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QUINOLINEMETHANOLS[1]

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The quinolinemethanols reported in literature have been, for the most part, prepared by a crossed Cannizzaro reaction between formaldehyde and the corresponding quinolinealdehyde. The latter substances were obtained by a selenium dioxide oxidation of the corresponding methylquinoline. Radionov and Berkenheim (1) have reported the preparation of the 5-, 6-, 7-, and 8-quinolinemethanols. Phillips (2) and McDonald (3) have described the formation of 4-quinolinemethanol by the crossed Cannizzaro and an aluminum isopropoxide reduction, respectively, of cinchoninaldehyde. Very recently, the preparation of 3-quinolinemethanol has been reported (4). Hammich (5) has described the preparation of 2-quinolinemethanol by the action of alcoholic silver nitrate upon ω-bromoquinaldine. An improved method (4) for the formation of the latter substance has been reported recently.

It was of interest to determine the usefulness of the reduction of esters of quinolinecarboxylic acids by lithium aluminum hydride as a method for the preparation of the quinolinemethanols. The method used for reduction is essentially the procedure described by Nystrom and Brown (6). The reduction of the methyl and ethyl esters of 4-, 5-, 6-, 7-, and 8-quinolinecarboxylic acids proceeded smoothly in ether solution. The yield was somewhat higher when the reduction was accomplished at 0° or lower. However, 8-quinolinemethanol could be obtained in a pure state only when it was extracted from an ether solution with 2% sulfuric acid and then reprecipitated from the acid solution. Sharp melting points could be obtained only when the quinolinemethanols were scrupulously dry. The melting points obtained agreed with those reported in literature. The results for the above quinolinemethanols are summarized in Table I.

The yields of 2- and 3-quinolinemethanols by the reduction of the corresponding quinolinecarboxylic esters were not as high as for the quinolinemethanols summarized in Table I. In both cases the best yield was obtained when the reduction was carried out at −50°. Both gave as by-products, oils and higher-melting solids. Some of the by-products may have arisen from reduction of the heterocyclic portion of the ring. The by-product which accompanied 3-quinolinemethanol was a white crystalline material which melted at 137°. It always constituted about 30% of the material obtained. The substance does not form a phenylurethan. The main by-product in the reduction of methyl quinaldate is a high-boiling oil. Presumably, the high-melting solid (m.p. 197–199°) also present is formed from the oil, since the latter, on standing, deposits this solid. The liquid distills at 105–108° at 0.1 mm. yielding a clear yellow oil. There is no evidence of quinaldine in the oil. Jones and Kornfeld (7) have reported the

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reduction of an α-carbethoxy group to a methyl group in certain substituted pyridinecarboxylic esters. No attempt has been made as yet to determine the structure of the two by-products.

The reduction of ethyl 4-chloro-3-quinolinecarboxylate to the corresponding methanol proceeded smoothly without either the loss of halogen or the formation of by-products. Because of the limited solubility in ether, the reduction product was more readily isolated by extraction of the dried residue with absolute ethyl alcohol in a manner similar to that reported by Jones and Kornfeld (7). In this case as well as the others, isolation of the quinolinemethanol was also much simpler when the hydrolysis was carried out using sodium hydroxide as described by Amundsen and Nelson (8).

TABLE I

QUINOLINEMETHANOLS AND THEIR DERIVATIVES

QUINOLINEMETHANOL	M.P., °C.	YIELD, %	PHENYLURETHAN			
			m.p., °C.	Empirical Formula	Analysis, N	
					Calc'd	Found
4-CH_2OH	97–98	81	162–163			
5-CH_2OH	137–138	76	164–165	$C_{17}H_{14}N_2O_2$	10.07	9.99
6-CH_2OH	79–80	75	155–156	$C_{17}H_{14}N_2O_2$	10.07	10.09
7-CH_2OH	59–60	83	151–152	$C_{17}H_{14}N_2O_2$	10.07	10.23
8-CH_2OH	77–78	81	145–146	$C_{17}H_{14}N_2O_2$	10.07	10.33

EXPERIMENTAL[2]

5-Quinolinecarboxylic acid (9), *6-quinolinecarboxylic acid* (10), *7-quinolinecarboxylic acid* (11), and *8-quinolinecarboxylic acid* (12) and the *esters* used in the preparation of the quinolinemethanols listed in Table I were obtained according to published methods. *Ethyl 4-quinolinecarboxylate* was prepared from available cinchoninic acid. *Quinaldic acid* and its methyl ester were prepared according to the method of Campbell (13).

Ethyl 4-chloro-3-quinolinecarboxylate (I). A mixture of 92 g. (0.6 mole) of phosphoryl trichloride and 66 g. (0.35 mole) of ethyl 4-hydroxy-3-quinolinecarboxylate (14) was heated on a steam-bath for 10–15 minutes, then allowed to cool somewhat and poured onto one liter of ice to which had been added 165 ml. of concentrated ammonia water. The mass was stirred and kept cold until it became entirely granular after which it was extracted with two 500-ml. portions of ether. After drying over magnesium sulfate, the ether was removed and the residue was distilled at 128–129° at 0.2 mm. pressure with the bath temperature at 160–162°. The yield was 68 g. (83%); m.p. 45–46°. After recrystallizaton from petroleum ether (b.p. 40–60°), I was obtained as white prisms, m.p. 46–47°.

Anal. Calc'd for $C_{12}H_{10}ClNO_2$: N, 5.94. Found: N, 5.78.

Ethyl 3-quinolinecarboxylate (II). One-tenth mole (23.6 g.) of I was reduced in acetic acid at room temperature using a palladium-charcoal catalyst (15). After the theoretical amount of hydrogen had been taken up, the palladium-charcoal was removed and most of the acetic acid was taken off in a vacuum. The residue was diluted, made slightly alkaline, and extracted with ether. The ether extract was filtered to remove a white solid (1.8 g.),

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[2] Microanalyses performed by Micro-Tech Laboratories, Skokie, Illinois.

then dried, and the solvent removed. The red-colored oil was added to 250 ml. of water and 10% hydrochloric acid was added carefully until no further solution occurred; the solution then was filtered and the ice-cold filtrate neutralized with ammonia water. A yield of 12 g. of crude II (m.p. 63–65°) was obtained. After recrystallization from petroleum ether, pure II melted at 67–68°. The melting point of II reported by Kindler (16) is 66–67°.

The ether-insoluble residue was shown by a mixture melting point determination to be ethyl 4-hydroxy-3-quinolinecarboxylate. An additional 2.1 g. of the same substance was recovered by extraction of the spent palladium-charcoal catalyst with glacial acetic acid. The replacement of a halogen atom by the OH group has been shown by Cutler and Surrey (17) to occur in glacial acetic acid at an elevated temperature. This behavior at room temperature has not been reported previously.

4-Chloro-3-quinolinemethanol (III). To a stirred solution of 4.5 g. (0.12 mole) of lithium aluminum hydride in 300 ml. of ether, cooled to −50°, was added dropwise a solution of 23.5 g. (0.1 mole) of I in 300 ml. of ether. The addition required 35–40 minutes and the temperature was not allowed to go higher than −45°. The stirring was continued for 10–15 minutes while the solution warmed to −25° and then 150 ml. of ether saturated with water was added. After warming to 0–5°, a solution of 6 g. of sodium hydroxide in 35 ml. of water was added while the stirring was continued. The solution was filtered and the solid washed with two 100-ml. portions of ether. The ether filtrate was washed with water, dried, and the solvent removed to give 6.4 g. of III. The white filter cake was triturated with 100 ml. of 5% sodium hydroxide, the solid was removed by filtration and washed with water, and then dried in air and finally in a vacuum. The dried solid was extracted with 200 ml. of boiling absolute ethanol, filtered while hot, and 50 ml. of benzene was added to the filtrate. After cooling in an ice-box, the yield of III was 9.2 g.; an additional 3.2 g. was recovered from the mother liquor. The combined fractions of III (18.8 g.) were recrystallized from ethyl alcohol-benzene (5:1), yielding 16.7 g. (86%) of long white needles, m.p. 147–147.5°.

Anal. Calc'd for $C_{10}H_8ClNO$: N, 7.23. Found: N, 7.08.

The *phenylurethan* of III was prepared and recrystallized from benzene; m.p. 171.5–172°.

Anal. Calc'd for $C_{17}H_{13}ClN_2O_2$: N, 8.96. Found: N, 8.80.

3-Quinolinemethanol (IV). Ethyl 3-quinolinecarboxylate (20.1 g., 0.1 mole) was reduced with lithium aluminum hydride and the hydrolysis was carried out in exactly the same manner as for III. Since IV is very soluble in ether, the ether layer was separated, washed with water, and dried over magnesium sulfate. After removal of the solvent, a residue of 14.4 g. of low-melting crude IV remained. The substance was recrystallized from 40 ml. of benzene, yielding 3.8 g. of small white platelets (V), m.p. 131–134°. A second recrystallization raised the melting point to 136.5–137.5°. Compound V did not form a phenylurethan with phenyl isocyanate; it was recovered unchanged. The benzene mother liquor from V was heated to boiling and diluted with 30 ml. of ligroin (b.p. 67–75°). After cooling there was obtained 7.9 g. of a white granular solid, m.p. 71–77°. After two recrystallizations from benzene-ligroin (3:1), a yield of 6 g. (38%) of IV was obtained as clusters of short white needles, m.p. 83.5–84°. Hammich and co-workers (4) have reported the melting point of IV as 65–67°.

Anal. Calc'd for $C_{10}H_9NO$: N, 8.80. Found: N, 8.72.

V was found to contain 6.77% nitrogen.

The *phenylurethan* of IV was prepared and recrystallized from benzene; m.p. 152–153°.

Anal. Calc'd for $C_{17}H_{14}N_2O_2$: N, 10.07. Found: N, 10.15.

2-Quinolinemethanol (VI). Methyl quinaldate (18.4 g., 0.1 mole) was reduced with lithium aluminum hydride and the hydrolysis and extraction were carried out by the same method as for IV. After drying and removal of the solvent, a yield of 16.8 g. of a red semi-solid mixture was obtained. The substance was dissolved in 50 ml. of dry ether and filtered to remove an insoluble white solid (m.p. 196–198°); then the filtrate was diluted slowly with petroleum ether (30–60°). After standing overnight in an ice-box, a yield of 10.4 g. (65%) of slightly yellow needles was obtained; m.p. 66–67°. The substance may be recrystallized also from ligroin-benzene (2.5:1). The melting point of VI[3] reported by Hammich (5) is 64°.

Anal. Calc'd for $C_{10}H_9NO$: N, 8.80. Found: N, 8.83.

The *phenylurethan* of VI was prepared and recrystallized from ligroin (b.p. 75–82°)-benzene (1:2); m.p. 125–126°.

Anal. Calc'd for $C_{17}H_{14}N_2O_2$: N, 10.07. Found: N, 10.20.

SUMMARY

The lithium aluminum hydride reduction of 2-, 3-, 4-, 5-, 6-, 7-, and 8-quinolinecarboxylic acid esters to the corresponding quinolinemethanols is reported. It was found that ethyl 4-chloro-3-quinolinecarboxylate reduced to 4-chloro-3-quinolinemethanol without the loss of chlorine.

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REFERENCES

(1) RADIONOV AND BERKENHEIM, *Chem. Abstr.*, **39**, 4606 (1945); **40**, 4066 (1946).
(2) PHILLIPS, *J. Am. Chem. Soc.*, **68**, 2568 (1946).
(3) MCDONALD, *J. Am. Chem. Soc.*, **69**, 1219 (1947).
(4) BROWN, HAMMICH, AND THEWLIS, *J. Chem. Soc.*, 1145 (1951).
(5) HAMMICH, *J. Chem. Soc.*, 1302 (1926).
(6) NYSTROM AND BROWN, *J. Am. Chem. Soc.*, **69**, 1197 (1947).
(7) JONES AND KORNFELD, *J. Am. Chem. Soc.*, **73**, 107 (1951).
(8) AMUNDSEN AND NELSON, *J. Am. Chem. Soc.*, **73**, 242 (1951).
(9) BRADFORD, ELLIOT, AND ROW, *J. Chem. Soc.*, 437 (1947).
(10) WALEY, *J. Chem. Soc.*, 2008 (1948).
(11) SEIBERT, NORTON, BENSON, AND BERGSTROM, *J. Am. Chem. Soc.*, **68**, 2721 (1946).
(12) CAMPBELL, KERWIN, LAFORGE, AND CAMPBELL, *J. Am. Chem. Soc.*, **68**, 1844 (1946).
(13) CAMPBELL, HELBING, AND KERWIN, *J. Am. Chem. Soc.*, **68**, 1840 (1946).
(14) REIGEL, LAPPIN, ADELSON, JACKSON, ALBISETTI, DODSON, AND BAKER, *J. Am. Chem. Soc.*, **68**, 1264 (1946).
(15) NEUMAN, SOMMER, KASLOW, AND SHRINER, *Org. Syntheses*, **26**, 45 (1946).
(16) KINDLER, *Ber.*, **69**, 2792 (1936).
(17) CUTLER AND SURREY, *J. Am. Chem. Soc.*, **72**, 3394 (1950).
(18) ROSENMUND AND ZYMALKOWSKI, *Ber.*, **85**, 152 (1952).

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[3] Added in proof: The authors wish to thank the assistant editor (FLS) for calling their attention to the work of Rosenmund and Zymalkowski (18). These authors report the reduction of ethyl quinaldate by lithium aluminum hydride to give 2-quinolinemethanol as a high-boiling oil. The latter reagent was also used in the reduction of ethyl cinchoninate to 4-quinolinemethanol which was isolated as the hydrobromide only.