Notes

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3-Hexyl- and 3-Octyladipic Acids[1,2]

DAVID W. GOHEEN AND WYMAN R. VAUGHAN

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In the course of studies on the physical properties of liquids designed as potential lubricating oils, certain glycol ethers were prepared. The present report describes the preparation of two intermediates for glycols which were desired for these studies. Full details of their conversion to glycols and glycol ethers will be published elsewhere. The hexyl group is "normal" and the octyl group is derived from diisobutylene. Thus the octyl acid is 3-(2′,4′,4′-trimethylpentyl)adipic acid.

EXPERIMENTAL[3,4]

4-Hydroxycaprophenone was prepared from 129 g. (1.37 moles) of phenol, 186 g. (1.40 moles) of aluminum chloride, and 184 g. (1.37 moles) of caproyl chloride. The product distilled to give two fractions: (*1*) 2-hydroxycaprophenone, 98.2 g. (37.5%), b.p. 104–106°/1.0 mm. (reported 142–143°/10 mm.[5]); and (*2*) 4-hydroxycaprophenone, 91.5 g. (35%), b.p. 155–158°/1.0 mm. (reported 207–208°/10 mm.[5]).

4-Hexylphenol. Distillation of the product of Clemmensen reduction of 4-caprophenone afforded 91.5 g. (78%) of water-white 4-hexylphenol, b.p. 110–114°/1.0 mm. (reported 146–147°/10 mm.[6]).

4-Hexylcyclohexanol. The 4-hexylphenol was reduced using Raney nickel[6] at 150° and 100 atm. After an induction period of 15–30 min., the reduction started and proceeded rapidly, being complete in 3 hr. The catalyst was filtered off, and the alcohol (from the catalyst) was distilled out of the filtrate. The crude 4-hexylcyclohexanol was not purified but was converted directly to 3-hexyladipic acid, as described below.

3-Hexyladipic acid. A solution of 50% nitric acid (100 g., 0.80 mole) was heated nearly to boiling and 40 mg. of ammonium vanadate was added. The mixture was stirred and 44.0 g. (0.24 mole) of crude 4-hexylcyclohexanol was added slowly, the temperature being maintained at 60–65° by means of an ice bath. After complete addition the mixture was stirred for an additional hour and then was cooled. The acid formed a solid cake which was filtered off, washed with water to remove nitric acid and then was taken up in ether, washed thoroughly and was distilled at 176–179°/0.2 mm. to give 36.0 g. (65%) of 3-hexyladipic acid. Recrystallization from 70–90° petroleum ether afforded white plates, m.p. 71–72°.

Anal. Calcd. for $C_{12}H_{22}O_4$: C, 62.58; H, 9.62. Found: C, 62.84; H, 9.73.

4-Octylcyclohexanol. A 120 g. batch of 4-octylphenol[7] was hydrogenated at 150° and 1000 p.s.i. using a Raney nickel catalyst. There was obtained 100 g. (81%) of 4-octylcyclohexanol, b.p. 100–104°/0.3 mm.

3-Octyladipic acid. The oxidation of 4-octylcyclohexanol (100 g., 0.472 mole) was carried out as with 4-hexylcyclohexanol using 200 g. of 50% nitric acid and 95 mg. of ammonium vanadate. Upon completion of the reaction the mixture was placed in an ice bath and allowed to stand thus overnight. The nitric acid was decanted from the pasty mass which was then washed several times with water and dissolved in ether. The ethereal solution was thrice washed with water and was dried over magnesium sulfate. Evaporation afforded a yellow oil which rapidly solidified. Recrystallization from benzene yielded 3-octyladipic acid as colorless platelets, m.p. 133–135°, 68.5 g. An additional crop of 8 g. was obtained by concentration of the mother liquor to half its volume; thus the over-all yield was 76.5 g. (63%). Further recrystallization from cyclohexane-ethyl acetate raised the m.p. to 136–137°.

Anal. Calcd. for $C_{14}H_{26}O_4$: C, 65.08; H, 10.14. Found: C, 65.26; H, 10.03.

CHEMISTRY LABORATORY
UNIVERSITY OF MICHIGAN
ANN ARBOR, MICH.

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(2) Abstracted from a portion of WADC Technical Report 53-45, June 1953. Released for publication by Mr. Harold Rosenberg, Senior Materials Laboratory, Directorate of Research.

(3) Melting points and boiling points are uncorrected.

(4) Microanalyses by Microtech Laboratories, Skokie, Ill.

(5) G. Sandelescu and A. Girard, *Bull. soc. chim.* (4), **47**, 1300 (1930).

(6) A. A. Pavlic and H. Adkins, *J. Am. Chem. Soc.*, **68**, 1471 (1946).

(7) Kindly supplied by Rohm & Haas Co., Philadelphia, Pa. The substance is prepared by alkylating phenol with diisobutylene.

Halogen Derivatives of 8-Aminoquinoline

EVERETT C. HURDIS

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In the course of work on the preparation of several new "ferroin" type oxidation-reduction indicators, it became of interest to synthesize certain trihalo-8-aminoquinolines. The specific derivatives desired were those in which all the available benzene ring positions (that is, positions 5, 6, and 7) are substituted by chlorine and/or bromine. Such derivatives have not heretofore been reported. However, it is known that the 5 and 7 positions, being strongly activated by the amino group, are easily halogenated directly.[1,2] Therefore, it was judged that the desired trihalo-8-

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(2) R. C. Elderfield and E. F. Claflin, *J. Am. Chem. Soc.*, **74**, 2953 (1952).

TABLE I

HALOGEN DERIVATIVES OF 8-AMINOQUINOLINE

Compound	M.P., °C.[a]	Nitrogen Calcd.	Nitrogen Found	Bromine Calcd.	Bromine Found	Chlorine Calcd.	Chlorine Found	Yield %
8-Amino-5,6,7-tribromoquinoline	154.5–155.5	7.36	7.38	62.94	62.66			81
8-Amino-5,7-dibromo-6-chloroquinoline	169–169.5	8.33	8.30	47.5	45.9	10.5	11.2	79
8-Amino-6-bromo-5,7-dichloroquinoline	160.5–161.5	9.60	9.57	27.4	26.6	24.3	23.9	77
8-Amino-5,6,7-trichloroquinoline	169–170	11.32	11.42			43.0	42.7	67
8-Amino-5,7-dichloroquinoline	125.5–126.5	13.15	13.54			33.28	33.36	60

[a] All melting points are corrected.

aminoquinolines would be readily preparable by direct bromination or chlorination of the known compounds 8-amino-6-bromoquinoline and 8-amino-6-chloroquinoline. Experimentally it proved possible to verify this prediction. 8-Amino-6-bromoquinoline and 8-amino-6-chloroquinoline were prepared by a modification of the method of Richter and Smith.[3,4] Bromination of these compounds in acetic acid solution yielded 8-amino-5,6,7-tribromoquinoline and 8-amino-5,7-dibromo-6-chloroquinoline respectively. By chlorination, using sulfuryl chloride in acetic acid solution, the 8-amino-6-bromoquinoline gave 8-amino-6-bromo-5,7-dichloroquinoline, while 8-amino-6-chloroquinoline gave 8-amino-5,6,7-trichloroquinoline. Convenient procedures were developed for these reactions, giving the desired compounds in satisfactory yields and high purity. Analytical and yield data for the individual compounds are listed in Table I.

The structures of these trihalo-8-aminoquinolines, as given, were assigned on the following basis: The pyridine ring in 8-aminoquinoline is known to be inert to halogenation under mild conditions. Thus, bromination[1] and chlorination[2] of 8-aminoquinoline have been found to give substitution only at the 5 and 7 (benzene ring) positions. In the work reported here, 8-amino-6-bromoquinoline and 8-amino-6-chloroquinoline were halogenated under very mild conditions, such as were used for 8-aminoquinoline.[1,2] Therefore, the assumption could be made, with considerable confidence, that again only the 5 and 7 positions were substituted and that 5,6,7-trihalo-8-aminoquinolines resulted.

Elderfield and Claflin[2] have reported the preparation of 8-amino-5,7-dichloroquinoline by the action of chlorine gas on 8-aminoquinoline. Their yield of crude product, m.p. 113–116°, was 31%. It was found that this compound could be prepared in greater yield and higher purity by using sulfuryl chloride for the chlorination. By this means a 60% yield of material, m.p. 125.5–126.5°, was obtainable. (Analytical data for 8-amino-5,7-dichloroquinoline are listed in Table I.) The 8-aminoquinoline used for preparing this compound was made in excellent yield by a convenient modification of the method of Woroschtzow and Kogan.[5]

EXPERIMENTAL

8-Aminoquinoline. Woroschtzow and Kogan[5] reported the preparation of 8-aminoquinoline from 8-quinolinol in 89% yield. By modifying their method somewhat, the inconvenience of working with sulfur dioxide gas was avoided, and an even higher yield was obtained. A mixture of 145.2 g. (1 mole) of 8-quinolinol, 335 g. of ammonium sulfite monohydrate, 153 ml. of 28% aqueous ammonia, and 300 ml. of water was charged into a pressure vessel of 1300 ml. capacity. The mixture was heated with constant mechanical shaking for 7 hr. at 155°. The shaking was then continued while cooling the reactor to 25–35°. The crude product was removed by filtration, washed with water, dried, and vacuum distilled at 0.5 mm. gauge pressure. A 93% yield of material, m.p. 63–64°, was obtained.

8-Amino-6-bromoquinoline. 6-Bromo-8-nitroquinoline was prepared and reduced according to the directions of Richter and Smith[3,4] (starting with 1 mole of 4-bromo-2-nitroaniline). However, the steam distillation used by Richter and Smith to isolate the product was found to be very time-consuming because of the low volatility of 8-amino-6-bromoquinoline. The product was therefore isolated by the following more convenient procedure. After the stannous chloride reduction, the reaction mixture was poured into 3000 ml. of water and the solution neutralized by aqueous alkali. A solution of 675 g. of sodium hydroxide in 2250 ml. of water was added to dissolve the precipitated hydrous tin oxides. The precipitated crude product was then removed by filtration, dried, and extracted by several portions of hot benzene, totalling 1200 ml. Evaporation of the benzene, followed by recrystallization from hexane and finally vacuum distillation, gave material, m.p. 75–76°. The overall yield from 4-bromo-2-nitroaniline was 49%.

8-Amino-6-chloroquinoline. This compound was prepared from 4-chloro-2-nitroaniline by the same procedure used for 8-amino-6-bromoquinoline. The overall yield of 8-amino-6-chloroquinoline, m.p. 70–71°, was 50%.

Procedure for brominations. The amine (0.03 mole) was dissolved in 30 times its weight of acetic acid and the solution cooled to 15° in an ice water bath. A solution of 10.0 g. of bromine in 60 ml. of acetic acid was then added dropwise with constant mechanical stirring, keeping the temperature between 15° and 20°. After all the bromine had been added, the mixture was warmed to 25° and then poured into 750 ml. water. The small excess of bromine was destroyed by adding 0.3 g. of sodium bisulfite. The precipitate of crude product was removed by filtration, washed with water, dried and recrystallized from acetic acid.

Procedure for chlorinations. The amine (0.06 mole) was dissolved in 5 times its weight of acetic acid and the solution cooled to 10° in an ice water bath. A solution of 16.7 g. of

(3) F. P. Richter and G. F. Smith, *J. Am. Chem. Soc.*, **66**, 396 (1944).

(4) G. F. Smith and F. P. Richter, *Phenanthroline and Substituted Phenanthroline Indicators*, G. Frederick Smith Chemical Company, Columbus, Ohio, 1944, pp. 12 and 13.

(5) N. N. Woroschtzow and J. M. Kogan, *Ber.*, **65**, 142 (1932).

sulfuryl chloride (3% excess) in 25 ml. of acetic acid was added slowly with constant mechanical stirring. The mixture was then warmed gradually to room temperature and finally was heated for 20 min. on the steam bath at 70–75°. The reaction mixture was then poured into a solution of 40 g. sodium acetate in 300 ml. water. The precipitate of crude product was removed by filtration, washed with water, dried and recrystallized from acetic acid.

RESEARCH CENTER
UNITED STATES RUBBER COMPANY
WAYNE, N. J.

Some Observations on the Preparation of Salicylamide Esters of Acylated α-Amino Acids

RICHARD J. KERR AND CARL NIEMANN

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Acyl salicyclic acid esters frequently have been used as substrates in enzyme and non-enzyme catalyzed hydrolyses because of the ease with which such reactions may be followed spectrophotometrically.[1-8] However, these substrates when used in systems more alkaline than *p*H 5 will be present as the corresponding anions thus introducing a possible complication that would not be encountered with an uncharged substrate. Because of interest in the behavior of neutral as well as anionic substrates our attention was directed to the preparation of acyl esters of salicylamide whose spectral properties and those of the parent phenol[9,10] would be expected to be similar to those of salicyclic acid and its analogous esters.

The successful use of trifluoroacetic anhydride as a condensing agent in the synthesis of benzoyl-DL-phenylalanine α-naphthyl ester[11] suggested the use of this reagent for the preparation of the salicylamide esters of acetyl-DL- and L- and benzoyl-DL- and L-phenylalanine. While the two DL-compounds were obtained in good yield the attempted preparation of benzoyl-L-phenylalanine salicylamide ester gave a racemized product, even when the reaction was conducted at −20 to −30°. This result was not totally unexpected since it is known that many optically active α-acylamino acids are readily racemized in the presence of acetic or trifluoroacetic anhydride[12-16] presumably *via* an intermediate mixed anhydride and oxazolonium ion.[17-20]

The observations of Weygand *et al.*[14-16] and of Schallenberg and Calvin[21] relative to the preparation of optically active α-trifluoroacetamido acid chlorides and their use in the acylation of amines without attendant racemization led us to investigate the usefulness of such acid chlorides in the synthesis of the desired salicylamide esters.

Trifluoroacetyl-DL-phenylalanine was prepared by a procedure similar to that described by Weygand and Leising[15] and was converted to the acid chloride by treatment with phosphorus pentachloride. Reaction of the acid chloride with the sodium salt of salicylamide gave the DL-ester in good yield. However, when the above reaction sequence was repeated with L-phenylalanine a substantially racemized product was obtained.

In order to locate the point at which racemization had occurred the above synthesis was repeated, this time isolating each intermediate and determining its optical purity. As before,[14-17,21] it was found that trifluoroacetyl-L-phenylalanyl chloride could be prepared without difficulty but in contrast to previous experience with the reaction of this acid chloride with aniline,[15,21] its reaction with the sodium or triethylamine salt of salicylamide led to a substantially racemized product.

The absence of racemization in the preparation of trifluoroacetyl-L-phenylalaninanilide[21] and of trifluoroacetyl-L-alaninanilide[15] suggested the desirability of examining the reaction of trifluoroacetyl-L-phenylalanyl chloride with anthranilamide. Because of the poor yields obtained in the ammonolysis of methyl anthranilate,[22,23] the amide was prepared from *o*-nitrobenzamide by reduction

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(5) B. H. J. Hofstee, *Biochim. Biophys. Acta*, **24**, 211 (1957).
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(7) H. Brandenberger and W. H. Weihe, *Helv. Chim. Acta*, **38**, 1347 (1955).
(8) The monovalent anion of salicylic acid has a prominent absorption band at 298–300 mμ that is absent in the corresponding ester.
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(13) H. E. Carter and C. M. Stevens, *J. Biol. Chem.*, **133**, 117 (1940).
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