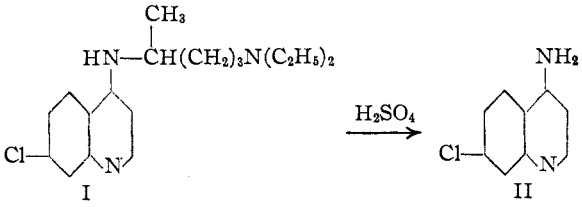
NOTES

The Dealkylation of 4-(4-Diethylamino-1-methylbutylamino)-7-chloroquinoline, SN 7618[1]

BY ROBERT H. BAKER, R. M. DODSON[2] AND BYRON RIEGEL

In an attempted sulfonation of 4-(4-diethylamino-1-methylbutylamino)-7-chloroquinoline,[3] SN 7618, I, it was found that concentrated sulfuric acid at 200° would remove the side chain from the compound and that 4-amino-7-chloroquinoline, II, could be isolated from the reaction in 41% yield.



Sulfur dioxide was evolved during the reaction and carbonaceous material was formed. This reaction proved useful in determining the structure of 3-bromo-4-(4-diethylamino-1-methylbutylamino)-quinoline.[4] When a solution of this compound in concentrated sulfuric acid was heated to 180–190° for fifteen minutes, the side chain was removed. 3-Bromo-4-aminoquinoline, m. p. 202° after recrystallization from low boiling petroleum ether, was isolated from the reaction solution. Claus and Howitz[5] report the melting point of this compound to be 203°. No attempt was made to isolate the degradation products of the side chain from either of these reactions.

This reaction appears to be very similar to that used by Hickinbottom[6] for the elimination of tertiary alkyl groups from alkylanilines. He found that *t*-butyl-, *t*-amyl- and *t*-hexylaniline yielded aniline when heated with 15 *N* sulfuric acid at 110–140°. Concentrated hydrobromic acid and hydriodic acid and 70% phosphoric acid were found to have a similar action. It should also be noted that Drake[7] has reported that hydriodic acid at temperatures above 100° will cleave an excessive amount of the side chain from 8-(5-*i*-propylaminoamylamino)-6-methoxyquinoline. Concentrated sulfuric acid can be used for the dealkylation of these quinoline derivatives because of the resistance of the quinoline nucleus to sulfonation.

(1) This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Northwestern University.

(2) National Research Council Predoctoral Fellow, 1946–1947.

(3) N. L. Drake, H. J. Creech, D. Draper, J. A. Garman, S. Haywood, R. M. Peck, E. Walton and J. O. Van Hook, THIS JOURNAL, **68**, 1214 (1946).

(4) B. Riegel, G. R. Lappin, C. J. Albisetti, Jr., B. H. Adelson, R. M. Dodson, L. G. Ginger and R. H. Baker, *ibid.*, **68**, 1229 (1946).

(5) Ad. Claus and H. Howitz, *J. prakt. Chem.*, **158**, 232 (1894).

(6) W. J. Hickinbottom, *J. Chem. Soc.*, 1070 (1933).

(7) N. L. Drake, J. Van Hook, J. A. Garman, R. Hayes, R. Johnson, G. W. Kelley, S. Melamed and R. M. Peck, THIS JOURNAL, **68**, 1529 (1946).

Experimental[8]

4-Amino-7-chloroquinoline, II.—A solution of 5.0 g. of 4-(4-diethylamino-1-methylbutylamino)-7-chloroquinoline, I, in 22 ml. of concentrated sulfuric acid was heated rapidly in an oil-bath. At 180° a gas containing sulfur dioxide was evolved. This evolution ceased within fifteen to twenty minutes after the temperature had reached 200–210°. The black reaction mixture was then cooled rapidly and poured over ice. The resulting solution was diluted to 200 ml. with water, decolorized with Nuchar C, and made basic with ammonium hydroxide. The product which precipitated was extracted with ether; the ether solution was dried with sodium sulfate, and the ether was removed on a steam-bath. The residue that remained was crystallized from a mixture of benzene and Skellysolve B (petroleum ether, b. p. 60–70°) to give 1.14 g. of product, m. p. 148.5–149.5°. The reported[9] m. p. is 147°.

Anal. Calcd. for $C_9H_7ClN_2$: C, 60.52; H, 3.95; N, 15.69. Found: C, 60.92; H, 4.08; N, 15.03.

3-Bromo-4-(4-diethylamino-1-methylbutylamino)-quinoline,[4] when treated in the same manner, gave 3-bromo-4-aminoquinoline, m. p. 202°.[5]

(8) We are indebted to Margaret Ledyard for the microanalyses. All melting points were taken with a Fischer–Johns melting point apparatus.

(9) U. S. Patent 2,233,970, March 4, 1941.

DEPARTMENT OF CHEMISTRY
NORTHWESTERN UNIVERSITY
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A Structure Proof for 4-(4-Diethylamino-1-methylbutylamino)-7-phenoxyquinoline

BY R. O. CLINTON[1] AND C. M. SUTER

Drake and co-workers[2] and Riegel and co-workers[3] have recently published the synthesis of 4-(4-diethylamino-1-methylbutylamino)-7-phenoxyquinoline (SN-10,663), tentatively assigning the structure on the basis of analogy with similar compounds prepared by the ethoxymethylene malonic ester synthesis. The same compound had been prepared in these Laboratories by the oxalacetic ester synthesis[4,5] prior to the appearance of the above-cited papers, and the structure rigorously proved to be that of the 7-isomer by two independent methods, as outlined in the accompanying chart.

4-Chloro-7-phenoxyquinoline was converted to the 4-hydrazino compound, which when oxidized with copper sulfate solution[6] gave 7-phenoxy-

(1) Present address: Gasparcolor, Inc., Hollywood, California.

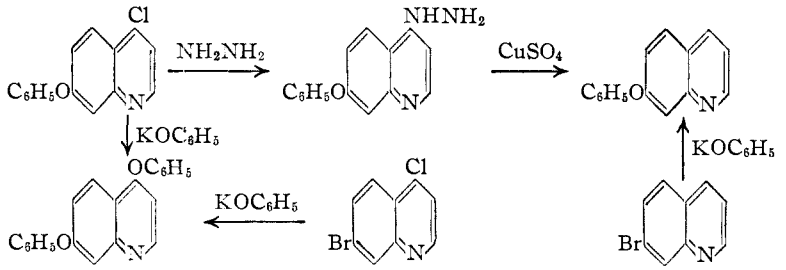
(2) Drake, *et al.*, THIS JOURNAL, **68**, 1208 (1946).

(3) Riegel, *et al.*, *ibid.*, **68**, 1264 (1946).

(4) Surrey and Hammer, *ibid.*, **68**, 113 (1946).

(5) Steck, Hallock and Holland, *ibid.*, **68**, 129 (1946).

(6) Thielepape, *Ber.*, **55**, 136 (1922); Thielepape and Spreckelsen, *ibid.*, 2929 (1922).



quinoline, identical with the compound prepared from 7-bromoquinoline and potassium phenolate by the Ullmann method.

4-Chloro-7-phenoxyquinoline when treated with potassium phenolate gave 4,7-diphenoxyquinoline, identical with the compound prepared in a similar manner from 7-bromo-4-chloroquinoline.[4]

The identity was further confirmed in each case by the comparison of picrates and methiodides.

4-Hydroxy-7-phenoxyquinoline or its precursors could not be successfully oxidized to an anthranilic acid derivative by either alkaline potassium permanganate or alkaline sodium hypobromite solution.

Experimental[7]

3-Phenoxyaniline.—The Ullmann reaction[8] between potassium phenolate and 3-bromonitrobenzene gave a 77.8% yield of 3-phenoxynitrobenzene, b. p. 145–155° at 3 mm.

Reduction of the nitro-compound with reduced iron powder and hydrochloric acid in aqueous alcohol, by a method analogous to that of West,[9] afforded 3-phenoxyaniline, b. p. 145–148° at 1 mm., in 84% yield. The hydrochloride had m. p. 140–141° (lit.[8] m. p. 139°).

3-Phenoxyaniline was also prepared directly from 3-bromoaniline by the Ullmann procedure[8]; however, the over-all yield from 3-nitrobromobenzene by this route was only 43%.

4-Hydroxy-7-phenoxyquinoline-2-carboxylic Acid.—A mixture of 319.4 g. of ethyl oxalacetate, 303 g. of 3-phenoxyaniline and 1100 ml. of methylene chloride was refluxed for twenty-four hours under a water separator, after which period 27.7 ml. of water had separated and the reaction had ceased. The methylene chloride was removed *in vacuo* and the residual oil was heated at 135° and 0.4 mm. for one hour to remove unchanged starting materials. The weight of residual viscous pale orange azomethine was 560 g. (95.6% crude).[10] The crude azomethine was cyclized to the quinoline in mineral oil at 250–255° by the usual procedure.[4,5] After completion of the cyclization, as evidenced by distillation of the theoretical amount of alcohol, the black, tarry mineral oil suspension was cooled to 70° and filtered. The sticky semisolid material was washed thoroughly with Skellysolve B and air dried. No pure compounds could be isolated from this crude material; it was therefore saponified by refluxing with a mixture of 1500 ml. of water, 1000 ml. of alcohol and 280 g. of sodium hydroxide for five hours. The alcohol was removed *in vacuo* and the residual deep brown homogeneous aqueous solution acidified with hydrochloric acid. The resulting precipitate was filtered, washed well with water and air dried. The crude dry acid mixture was refluxed for fifteen minutes with 1000 ml. of acetone, cooled and filtered. The pale yellow insoluble powder, after air drying, weighed 203.4 g., m. p. 250–254° (dec.). Evaporation of the acetone extract gave 172.3 g. of a friable black resin, from which, in spite of numerous attempts, no pure material could be obtained. This material probably contained the 5-isomer.

The acetone-insoluble 4-hydroxy-7-phenoxyquinoline-2-carboxylic acid crystallized from dilute alcohol with but little loss, in small, pale yellow needles, m. p. 254–256° (dec.).

Anal. Calcd. for $C_{16}H_{11}NO_4$: N, 4.98. Found: N, 4.91.

4-Hydroxy-7-phenoxyquinoline.—The acid was decarboxylated in mineral oil at 270°.[4,5] Upon working up in the usual manner there was obtained a 94.5% yield of crude product, m. p. 175–180°. The pure compound formed large white needles from dilute acetone, m. p. 185–186° (lit.[3] m. p. 183–184°). The yield of pure material was 92.3%.

4-Chloro-7-phenoxyquinoline.—The hydroxy compound was converted to the chloro compound essentially by the procedure of Riegel, *et al.*[3] The product was obtained in 76% yield, b. p. 175–182° at 1.5 mm., m. p. 51.5–52.5° (lit.[3] m. p. 50–51°).

Proof of Structure. 7-Phenoxyquinoline, from 7-Bromoquinoline.—3-Bromoaniline was converted to a mixture of 5- and 7-bromoquinolines in 66% yield by the Skraup reaction as modified by Richter and Smith.[11] Pure 7-bromoquinoline was separated from this mixture by the procedure of Claus and Vis.[12] The nitrate had m. p. 201.5–203° (dec.) (lit.[12] m. p. 199° (dec.)).

To a solution of 6.1 g. of potassium hydroxide in 23.7 g. of phenol (dehydrated by heating to an internal temperature of 185°) was added 17.5 g. of 7-bromoquinoline and 1 g. of copper bronze, and the resulting mixture was stirred at 180–185° for three hours. The cooled reaction product was taken up in ether, filtered, and the filtrate washed thoroughly with 10% sodium hydroxide solution. After drying the ethereal extract over anhydrous potassium carbonate, the ether was removed *in vacuo*. The residue was crystallized twice from Skellysolve B with decolorization, yielding 14.8 g. of **7-phenoxyquinoline** as white needles, m. p. 72.5–73.5°.

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.42; H, 5.01; N, 6.33. Found: C, 81.25; H, 5.03; N, 6.45.

The **picrate** formed short, brilliant yellow needles from alcohol, m. p. 185–186°.

Anal. Calcd. for $C_{21}H_{14}N_4O_8$: N, 12.44. Found: N, 12.40.

The **methiodide** crystallized from benzene–absolute alcohol in bright yellow leaflets, m. p. 217–218° (dec.).

Anal. Calcd. for $C_{16}H_{14}INO$: N, 3.86. Found: N, 3.93.

From 4-Chloro-7-phenoxyquinoline.—A mixture of 10.0 g. of 4-chloro-7-phenoxyquinoline, 18.4 g. of 85% hydrazine hydrate and 35 ml. of alcohol was refluxed for five hours. The solvent was removed *in vacuo* and the residual gum was dissolved in 100 ml. of benzene. On standing, long white slender needles of **4-hydrazino-7-phenoxyquinoline** separated (11.8 g., m. p. 190–200° (dec.)); the hydrazine was unstable, however, and was not analyzed. Five and four-tenths grams of the crude hydrazine was suspended in 50 ml. of water, the mixture was heated under reflux with stirring, and treated during forty-five minutes with 125 ml. of 10% copper sulfate solution. After refluxing and stirring for an additional one-half hour there was added an excess of 10% sodium hydroxide solution. The mixture was refluxed and stirred for one-half hour and filtered hot through Filtercel. The filter cake

(7) All melting points and boiling points are corrected. The authors are indebted to Mr. Morris Auerbach and staff for the analyses.

(8) Ullmann and Sponagel, *Ann.*, **350**, 104 (1906).

(9) West, *J. Chem. Soc.*, **127**, 494 (1925).

(10) Purification of the crude azomethine by the washing technique of Steck, Hallock and Holland, ref. 5, did not improve the subsequent steps.

(11) Richter and Smith, THIS JOURNAL, **66**, 369 (1944).

(12) Claus and Vis, *J. prakt. Chem.*, [2] **40**, 384 (1889).

was washed thoroughly with ether, the ether layer was separated from the filtrate, decolorized, and evaporated *in vacuo*. Crystallization of the residue from Skellysolve B gave 3.2 g. (67%) of **7-phenoxyquinoline**, m. p. and mixed m. p. with the above-described authentic sample, 72.5–73.5°. The picrate and methiodide derivatives corresponded in m. p. and mixed m. p. with those described above.

4,7-Diphenoxyquinoline. From 7-Bromo-4-chloroquinoline.—To a solution of anhydrous potassium phenolate prepared from 3.1 g. of potassium hydroxide and 20 g. of phenol was added 5.0 g. of 7-bromo-4-chloroquinoline[4,13] and 0.5 g. of copper bronze. The resulting mixture was stirred at 185° for one and one-half hours. Upon working up by the general method described above there was obtained 5.6 g. (86%) of product, white prisms from Skellysolve B, m. 81.5–82.0°.

Anal. Calcd. for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.83; N, 4.47. Found: C, 80.49; H, 4.86; N, 4.49.

The **picrate** formed long, brilliant yellow needles from alcohol, m. p. 185–186°.

Anal. Calcd. for $C_{27}H_{18}N_4O_9$: N, 10.33. Found: N, 10.07.

The **methiodide** formed pale yellow prisms from alcohol, m. p. 262–264° (dec.).

Anal. Calcd. for $C_{22}H_{18}INO_2$: N, 3.08. Found: N, 3.02.

From 4-Chloro-7-phenoxyquinoline.—Treatment of 4-chloro-7-phenoxyquinoline with potassium phenolate and copper bronze by the above method afforded a 90% yield of **4,7-diphenoxyquinoline**, m. p. and mixed m. p. with the above-described authentic sample, 81.5–82.0°. The picrate and methiodide derivatives corresponded in m. p. and mixed m. p. with those previously described.

4-(4-Diethylamino-1-methylbutylamino)-7-phenoxyquinoline.—This compound was prepared in the usual manner.[2,4,5] The product was obtained in 65.5% yield, b. p. 230–235° at 0.1 mm., m. p. 102–102.5° (lit.[2] m. p. 102–104°).

The **citrate** formed rosets of white prisms from alcohol–ether, m. p. 122.5–124.5° (gas evolution).

Anal. Calcd. for $C_{24}H_{31}N_3O \cdot C_6H_8O_7$: N, 7.39. Found: N, 7.41.

(13) Although the original description of this compound did not give a rigorous proof of structure, subsequent work in these laboratories has confirmed the assigned structure. Oxidation of 7-bromo-4-hydroxyquinoline with alkaline sodium hypobromite solution by a method analogous to that of Vaughan (THIS JOURNAL, **68**, 324 (1946)) gave a 62% yield of 4-bromoanthranilic acid. The m. p. and mixed m. p. with an authentic sample (Claus and Scheulen, *J. prakt. Chem.*, [2] **43**, 206 (1891)) was 220–221° (dec.).

STERLING-WINTHROP RESEARCH INSTITUTE
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o- and *p*-Nitroacetophenones by Liquid Phase Oxidation

BY WILLIAM S. EMERSON, JOSEF W. HEYD, VICTOR E. LUCAS, JAMES K. STEVENSON AND THOMAS A. WILLS

Ford-Moore and Rydon[1] have recently described two methods for the preparation of *o*- and *p*-nitroacetophenone. One method comprised the nitration and subsequent oxidation of methylphenylcarbinol and the other the treatment of *o*- and *p*-nitroethylbenzene with *t*-butyl nitrite and sodium *t*-butoxide followed by the hydrolysis of the resulting oximes.

(1) Ford-Moore and Rydon, *J. Chem. Soc.*, 679 (1946).

We have found liquid phase oxidation[2,3] to be suitable for the preparation of these compounds. While the conversions are not as high as is usually the case (14% for the *ortho* and 20% for the *para* isomer), the yields are satisfactory (63 and 66%, respectively) and the procedure is comparatively simple.

Experimental

The *o*-nitroethylbenzene[4] used boiled at 116° (22 mm.), $n^{25}D$ 1.5338, and the *p*-nitroethylbenzene at 134–136° (23 mm.), $n^{25}D$ 1.5431.

***o*-Nitroacetophenone.**—*o*-Nitroacetophenone was prepared by blowing air through an alundum disperser for twenty-eight hours, into 250 g. of *o*-nitroethylbenzene held at 135–145° and containing 4 g. of chromium oxide. This mixture was cooled, filtered, washed free of acid with aqueous sodium carbonate, and fractionated to separate the product. The pure *o*-nitroacetophenone boiled at 112.5–113.5° (2 mm.) [159° (16 mm.)],[5] $n^{25}D$ 1.5530, d^{25}_{25} 1.238, yield 39 g. (63%, 14% conversion).

Anal. Calcd. for $C_8H_7O_3N$: C, 58.2; H, 4.24. Found: C, 58.6; H, 4.75.

After two crystallizations from alcohol the oxime melted at 113–115° (115°).[6]

***p*-Nitroacetophenone.**—*p*-Nitroacetophenone was prepared in the same manner as the *ortho* isomer. The product, a solid, was collected at 123–130° (2 mm.) and crystallized from acetone and then from hexane, m. p. 78.5–80.0° (80–81°),[7] yield 29 g. (60%, 10% conversion). In a larger run of 900 g. the conversion rose to 20% with a 66% yield.

(2) Emerson, Heyd, Lucas, Chapin, Owens and Shortridge, THIS JOURNAL, **68**, 674 (1946).

(3) Emerson, Heyd, Lucas, Cook, Owens and Shortridge, *ibid.*, 1665 (1946).

(4) Cline and Reid, *ibid.*, **49**, 3150 (1927).

(5) Camps, *Ber.*, **32**, 3232 (1899).

(6) German Patent 109,663; *Chem. Zentr.*, **71**, II, 458 (1900).

(7) Drewsen, *Ann.*, **212**, 160 (1882).

CENTRAL RESEARCH DEPARTMENT
MONSANTO CHEMICAL COMPANY
DAYTON, OHIO RECEIVED NOVEMBER 9, 1946

A New Synthesis of Polygalitol Tetraacetate (Tetraacetyl-1,5-anhydro-D-sorbitol)

BY HEWITT G. FLETCHER, JR.

Richtmyer, Carr and Hudson[1] found that the reductive desulfurization of either octaacetyl-β,β-diglucosyl disulfide or tetraacetyl-β-glucothiose with Raney nickel afforded the tetraacetate of 1,5-anhydro-D-sorbitol (polygalitol). Recent work by Wolfrom and Karabinos[2] as well as by other authors[3] has further demonstrated the feasibility of reductive desulfurization as a preparative method. In the course of an investigation of sugar–alcohol anhydrides in this Laboratory it was found that ethyl tetraacetyl-D-glucopyranosyl

(1) N. K. Richtmyer, C. J. Carr and C. S. Hudson, THIS JOURNAL, **65**, 1477 (1943); *cf.* J. Bougault, E. Cattelain and P. Chabrier, *Compt. rend.*, **208**, 657 (1939), who introduced the use of Raney nickel for desulfurization.

(2) M. L. Wolfrom and J. V. Karabinos, THIS JOURNAL, **66**, 909 (1944); *ibid.*, **68**, 1455 (1946).

(3) O. Jeger, J. Norymberski, S. Szpilfogel and V. Prelog, *Helv. Chim. Acta*, **29**, 684 (1946); V. Prelog, J. Norymberski and O. Jeger, *ibid.*, 360 (1946); R. Jeanloz, D. A. Prins and T. Reichstein, *ibid.*, 371 (1946).