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Cyclization Studies in the Quinoline Series. A New Synthesis of 4-Aminoquinolines

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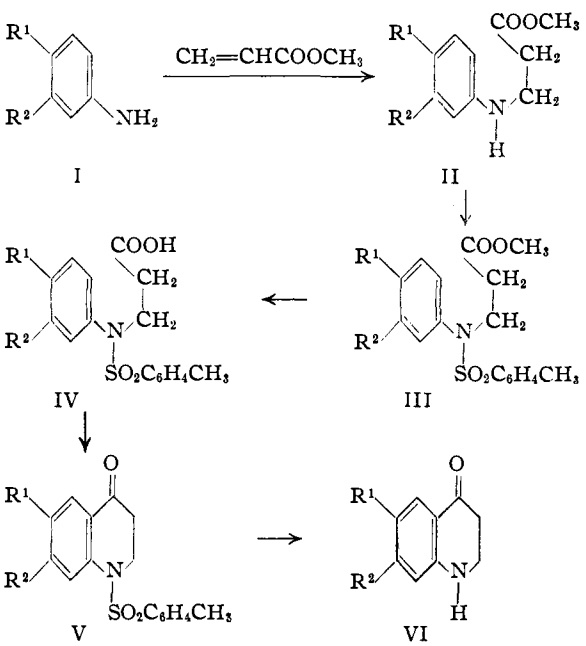
In 1946 Elderfield and his collaborators[1] reinvestigated the synthesis and cyclization of β-anilinopropionic acid derivatives (like IV).[2] Although they realized substantial improvement in the method of preparing these acids, attempts to effect ring closure with a number of variously substituted acids under a variety of conditions were either unsuccessful or gave low yields. Since the cyclization products—formerly presumed to be dihydro-4-quinolones (like V)[2]—resisted aromatization by conventional methods, the authors finally concluded that "doubt is cast on the structures assigned to them."

In the present work,[3] which was already at an advanced stage when the paper of Elderfield, *et al.*, appeared, a method is described for effecting the cyclization (IV → V) in excellent yields, and unequivocal proof is presented for the structure of the cyclization products by aromatization and conversion to 4-aminoquinolines. The method, moreover, provides a synthetic route to promising intermediates for the preparation of important medicinals.

The scheme for the synthesis of the N-tosyl-β-anilinopropionic acids (IV) was formally similar to that employed by Elderfield, *et al.*[1] Three series were studied (formulas I → IV), the unsubstituted series ($R^1 = R^2 = H$), the chloro series ($R^1 = H$, $R^2 = Cl$), and the methoxy series ($R^1 = OCH_3$, $R^2 = H$). The addition of the aromatic amines (I) to methyl acrylate proceeded readily in the presence of a small proportion of acetic acid[4] or



(R^1 = H or OCH_3, R^2 = H or Cl)

stannic chloride[5] to give crystalline esters (II) in 69, 54 and 63% yields, respectively. The crystalline N-tosyl derivatives (III) were all obtained in over 90% yield by the action of *p*-toluenesulfonyl chloride on the esters II in pyridine.[6] Saponification of the N-tosyl esters III under ordinary conditions of refluxing was accompanied by considerable β-elimination giving, along with the desired acid, an appreciable proportion of the *p*-toluene-

(1) Elderfield, Gensler, Bembry, Kremer, Brody, Hageman and Head, THIS JOURNAL, **68**, 1259 (1946).

(2) For the early work see Clemo and Perkin, *J. Chem. Soc.*, 1608 (1924); 2297 (1925). See also Backeberg, *ibid.*, 618 (1933), and Diesbach and Kramer, *Helv. Chim. Acta*, **28**, 1399 (1945).

(3) Initiated in 1944, Sonnemann, B.S. thesis, University of Wisconsin, 1944.

(4) British Patent 466,316 [*Chem. Abst.*, **31**, 7887 (1937)].

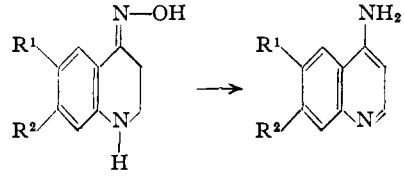
(5) *Cf.* Enkoist, Monoman and Sorderland, *Finska. Kemistsamfundets Medd.*, **53**, No. 314, 66 (1944) [*Chem. Abst.*, **41**, 4103 (1947)].

(6) Our product III of the unsubstituted series ($R^1 = R^2 = H$) melted at 46.4–47.8° instead of at 61–62° as reported by Clemo and Perkin, ref. 2).

sulfonanilide. The extent of the side reaction could be decreased by employing milder conditions (room temperature with low concentration of alkali); thus in the unsubstituted series the crystalline acid IV ($R^1 = R^2 = H$) was obtained in 92% yield, and in the methoxy series the yield of crystalline IV ($R^1 = OCH_3$, $R^2 = H$) was 87%. In the chloro series ($R^1 = H$, $R^2 = Cl$), even with the mild saponification treatment, there was considerable β-elimination and the acid was obtained in only 48% yield. The failure of previous workers[1] to obtain good yields is also undoubtedly associated with this susceptibility to β-elimination. Excellent yields (92–94%) of crystalline IV ($R^1 = H$, $R^2 = Cl$) were realized, in the present work, when the ester III ($R^1 = H$, $R^2 = Cl$) was submitted to acid hydrolysis with hydrochloric acid in dioxane. This procedure also gave good yields (85–87%) in the methoxy series.

The cyclization of the acid IV was studied most thoroughly in the unsubstituted series ($R^1 = R^2 = H$). Attempts to effect ring closure with hydrogen fluoride[7] or with zinc chloride, acetic acid and acetic anhydride[8] failed. However, when the acid was converted to the chloride and treated with stannic chloride in benzene, a 95% yield of the crystalline cyclic ketone V ($R^1 = R^2 = H$) was obtained. When this method was applied to the acid IV in the chloro series ($R^1 = H$, $R^2 = Cl$), the cyclization did not proceed satisfactorily. The inverse aluminum chloride Friedel–Crafts method of ring closure,[9] however, gave the hitherto unknown crystalline quinolone V ($R^1 = H$, $R^2 = Cl$) in 63% yield. The crude product was obtained in 87% yield but was contaminated with phenyl-*p*-tolylsulfone, $C_6H_5SO_2C_6H_4CH_3$, evidently arising from acylation of the solvent (benzene) by the *p*-toluenesulfonyl radical produced by cleavage of either the acid or ketone. In one experiment the sulfone was the main product. No material corresponding to ring closure ortho to the chloro group was isolated. In the methoxy series the inverse Friedel–Crafts method of cyclization[9] was especially effective giving crystalline quinolone V ($R^1 = OCH_3$, $R^2 = H$) of good purity in 99% yield. Previous attempts to effect ring closure in this series (N-acetyl instead of N-tosyl) with stannic chloride failed.[1] The tosyl ketones V were cleaved to the yellow crystalline amino ketones VI[10] in excellent yields by hydrolysis with a mixture of hydrochloric and acetic acid.

That the cyclization products are truly quinolones was proved by the aromatization experiments described below and by conversion of VI ($R^1 = R^2 = H$) into tetrahydroquinoline by Wolff–Kishner reduction of the carbonyl group. The N-benzenesulfonyl derivative of the product melted at 66° alone or when mixed with the derivative prepared from the reduction product of quinoline.



VII VIII

Aromatization of the quinolones VI was accomplished by dehydration of the oximes VII.[11] The conditions reported for the conversion of 1-tetralone oxime into α-naphthylamine,[12] *e. g.*, treating a hot solution of the derivative or its acetate in acetic acid with hydrogen chloride, failed in the present case, unchanged starting material being largely recovered. The hypothesis that the stability of the heterocyclic compounds under these conditions is associated with the formation of stable salts, suggested that the dehydration might be successful with only traces of acid. On pyrolysis of VII ($R^1 = R^2 = H$) in the presence of a small amount of potassium acid sulfate or oxalic acid 4-aminoquinoline, VIII ($R^1 = R^2 = H$), was indeed produced although in very poor yield. Finally it was discovered that yields of 43% could be obtained by heating the oxime at reduced pressure in the presence of activated carbon. By this procedure 7-chloro-4-aminoquinoline, VIII ($R^1 = H$, $R^2 = Cl$) was obtained from VII ($R^1 = H$, $R^2 = Cl$) in 52% yield and 6-methoxy-4-aminoquinoline, VIII ($R^1 = OCH_3$, $R^2 = H$) from VII ($R^1 = OCH_3$, $R^2 = H$) in 50% yield. The identity of each of these products as well as of the parent compound VIII ($R^1 = R^2 = H$) was established by comparison of the free bases (and derivatives) with authentic specimens kindly supplied by Dr. A. R. Surrey of the Sterling–Winthrop Research Institute. The fact that the product in the chloro series proved to be the 7- rather than 5-chloro-4-aminoquinoline provided conclusive proof that the ring closure of IV ($R^1 = H$, $R^2 = Cl$) proceeded mainly into the position para to the chloro group.

Experimental[13]

Unsubstituted Series

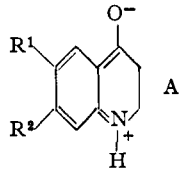
Methyl β-Anilinopropionate, II ($R^1 = R^2 = H$).—A mixture of 107.7 g. of aniline, 107.5 g. of methyl acrylate

(7) *Cf.* Fieser and Hershberg, THIS JOURNAL, **61**, 1272 (1939).

(8) *Cf.* Fieser and Hershberg, *ibid.*, **59**, 1028 (1937); **60**, 1893 (1938).

(9) Johnson and Glenn, *ibid.*, **71**, 1092 (1949).

(10) The yellow color of these substances may be explained by the increased resonance promoted by the contribution of the polar form A to the electronic state. This resonance is inhibited by a negative substituent on the nitrogen, hence the N-tosyl derivatives (V) are colorless.



A

(11) We are indebted to Drs. C. M. Suter and E. J. Lawson of the Sterling-Winthrop Research Institute for suggesting this approach.

(12) Schroeter, Gluschke, Götzky, Huang, Irmisch, Laves, Schrader and Stier, *Ber.*, **63**, 1308 (1930).

(13) All melting points are corrected.

and 3 ml. of acetic acid was boiled under reflux for fifteen hours. The red solution was distilled from a Claisen flask, and after removal of the forerun, the main fraction b. p. 156–160° (13–14 mm.) was collected. The yellow distillate amounted to 142.0 g. (69% yield) and crystallized in the receiver. This product, m. p. 36–38°, was of sufficient purity for the next step.

A sample prepared for analysis by Sonnemann[3] by repeated recrystallization from ether–petroleum ether (40–60°) was obtained as colorless plates, m. p. 37.5–38.5°.

Anal.[3] Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31. Found: C, 66.90; H, 7.01.

Methyl N-Tosyl-β-anilinopropionate, III ($R^1 = R^2 = H$).—To a solution of 20.0 g. of II ($R^1 = R^2 = H$) in 200 ml. of pyridine was added in small increments with swirling over a period of about five minutes, 23.2 g. of *p*-toluenesulfonyl chloride. After ten minutes at room temperature the mixture containing suspended pyridine hydrochloride was heated for fifteen minutes on a steam-bath, and then just to boiling on a hot plate. After cooling, 250 ml. of water was added and the mixture extracted with ether. The ether solution was washed thoroughly with 10% hydrochloric acid, then with 5% potassium hydroxide, water and saturated salt solution. The residue, after evaporation and drying was obtained as tan crystals, m. p. 42–45°; yield 36.00 g. (97%). Repeated recrystallization from ether–petroleum ether (40–60°) gave colorless needles m. p. 46.4–47.8° (reported,[2] 61–62°).

Anal. Calcd. for $C_{17}H_{19}O_4NS$: C, 61.24; H, 5.74. Found: C, 61.56; H, 5.78.

N-Tosyl-β-anilinopropionic Acid, IV ($R^1 = R^2 = H$).—To a solution of 34.0 g. of the crude ester in 200–250 ml. of 80% methanol was added in small increments with swirling 75 ml. of 10% potassium hydroxide. After sixteen hours at room temperature the clear solution was diluted with 500 ml. of water and then poured with stirring into an excess of cold dilute hydrochloric acid. The solid acid was separated, dissolved in sodium bicarbonate solution (with slight warming) filtered and acidified. The colorless precipitate amounted to 30.0 g. (92% yield), m. p. 138–142°. Recrystallization from benzene gave 27.7 g. (85% yield) of colorless needles, m. p. 145–146.5° (reported,[2] 144°). An additional 2.1 g. of material, m. p. 140–144°, was obtained from the mother liquor.

N-Tosyl-4-keto-1,2,3,4-tetrahydroquinoline, IV ($R^1 = R^2 = H$).—A mixture of 6.38 g. of recrystallized acid, 4.16 g. of phosphorus pentachloride and 40 ml. of dry thiophene-free benzene was refluxed (steam-bath) for thirty minutes. The solution was cooled to 0° in an ice-bath and 3.5 ml. of anhydrous stannic chloride in 15 ml. of thiophene-free benzene was added. After five minutes at 5° the yellow solution was allowed to stand for twelve hours at room temperature during which a bright yellow complex precipitated. This complex was decomposed with dilute hydrochloric acid and the product worked up as described in the general procedure for cyclization with aluminum chloride.[9] The crude yellow product, m. p. 133–139°, amounted to 5.70 g. (95% yield). Recrystallization from ethanol gave colorless needles, m. p. 141–142° (reported,[2] 140–141°).

The **azine** of the ketone V ($R^1 = R^2 = H$) crystallized from benzene as bright yellow needles, m. p. 242.5–243.5° with previous softening and darkening.

Anal. Calcd. for $C_{32}H_{30}O_4N_4S_2$: C, 64.19; H, 5.05; N, 9.36; S, 10.71. Found: C, 64.42; H, 5.29; N, 9.48; S, 10.80.

4-Keto-1,2,3,4-tetrahydroquinoline, VI ($R^1 = R^2 = H$).—A mixture of 30.0 g. of V ($R^1 = R^2 = H$), m. p. 142–143°, 110 ml. each of concentrated hydrochloric acid and acetic acid, and 50 ml. of water was refluxed for three hours. After one and one-half hours all of the solid had dissolved giving an orange-red solution. The solution was cooled, diluted with water (500 ml.) and extracted with ether to remove any unchanged starting material. The aqueous solution was neutralized with solid sodium carbonate and the liberated ketone extracted with ether. The ether solution was washed with 5% potassium hydroxide which removed the orange color, then with water followed by saturated salt solution, and finally dried over anhydrous sodium sulfate. Evaporation of the ether gave 14.31 g. (98% yield) of a yellow oil which on seeding turned to a yellow solid, m. p. 43–44.5° (reported,[2] 44°).

Reduction of 4-keto-1,2,3,4-tetrahydroquinoline (1.0 g.) was effected according to the procedure of Huang-Minlon[14] with 0.5 ml. of 85% hydrazine hydrate, 0.5 g. of potassium hydroxide and 10 ml. of diethylene glycol. A 0.37-g. sample of the brown oily product was shaken with 30 drops of benzenesulfonyl chloride and 15 ml. of 10% sodium hydroxide, and the resulting product crystallized from dilute alcohol. After recrystallization the benzenesulfonamide melted at 65.5–66.5° alone or when mixed with an authentic specimen of N-benzenesulfonyltetrahydroquinoline (m. p. 65–66°) prepared from quinoline.

4-Oximino-1,2,3,4-tetrahydroquinoline, VII ($R^1 = R^2 = H$).—This derivative was prepared from the crude ketone, m. p. 39–42°, produced by acid hydrolysis of 3.52 g. of the N-tosyl ketone as described above. Two grams of hydroxylamine hydrochloride, 15 ml. of ethanol and 1 ml. of pyridine were used. After refluxing for one and one-half hours, the solvent was evaporated, water added and the oxime, which is appreciably soluble in water, was extracted with ether. Crystallization of the crude product from ether–petroleum ether (40–60°) gave a total of 1.73 g. (91% yield) of yellow plates, m. p. 101–103°. Repeated recrystallization from benzene–petroleum ether (60–68°) gave cream-colored needles, m. p. 104–105.2°.

Anal. Calcd. for $C_9H_{10}ON_2$: C, 66.65; H, 6.21. Found: C, 66.45; H, 6.00.

4-Aminoquinoline.—An intimate mixture of 0.3 g. of the oxime, VII ($R^1 = R^2 = H$), m. p. 102.5–103.5° and 0.3 g. of purified Norit[15] was placed in the bottom of an 8-inch test-tube and covered with a plug of Pyrex glass wool. While supported in an almost horizontal position the tube was evacuated to about 25 mm. and heated at the bottom end to 150° for five minutes, 170–180° for fifteen minutes and at 240–250° for fifteen minutes. The pressure was then reduced to 0.4 mm. and the 4-aminoquinoline evaporatively distilled condensing as yellow crystals in the cool section of the tube. The yield was 0.13 g. (49%) of material melting at 150–152° with softening at 147°. Recrystallization from benzene gave 0.114 g. (43% yield) of pale yellow prisms, m. p. 151–153° (reported,[16] 154°), undepressed on admixture with authentic 4-aminoquinoline (m. p. 152–155°).[17]

The mono-acetyl derivative was obtained by treatment of Surrey's sample with excess acetic anhydride and pyridine in benzene solution. The pure material was obtained from benzene as colorless needles, m. p. 177.8–179° (reported,[16] 176°).

Anal. Calcd. for $C_{11}H_{10}ON_2$: C, 70.95; H, 5.41. Found: C, 71.03; H, 5.37.

A sample of the acetyl derivative prepared from the product of dehydration of the oxime melted at 176–177.5° and on admixture did not depress the m. p. of the specimen described above.

When the Surrey sample was treated with benzenesulfonyl chloride by the Schotten–Baumann method, the main product was a **bis-benzenesulfonyl derivative**, presumably IX. It crystallized from ethyl acetate as colorless needles, melting at 199.5–201.5° with softening at 197°, but in a Pyrex tube evacuated to 0.6 mm. the m. p. was raised to 206–207° with softening at 200.5°.

Anal. Calcd. for $C_{21}H_{16}O_4N_2S_2$: C, 59.42; H, 3.80. Found: C, 59.68; H, 3.61.

The bis-benzenesulfonyl derivative prepared from the oxime dehydration product had the m. p. 196–198.5°.

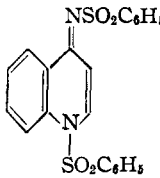
(14) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

(15) The Norit was treated as described by Mozingo, *Org. Syn.*, **26**, 77 (1946). Material which was not washed with acid was shown to be about as effective for the aromatization.

(16) Claus and Frobenius, *J. prakt. Chem.*, [2] **56**, 181 (1897).

(17) Prepared from the 4-chloro compound by Dr. A. R. Surrey of the Sterling–Winthrop Research Institute, unpublished work.

A mixture with the sample described above melted at 197–200°.



IX

When the dehydration of the oxime was carried out as described above except that the pressure was reduced to 0.4 mm. before heating was begun, some unchanged oxime volatilized along with the 4-aminoquinoline. Recrystallization of the mixture yielded a stable complex of amine and oxime in the molecular ratio 1 to 1 as indicated by analysis. It crystallized from benzene in the form of tan needles, m. p. 160–162.5°. The same product could be obtained by crystallizing equimolar amounts of VII and VIII ($R^1 = R^2 = H$) from benzene.

Anal. Calcd. for $C_{18}H_{18}ON_4$: C, 70.56; H, 5.92. Found: C, 70.68; H, 5.68.

The Chloro Series

Methyl β-(*m*-Chloroanilino)-propionate, II ($R^1 = H$, $R^2 = Cl$).—A mixture of 42.2 g. of *m*-chloroaniline, 28.41 g. of methyl acrylate and 2.0 ml. of acetic acid was refluxed for twenty-eight hours, then distilled giving 37.8 g. (54% yield) of crystalline product, b. p. 194–198° (20 mm.), m. p. 35–39°. Recrystallization from benzene–petroleum ether (90–100°) gave a total of 33.2 g. of cream colored needles, m. p. 36–40°. A sample purified by repeated recrystallization was obtained as colorless blades, m. p. 39.6–40.6°.

Anal. Calcd. for $C_{10}H_{12}O_2ClN$: C, 56.21; H, 5.66. Found: C, 56.08; H, 5.37.

Methyl N-tosyl-β-(*m*-chloroanilino)-propionate, III ($R^1 = H$, $R^2 = Cl$) was prepared from 10.00 g. of the above ester (m. p. 37.5–39°), 50 ml. of pyridine and 10.28 g. of *p*-toluenesulfonyl chloride as described above for the unsubstituted series. The crude product was obtained as a nearly colorless solid, m. p. 75–78°; yield 16.69 g. (97%). Repeated recrystallization from benzene–petroleum ether (90–100°) gave colorless prisms, m. p. 77–78.2°.

Anal. Calcd. for $C_{17}H_{18}O_4ClNS$: C, 55.51; H, 4.93. Found: C, 55.31; H, 5.23.

N-Tosyl-β-(*m*-chloroanilino)-propionic Acid, IV ($R^1 = H$, $R^2 = Cl$) (*a*) *By Alkaline Hydrolysis.*—Twenty-five grams of III ($R^1 = H$, $R^2 = Cl$) was saponified in 250 ml. of alcohol with a solution of 4.18 g. of potassium hydroxide in 40 ml. of water. After thirty hours at room temperature the solution was acidified, extracted with ether, and the ether solution extracted with saturated sodium bicarbonate. Acidification of the bicarbonate solutions gave the crude acid which after crystallization from benzene–petroleum ether (90–100°) amounted to 11.61 g. (48% yield), m. p. 104–106°. Repeated recrystallization of a sample from benzene–petroleum ether (90–100°) gave colorless prisms, m. p. 105.8–106.8°.

Anal. Calcd. for $C_{16}H_{16}O_4ClNS$: C, 54.31; H, 4.56. Found: C, 54.65; H, 4.74.

From the ether solution there was obtained 4.37 g. of colorless material, m. p. 133–135°, undepressed on admixture with an authentic specimen of N-tosyl-*m*-chloroaniline (m. p. 133.5–134.5°).

(*b*) *By Acid Hydrolysis.*—A mixture of 40.0 g. of III ($R^1 = H$, $R^2 = Cl$), 500 ml. of dioxane, 180 ml. of water and 60 ml. of concentrated hydrochloric acid was refluxed for three hours. The solution was concentrated to about one-half the original volume by warming on a steam-bath in a current of air, and neutralized with an excess of solid sodium bicarbonate while warm. Extraction with ether removed 2.01 g. of unchanged starting material, m. p. 73.5–77°. Acidification of the aqueous solution gave 36.00 g. (93% yield) of tan product, m. p. 105–106.5°. On the basis of recovered ester the yield was 98%.

N-Tosyl-4-keto-7-chloro-1,2,3,4-tetrahydroquinoline, V ($R^1 = H$, $R^2 = Cl$).—A 3.54-g. sample of the above acid (m. p. 104–106°) was cyclized according to a procedure already described in detail.[9] The acid chloride was formed with 2.08 g. of phosphorus pentachloride in 25 ml. of benzene. After removal of the volatile phosphorus compounds the acid chloride was dissolved in 40 ml. of benzene and added to 1.50 g. of aluminum chloride suspended in 40 ml. of benzene. After thirty minutes in the cold, and six hours at 23° the complex was hydrolyzed with 100 ml. of 20% hydrochloric acid and worked up as previously described.[9] The crude product amounted to 2.92 g. (87% yield), m. p. 95–115° and was employed without further purification for the next step of the synthesis. Recrystallization from ethanol gave 1.88 g. of yellow needles, m. p. 124–125° in the first crop and 0.22 g., m. p. 121–123°, in the second. The recovered starting acid amounted to 0.32 g., m. p. 103–104.5°. A sample of the ketone purified by repeated recrystallization from ethanol was obtained as colorless needles, m. p. 129.2–129.8°.

Anal. Calcd. for $C_{16}H_{14}O_3ClNS$: C, 57.22; H, 4.20. Found: C, 57.12; H, 4.19.

The **semicarbazone** crystallized from benzene as colorless needles m. p. 224.8–226.6° (dec.) when introduced at 200°.

Anal. Calcd. for $C_{17}H_{17}O_3ClN_4S$: C, 51.97; H, 4.36. Found: C, 52.30; H, 4.08.

The above procedure was repeated successfully several times, but in one run, carried out as described above except that the reaction period was five hours at 25°, the crude product melted at 78–90°. Crystallization from methanol gave in a poor recovery colorless plates, m. p. 125–126.5°. This product failed to form a semicarbazone, and the m. p. was depressed to 100–110° on admixture with the ketone described above. A sample purified by repeated recrystallization from ethanol was obtained as colorless plates, m. p. 126.6–127.4°. Although the found analytical values (C, 66.49; H, 4.61) were low for those calculated for phenyl-*p*-tolylsulfone (C, 67.21; H, 5.22), the m. p. was not depressed on admixture with an authentic specimen (colorless plates, m. p. 126.4–127.2°) prepared by the method of Newell.[18]

4-Keto-7-chloro-1,2,3,4-tetrahydroquinoline, VI ($R^1 = H$, $R^2 = Cl$).—A mixture of 20.0 g. of the crude cyclization product (m. p. 98–115°), 200 ml. each of acetic and concentrated hydrochloric acid and 50 ml. of water was refluxed for three hours. The product was worked up as described above for the unsubstituted series, and the yield of crude brown ketone was 9.16 g. (85%), m. p. 124.5–128.5°. Evaporative distillation at 135–150° (0.1 mm.) gave 8.20 g. (76% yield or 60% over-all from the acid) of pale orange-yellow product, m. p. 126–131°. A sample repeatedly recrystallized from benzene–petroleum ether (60–68°) was obtained as yellow needles, m. p. 133.2–134°.

Anal. Calcd. for C_9H_8OClN: C, 59.51; H, 4.44. Found: C, 59.18; H, 4.27.

4-Oximino-7-chloro-1,2,3,4-tetrahydroquinoline, VII ($R^1 = H$, $R^2 = Cl$), was prepared from 1.46 g. of ketone (m. p. 126–131°), 1.46 g. of hydroxylamine hydrochloride, 30 ml. of ethanol and 1 ml. of pyridine as described above for the unsubstituted series except that the ether extraction was unnecessary. The crude product amounted to 1.47 g. (93% yield) of tan crystals, m. p. 157–160.5° with previous softening. Repeated recrystallization of a sample from benzene–petroleum ether (60–68°) gave light tan needles, m. p. 161.2–162.6°.

Anal. Calcd. for $C_9H_9OClN_2$: C, 54.97; H, 4.61. Found: C, 55.15; H, 4.36.

4-Amino-7-chloroquinoline, VIII ($R^1 = H$, $R^2 = Cl$).—A mixture of 0.300 g. of the crude oxime (m. p. 157–160.5°) and 0.15 g. of activated Norit[15] was dehydrated

(18) Newell, *Am. Chem. J.*, **20**, 302 (1898).

as described above in the unsubstituted series at 240°; ten minutes at 43 mm. and one hour at 0.06 mm. The distillate was crystallized from benzene to give 0.142 g. (52% yield) of pale yellow plates, m. p. 147.5–148.5° (reported,[19] 147–148°) undepressed on admixture with an authentic sample of 4-amino-7-chloroquinoline (m. p. 147–149.5°).[17]

Acetylation by the procedure described above for the formation of the mono-acetyl derivative of 4-aminoquinoline, gave in this case a **di-acetyl derivative** (possibly corresponding in structure to formula IX with —$COCH_3$ in place of —$SO_2C_6H_5$). It crystallized from benzene as colorless needles, m. p. 197.2–198.2°.

Anal. Calcd. for $C_{13}H_{11}O_2ClN_2$: C, 59.43; H, 4.22. Found: C, 59.64; H, 4.13.

Samples of this derivative prepared from both Surrey's[17] and our specimens had the same m. p. separately or on admixture.

The Methoxy Series

Methyl β-(*p*-Methoxyanilino)-propionate, II (R^1 = OCH_3, R^2 = H).—A mixture of 24.6 g. of *p*-anisidine, 19.8 g. of methyl acrylate, 20 ml. of benzene and 6 drops of anhydrous stannic chloride was refluxed for twenty-four hours, then distilled giving 26.5 g. (63% yield) of crystalline product, b. p. 143–152° (0.65 mm.), m. p. 35.5–38°. On the basis of recovered *p*-anisidine (5.88 g., m. p. 53–55°) the yield was 83%. A sample recrystallized several times from benzene–petroleum ether (60–68°), then from ether–petroleum ether (40–60°) was obtained as colorless needles, m. p. 37.6–38.2° with slight previous softening.

Anal. Calcd. for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.23. Found: C, 63.26; H, 7.08.

Methyl N-tosyl-β-(*p*-methoxyanilino)-propionate, III (R^1 = OCH_3, R^2 = H) was prepared according to the procedure described above for III (R^1 = R^2 = H) except that the proportion of pyridine was reduced, benzene being used as the solvent, and the reaction was carried out at room temperature. Thus from 26.53 g. of crude II (R^1 = OCH_3, R^2 = H), 100 ml. of pyridine, 40 ml. of benzene and 31.2 g. of *p*-toluenesulfonyl chloride there was obtained after forty-eight hours at room temperature, 42.2 g. (91% yield) of almost colorless material, m. p. 41–44°. A sample after repeated recrystallization from methanol, and finally from methanol–ether was obtained as colorless plates, m. p. 43–44.5°.

Anal. Calcd. for $C_{18}H_{21}O_5NS$: C, 59.49; H, 5.83. Found: C, 59.83; H, 5.75.

N-Tosyl-β-(*p*-methoxyanilino)-propionic Acid, IV (R^1 = OCH_3, R^2 = H) (*a*) *By Alkaline Hydrolysis.*—A 21.4-g. sample of the above ester was dissolved in 175 ml. of methanol and then treated with 45 ml. of water and 11 ml. of 6 *N* potassium hydroxide. After forty-eight hours at room temperature the mixture was worked up as described above in the chloro series except that benzene was used for the extraction. The crude product amounted to 17.91 g. (87% yield), m. p. 103–105° with softening at 78°. The neutral fraction yielded 1.14 g. of N-tosylanisidine, m. p. 111–112°. Recrystallization of the acid from benzene gave colorless crystals, m. p. 79–83.5° (reported,[1] 81–82°), which evidently contained loosely bound benzene of crystallization, since after drying at 65° (1 mm.) for three hours the m. p. rose to 104–106° (softening at 79°) and the neut. equiv. dropped from 383 to 370 (calcd. 349). Repeated recrystallization of the crude acid from ether–petroleum ether (40–60°) and ethyl acetate–petroleum ether (60–68°) gave colorless flat rods, m. p. 107.6–108.8°.

Anal. Calcd. for $C_{17}H_{19}O_5NS$: C, 58.44; H, 5.48; neut. equiv., 349.4. Found: C, 58.53; H, 5.38; neut. equiv., 348.6.

(19) Price, Leonard, Peel and Reitsema, THIS JOURNAL, **68**, 1807 (1946).

(*b*) *By Acid Hydrolysis.*—A 5.00-g. sample of the crude ester was hydrolyzed as described above in the chloro series, with 62 ml. of dioxane, 22 ml. of water and 9 ml. of concentrated hydrochloric acid. The yield of crude brown acid was 4.21 g. (87%), m. p. 104–107° with previous softening.

N-Tosyl-4-keto-6-methoxy-1,2,3,4-tetrahydroquinoline, V (R^1 = OCH_3, R^2 = H) was prepared from 3.50 g. of the pure acid IV (R^1 = OCH_3, R^2 = H) according to a procedure already described[9]; 2.20 g. of phosphorus pentachloride with 5 ml. of benzene were used for formation of the acid chloride, and 1.67 g. of aluminum chloride for the cyclization with a reaction time of four hours. The yield of pale yellow product was 3.28 g. (99%), m. p. 122.5–124.5° with previous softening. Recrystallization from methanol–acetone gave almost colorless flat rods, m. p. 126.2–127° (reported,[2] 124–125°).

4-Keto-6-methoxy-1,2,3,4-tetrahydroquinoline, VI (R^1 = OCH_3, R^2 = H) was produced by hydrolysis of 2.00 g. of the above cyclization product with 2 ml. each of acetic and hydrochloric acid, and 0.5 ml. of water. After refluxing for three and three-quarters hours the mixture was worked up as described above in the unsubstituted series. The bright yellow basic material amounted to 0.96 g. (90% yield), m. p. 113.5–114.5° (reported,[2] 112–113°).

4-Oximino-6-methoxy-1,2,3,4-tetrahydroquinoline, VII (R^1 = OCH_3, R^2 = Cl) was prepared from 0.200 g. of the above ketone, 0.20 g. of hydroxylamine hydrochloride, 2.00 ml. of alcohol and 0.20 ml. of pyridine as described above in the chloro series. The crude cream-colored oxime amounted to 0.200 g. (92% yield), m. p. 130.7–132.7° with previous softening. Recrystallization from benzene gave 0.164 g. of colorless flat rods, m. p. 132.2–133.7°. Repeated recrystallization raised the m. p. to 133.6–134.2°.

Anal. Calcd. for $C_{10}H_{12}O_2N_2$: C, 62.48; H, 6.29. Found: C, 62.67; H, 5.96.

4-Amino-6-methoxyquinoline, VIII (R^1 = OCH_3, R^2 = H).—A mixture of 0.300 g. of the above oxime and 0.15 g. of activated Norit[15] was dehydrated as described above in the unsubstituted series at 200–204°; fifteen minutes at 50 mm. and fifteen minutes at 0.2 mm. After an additional fifteen minutes at 210° (0.3 mm.) the distillate was crystallized from toluene giving 0.136 g. (50% yield) of a light tan product, m. p. 120–121.5°. Recrystallization from benzene gave light tan needles, which after drying for four hours at 100° (0.1 mm.) to remove benzene of crystallization, turned to powdery material, m. p. 121–122° (reported,[20] 120°), undepressed on admixture with authentic 4-amino-6-methoxyquinoline (m. p. 122–122.5°).[17] The **hydrochloride**, after recrystallization from ethanol, melted at 270–271°, dec. (inserted at 250°). The salt prepared from Surrey's[17] sample melted at 269.5–270.5°, dec. (inserted at 250°) alone or on admixture with our material. This derivative is reported to melt at 249°, dec.[20].

Anal. Calcd. for $C_{10}H_{11}OClN_2$: C, 57.01; H, 5.26. Found: C, 57.07; H, 5.04.

Summary

Previous attempts to cyclize β-anilinopropionic acid derivatives to dihydro-4-quinolones have generally given poor yields of products of questionable structure. In the present investigation a method is described for effecting cyclization of the N-tosyl derivatives in excellent yields. The structures of the products have been unequivocally established by conversion to 4-aminoquinolines. In this way 7-chloro- and 6-methoxy-4-aminoquinoline as well as the parent substance have been prepared.

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(20) Hirsch, *Monatsh.*, **17**, 333 (1896).