalline material, m. p. 137–138.5°. Two further recrystallizations from benzene–hexane raised the m. p. to 140.5–141°.

Anal. Calcd. for $C_{17}H_{14}ClNO_2$: C, 68.1; H, 4.7; N, 4.7. Found: C, 68.0; H, 4.7; N, 4.7.

The **oxime** of the above compound, prepared in pyridine–absolute alcohol, melted at 210–211° after recrystallization from ethanol.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: N, 8.6. Found: N, 8.9.

Reduction of 1-Benzoyl-4-keto-6-chloro-1,2,3,4-tetrahydroquinaldine to V.—A mixture of 3 g. of the above keto quinaldine (VI), 2 g. of redistilled aluminum isopropoxide and 30 ml. of anhydrous isopropyl alcohol was refluxed for thirty minutes. The flask was then equipped

(8) All melting points are corrected for stem exposure.

(9) Microanalyses by Miss Lois May of these laboratories, Clark Microanalytical Laboratory, Urbana, Illinois, or Dr. Francine Schwarzkopf, Elmhurst, Long Island.

with a 10-inch Vigreux column, and the mixture was slowly distilled. After two hours the 2,4-dinitrophenylhydrazine test for acetone in the distillate was negative. The solvent was removed under reduced pressure. The cooled residue was hydrolyzed with a cold solution of 3.5 ml. of hydrochloric acid (sp. gr. 1.19) and 20 ml. of water. The white insoluble material was collected and washed with 6 *N* hydrochloric acid. It was recrystallized first from dilute ethanol and then from benzene yielding 1.8 g. of material, m. p. 183–184°. When mixed with the substance prepared by benzoylation of II the m. p. was not depressed.

Dehydration and Disproportionation of 4-Hydroxy-6-chloro-1,2,3,4-tetrahydroquinaldine.—The disproportionation of similar substances to quinolines and tetrahydroquinolines has been described without appreciable experimental detail by Garrod, Jones and Evans.[4b]

A solution of 2 g. of II in 25 ml. of hydrochloric acid (sp. gr. 1.19) was refluxed for one hour and then concentrated to dryness under reduced pressure. After addition of 5 ml. of 10% potassium hydroxide solution to the residue, the mixture was extracted with 100 ml. of benzene and the extract was dried with magnesium sulfate. The dry benzene solution was then refluxed with 2 ml. of benzoyl chloride and 5 ml. of pyridine for two hours. After addition of 2 ml. of absolute ethanol, the mixture was refluxed for an additional thirty minutes. After acidification with hydrochloric acid, the aqueous layer was separated and made basic with sodium hydroxide solution which precipitated 0.93 g. of crude 6-chloroquinaldine. Recrystallization from dilute alcohol gave material which melted at 92°. Bartow and McCollum[10] report 6-chloroquinaldine as melting at 91°.

The benzene extract from the above was dried and concentrated to 5 ml. Dilution with hexane gave 1.4 g. of 1-benzoyl-6-chloro-1,2,3,4-tetrahydroquinaldine which melted at 132° after recrystallization from benzene.

Anal. Calcd. for $C_{17}H_{16}ClNO$: C, 71.4; H, 6.0; N, 4.9. Found: C, 71.4; H, 5.6; N, 4.7.

1-Benzoyl-6-chloro-1,2,3,4-tetrahydroquinaldine (VIII) by Wolff-Kishner Reduction of VI.—A mixture of 3 g. of the benzoyl ketone VI, 1.7 g. of potassium hydroxide, 13.5 ml. of 85% hydrazine hydrate and 135 ml. of diethylene glycol was gently boiled and the water present was removed by azeotropic distillation. The mixture was then refluxed at 195° for two hours. The cooled solution was diluted with an equal volume of water and extracted with benzene. The benzene extract was washed thoroughly with water for removal of diethylene glycol and dried azeotropically by concentration to 50 ml. The organic base was rebenzoylated as in the above case by refluxing the benzene solution with 2 ml. of benzoyl chloride and 5 ml. of pyridine yielding 2.4 g. of the benzoyltetrahydroquinaldine, m. p. 132°. The m. p. was not depressed on admixture of this material with that obtained by disproportionation as described above.

4-Keto-6-chloro-1,2,3,4-tetrahydroquinaldine VII.—A mixture of 3 g. of the benzoyl ketone VI, 15 ml. of hydrochloric acid (sp. gr. 1.19), and 15 ml. of glacial acetic acid was refluxed for three hours and then concentrated to dryness under reduced pressure. The solid residue was made basic with 10% sodium hydroxide solution and extracted with 25 ml. of benzene. The benzene extract was shaken with three 15-ml. portions of 10% hydrochloric acid and the combined acid extracts were neutralized in the cold with 10% potassium hydroxide solution. The curdy yellow precipitate (2.8 g.), which became crystalline after standing for a few hours in the cold, was collected and recrystallized twice from benzene–hexane yielding canary yellow crystals, m. p. 134°.

Anal. Calcd. for $C_{10}H_{10}ClNO$: C, 61.4; H, 5.2. Found: C, 61.4; H, 5.3.

β-(*p*-Chloroanilino)-butyric Acid. IX.—A solution of 12.8 g. of *p*-chloroaniline and 8.6 g. of crotonic acid in 50 ml. of benzene was heated just to the reflux point for sixteen hours. The deep red solution was poured into 50 ml. of benzene and a solution of 6 g. of potassium hydroxide in 250 ml. of water contained in a separatory funnel. After shaking for several minutes 0.5 g. of material separated at the interface between the two layers. This was collected and recrystallized twice from benzene yielding rhombic crystals, m. p. 142–143°. The analytical figures corresponded to those demanded for the *p*-chloroanilide of β-(*p*-chloroanilino)-butyric acid.

Anal. Calcd. for $C_{16}H_{16}Cl_2N_2O$: N, 8.7. Found: N, 8.5.

The basic aqueous layer was shaken with decolorizing carbon and filtered. The pale yellow filtrate, cooled in an ice-bath, was carefully acidified with dilute hydrochloric acid. A white gum settled out at *p*H 4–5. This solidified on refrigerating overnight yielding 16.4 g. of material, m. p. 81–82°. After two recrystallizations from benzene it melted at 83.5–84°.

Anal. Calcd. for $C_{10}H_{12}ClNO_2$: C, 56.2; H, 5.7; N, 6.6. Found: C, 56.4; H, 5.7; N, 6.7.

The same compound was also prepared as follows. A mixture of 12.8 g. of *p*-chloroaniline, 11.4 g. of ethyl crotonate and 2.5 ml. of glacial acetic acid was heated at 90° for twenty hours. The resulting deep red solution was treated directly with a solution of 5.5 g. of sodium hydroxide in 20 ml. of water. The two phases disappeared on boiling for ten minutes after which boiling was continued for an additional thirty minutes. After dilution with twice its volume of cold water, the solution was extracted with two 50-ml. portions of benzene to remove unreacted *p*-chloroaniline. The aqueous solution was then worked up as in the above case, yielding 15.8 g. of material, m. p. 83.5–84°.

N-Tosyl-β-(*p*-chloroanilino)-butyric Acid X.—A mixture of 4.3 g. of the anilino acid IX, 4 g. of *p*-toluenesulfonyl chloride, 50 ml. of dry benzene and 10 ml. of dry pyridine was heated on the steam-bath for three hours. The precipitate of pyridine hydrochloride was filtered off and washed with benzene. The combined benzene solution and washings were extracted thoroughly with 10% hydrochloric acid and then washed twice with water. The benzene solution was then extracted with three 100-ml. portions of 2% potassium hydroxide solution. After treatment with decolorizing carbon the *p*H of the alkaline solution was adjusted to 3 with dilute hydrochloric acid. Crystallization of the precipitated yellow oil slowly occurred on refrigeration and scratching. The crystalline material (6.1 g.) was purified by reprecipitation by acidification of its solution in aqueous sodium bicarbonate and finally by crystallization from ether–hexane. The pure acid melted at 124–125°.

Anal. Calcd. for $C_{17}H_{18}ClNO_4S$: C, 55.5; H, 4.9. Found: C, 55.6; H, 4.9.

N-Acetyl-β-(*p*-chloroanilino)-butyric Acid.—A mixture of 2.1 g. of the acid IX, 5 ml. of acetic anhydride and 5 ml. of glacial acetic acid was refluxed for two hours and then concentrated to dryness at the water pump. After warming the gummy residue with 50 ml. of water for thirty minutes, it was extracted with benzene and the benzene extract was washed with 5% hydrochloric acid. Addition of hexane to the dried and concentrated benzene solution gave 2.1 g. (84%) of the acetyl acid, m. p. 136–137° after recrystallization from benzene.

Anal. Calcd. for $C_{12}H_{14}ClNO_3$: C, 56.4; H, 5.5; N, 5.5. Found: C, 56.5; H, 5.5; N, 5.7.

All attempts at accomplishing ring closure of this acetyl acid to the corresponding 4-ketotetrahydroquinaldine failed. The use of phosphorus oxychloride, hydrogen fluoride, zinc chloride and acetic anhydride, sulfuric acid, phosphorus pentoxide, and aluminum chloride on the acid chloride prepared with thionyl chloride gave as products only *p*-chloroacetanilide or β-(*p*-chloroanilino)-butyric acid or unreacted starting material.

4-Keto-6-chloro-1,2,3,4-tetrahydroquinaldine VII by Ring Closure of X.—A mixture of 15 g. of the tosyl acid X and 50 ml. of phosphorus oxychloride protected by a cal-

(10) Bartow and McCollum, THIS JOURNAL, **26**, 703 (1904).

cium chloride tube was warmed on the steam-bath for twenty-five minutes. The excess phosphorus oxychloride was removed at the water pump and 100 ml. of water was carefully added to the residual dark red oil. This mixture was then made basic with 20% potassium hydroxide solution and the gum was thoroughly triturated. The gummy alkali insoluble material consisted for the most part of 1-tosyl-4-keto-6-chloro-1,2,3,4-tetrahydroquinaldine with small amounts of 1-tosyl-4,6-dichloro-1,2-dihydroquinaldine, and tosyl-*p*-chloroaniline. It was hydrolyzed directly for removal of the tosyl group by refluxing for four hours with 25 ml. of hydrochloric acid (sp. gr. 1.19) and 25 ml. of acetic acid. The solution was concentrated to dryness under reduced pressure and 10% potassium hydroxide solution was added to the residue. After extraction with benzene, the benzene extract was washed with three 50-ml. portions of 10% hydrochloric acid. The combined acid extracts were made basic with potassium hydroxide. The curdy yellow precipitate crystallized on refrigeration overnight yielding 3.2 g. (40%) of product m. p. 126–128°. After two recrystallizations from benzene–hexane, the compound formed canary yellow needles, m. p. 134°. This substance was identical with the compound obtained above by oxidation and hydrolysis of 1-benzoyl-4-hydroxy-6-chloro-1,2,3,4-tetrahydroquinaldine (V). Mixed m. p.'s of both the free amines and their benzoyl derivatives prepared by either route showed no depression.

4-Hydroxy-6-chloroquinaldine (XII).—A mixture of 2 g. of VII, 2 g. of maleic acid, 4 g. of anhydrous potassium carbonate, 0.2 g. of palladium black, 0.2 g. of 30% palladium on carbon,[11] and 30 ml. of water was refluxed for twenty-four hours. The cooled solution was made strongly alkaline with sodium hydroxide and filtered from the catalyst. The recovered catalyst can be used for further dehydrogenations. Acidification of the alkaline filtrate to *p*H 6 with acetic acid gave 95% of crude XII which melted directly as obtained at 320–322° (dec.). Recrystallization from methanol raised the m. p. to 321–323° (dec.). When this material was mixed with an authentic sample of 4-hydroxy-6-chloroquinaldine, m. p. 323–325° (dec.), prepared by the Conrad–Limpach method according to Kermack and Weatherhead[12] the m. p. was not depressed.

4,6-Dichloroquinaldine.—A mixture of 2 g. of the hydroxyquinaldine (XII) and 10 ml. of phosphorus oxychloride was refluxed for one hour. After removal of the excess phosphorus oxychloride at the water pump, the residue was stirred with ice and 20 ml. of 10% potassium hydroxide solution. Recrystallization of the white curdy precipitate from aqueous methanol gave 82% of 4,6-dichloroquinaldine, m. p. 83–84°, as silky needles. As thus obtained the substance contains one mole of water of crystallization which is lost on drying at 75° *in vacuo*.

Anal. Calcd. for $C_{10}H_7Cl_2N \cdot H_2O$: C, 52.2; H, 3.5. Found: C, 52.4; H, 3.7. Calcd. for $C_{10}H_7Cl_2N$: C, 56.6; H, 3.3. Found: C, 56.7; H, 3.3.

The m. p. of the above substance was not depressed on admixture with a known sample prepared from authentic XII.

Ethyl β-(*p*-Chloroanilino)-propionate.—This was prepared substantially as described previously for ethyl β-(*p*-anisidino)-propionate[1] by heating a mixture of 10 g. of ethyl acrylate, 2.5 g. of glacial acetic acid and 12.8 g. of *p*-chloroaniline under reflux at 90° for sixteen hours. Upon distillation of the reaction product under reduced pressure 1.8 g. of *p*-chloroaniline, m. p. 72°, was recovered and 15.9 g. of the anilino ester was obtained; yield 70% or 81.5% based on *p*-chloroaniline actually reacted.

Anal. Calcd. for $C_{11}H_{14}ClNO_2$: C, 58.0; H, 6.2. Found: C, 57.8; H, 6.2.

β-(*p*-Chloroanilino)-propionic Acid XIII, R = Cl.—Hydrolysis of the above ester (22.8 g.) by boiling with a solution of 2 g. of sodium hydroxide in 20 ml. of water for a half hour gave 92% of the acid, m. p. 125° after recrystallization from benzene.

Anal. Calcd. for $C_9H_{10}ClNO_2$: C, 54.1; H, 5.1. Found: C, 54.1; H, 5.1.

When the ester was hydrolyzed directly without isolation from the reaction mixture, the over-all yield of acid, m. p. 125°, was 75%.

N-Tosyl-β-(*p*-chloroanilino)-propionic Acid, XIV, R = Cl.—The acid was tosylated as was the analogous butyric acid described above. The yield of material, m. p. 126–127°, was 80%.

Anal. Calcd. for $C_{16}H_{18}ClNO_4S$: C, 54.3; H, 4.6. Found: C, 54.4; H, 4.6.

The same substance was prepared by alkaline hydrolysis of N-tosylethyl β-(*p*-chloroanilino)-propionate in 55% over-all yield from *p*-chloroaniline.

N-Acetyl-β-(*p*-chloroanilino)-propionic Acid.—This was prepared as was the butyric acid derivative and melted at 111–112°.

Anal. Calcd. for $C_{11}H_{12}ClNO_3$: C, 54.7; H, 5.1; N, 5.8. Found: C, 54.8; H, 5.0; N, 5.7.

As in the case of the analogous butyric acid derivative all attempts at ring closure were unsuccessful.

4-Keto-6-chloro-1,2,3,4-tetrahydroquinoline, XVI, R = Cl.—When 35 g. of the above tosylpropionic acid was treated with phosphorus oxychloride as in the case of the butyric acid and the tosylated keto intermediate was hydrolyzed without purification 7.5 g. of canary yellow rhombic crystals of the keto tetrahydroquinoline, m. p. 112° after recrystallization from ether–hexane, was obtained.

Anal. Calcd. for C_9H_8ClNO: C, 59.5; H, 4.4. Found: C, 59.6; H, 4.6.

4-Hydroxy-6-chloroquinoline, XVII, R = Cl.—The above compound was dehydrogenated as was done with the quinaldine derivative (XII) except that addition of potassium carbonate to the reaction mixture was unnecessary. The product (95–100% yield) melted at 273–274° and the m. p. of mixtures of it with an authentic sample of 4-hydroxy-6-chloroquinoline prepared according to Riegel, *et al.*[13] was not depressed.

4,6-Dichloroquinoline prepared from the above hydroxy compound melted at 105° and did not depress the m. p. of an authentic sample.[14]

β-(*p*-Anisidino)-propionic Acid, XIII, R = OCH_3.—This acid, m. p. 87–88°,[1] was prepared in 74% yield (based on *p*-anisidine) by the procedure used for the chloroanilino acid except that the product was salted out with ammonium sulfate after hydrolysis of the ester.

N-Tosyl-β-(*p*-anisidino)-propionic Acid, XIV, R = OCH_3.—The yield of tosyl acid, m. p. 81–82°,[1] from benzene–hexane was 76%.

4-Keto-6-methoxy-1,2,3,4-tetrahydroquinoline, XVI, R = OCH_3.—Ring closure of 35 g. of the above tosyl acid with 105 g. of phosphorus oxychloride for twenty-five minutes and working up as in the preceding cases gave 9.3 g. of the keto compound as canary yellow rhombic crystals, m. p. 112°,[1] from benzene–hexane.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 68.0; H, 6.2. Found: C, 68.0; H, 6.0.

4-Hydroxy-6-methoxyquinoline, XVII, R = OCH_3.—Dehydrogenation of the above substance as in the preceding cases gave 95–100% of the methoxyquinoline, m. p. 245–247°, from alcohol. The m. p. was not depressed on mixing the material with an authentic sample.[14]

4-Chloro-6-methoxyquinoline prepared from the above compound and from an authentic sample melted alone and mixed at 77–78°. Bachman and Cooper[15] report the m. p. as 79°.

Summary

1. Cyclization of tosyl-β-anilinopropionic and

(11) *Org. Syntheses*, **26**, 77 (1946).

(12) Kermack and Weatherhead, *J. Chem. Soc.*, 563 (1939).

(13) Riegel, *et al.*, THIS JOURNAL, **68**, 1264 (1946).

(14) Courtesy of Dr. Byron Riegel of Northwestern University.

(15) Bachman and Cooper, *J. Org. Chem.*, **9**, 302 (1944).

butyric acids has been shown to give 4-keto-1,2,-3,4-tetrahydroquinoline derivatives.

2. 4-Keto-1,2,3,4-tetrahydroquinolines may be dehydrogenated to 4-hydroxyquinolines in good yield with palladium in the presence of maleic acid.

3. The cyclic structure for the "aldol bases" of Miller and Plöchl has been confirmed.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

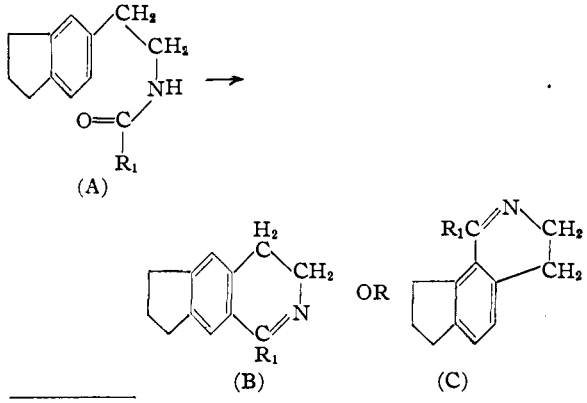
Synthetic Studies in the Isoquinoline Series

BY EVERETT M. SCHULTZ[1a,b] AND R. T. ARNOLD

Compounds having a 1-benzylisoquinoline structure occur in nature as minor constituents of opium. Of these, the most important is papaverine, 1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline, which finds use as an antispasmodic. Synthetic isoquinolines that have been reported have most frequently carried alkoxy or methylenedioxy substituents, and but few having carbocyclic substituents have been described. Perhaps the most fruitful approach to the synthesis of 1-benzylisoquinoline is by the reaction of Bischler and Napieralski.[2] This reaction, which consists in cyclization through the dehydration of a substituted or unsubstituted β-arylethylamide, results in a 3,4-dihydroisoquinoline. The latter can be readily dehydrogenated catalytically by means of palladium[3] to yield an isoquinoline.

In the present work, a number of 1-benzyl-6,7-cyclopenteno- and 6,7-cyclohexeno-isoquinolines (Chart I) were synthesized by these methods in order to obtain compounds for physiological assay and to study the Bischler and Napieralski reaction in the hydrindene and tetralin series.

In the case of ring closure of a β-5-hydrindenyl- or β-6-tetralylethylamide (A), it is possible for cyclization to occur in one of two directions, one of which would lead to a 6,7-cycloalkeno-3,4-dihydroisoquinoline (B) and the other would lead to the 7,8-cycloalkeno-isomer (C).



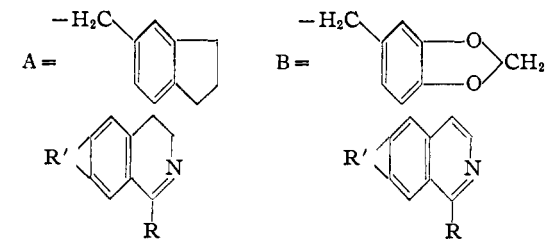
That cyclization led exclusively to structure B in both the hydrindene and tetralin series was demonstrated by nitric acid oxidation[4] of representative dihydroisoquinolines of both series. Such a degradation oxidizes the heterocyclic and alicyclic rings and yields a benzene tetracarboxylic acid. In both the hydrindene and tetralin series, the only product of the oxidation was 1,2,4,5-benzenetetracarboxylic acid. It must be concluded, therefore, that cyclization took place in such a direction as to form structure B exclusively.

The 3,4-dihydroisoquinolines, with one exception (III), were such extremely viscous, high-boiling sirups that rigorous fractionation was impossible and so analyses were made only on their picrates.

The amides of β-5- and 6-arylethylamines necessary for the synthesis of I through IX were obtained from the corresponding β-arylethylamines and a suitably substituted arylacetic acid or acetyl chloride. When the acid was used the amide was formed by dehydration of the amine carboxylic acid salt. If the acid chloride was employed, the amine and acid chloride were allowed to react in benzene solution in the presence of pyridine.

The β-arylethylamines and substituted acetic acids were obtained by reduction[5] or hydrolysis, respectively, of the proper nitriles. Compound VIII is probably the first example of a 1-substituted-6,7-benzoisoquinoline. Although Kindler, *et al.*,[6] have reported 1-phenyl-6,7-benzo-3,4-dihy-

CHART I



Dihydroisoquinolines			Isoquinolines		
No.	R	R′	No.	R	R′
I	—A	—$(CH_2)_3$—	VI	—B	—$(CH_2)_3$—
II	—B	—$(CH_2)_3$—	VII	—A	—$(CH_2)_3$—
III	—A	CH_2O_2=	VIII	—$CH_2C_6H_5$	—(CH=CH)₂—
IV	—CH_3	—$(CH_2)_3$—	IX	—A	CH_2O_2=
V	—$CH_2C_6H_5$	—$(CH_2)_4$—			

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(1b) Abstracted from a thesis presented to the faculty of the Department of Organic Chemistry, University of Minnesota, in partial fulfilment of the requirements for the Ph.D. degree, July, 1944.

(2) Bischler and Napieralski, *Ber.*, **26**, 1903 (1893).

(3) Spaeth and Burger, *ibid.*, **60**, 704 (1927).

(4) Campbell, Soffer and Steadman, THIS JOURNAL, **64**, 425 (1942).

(5) Adkins and Schwoegler, *ibid.*, **60**, 408 (1938).

(6) Kindler, Peschke and Pludemann, *Arch. Pharm.*, **277**, 25 (1939).