Total Yield of all-*trans*-β-Carotene.—One hundred mg., recrystallized; this represents a 10% yield, based on C_{19}-aldehyde; specific activity, 1 μc. per mg., which is a 1.2% yield, based on activity.

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Halomethylquinolines[1]

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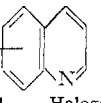
Several of the halomethylquinolines have been reported, particularly those with the $-CH_2X$ group attached to the pyridine portion of quinoline molecule. 2-Bromomethylquinoline[2] has been prepared by the reduction of 2-tribromomethylquinoline with stannous bromide in hydrobromic acid. It has been obtained also by the action of N-bromosuccinimide upon quinaldine.[3] 8-Bromomethylquinoline[4] was produced, with other materials, when 8-methylquinoline hydrobromide perbromide was heated to 150°. The corresponding 8-chloromethyl[4] compound was obtained by the action of hydrochloric acid upon 8-bromomethylquinoline. Campbell[5] has prepared 4-bromomethylquinoline by the bromination of lepidine with N-bromosuccinimide. Both 3- and 4-bromomethylquinoline have been obtained by the action of phosphorus tribromide upon the corresponding quinolinemethanol.[2]

It was of interest to study the remaining chloro- and bromomethylquinolines. These were prepared from the corresponding quinolinemethanols which were obtained, in turn, by a method[6] reported previously. Experimental conditions were worked out using 6-quinolinemethanol. The phosphorus tribromide method was not usable in the preparation of 6-bromomethylquinoline. About a 60% yield could be obtained when 6-quinolinemethanol was warmed with excess 48% hydrobromic acid at 70–80°. However, the best method consisted of treating a glacial acetic acid solution of the quinolinemethanol with gaseous hydrogen bromide then precipitation of the hydrobromide by dilution of the solution with absolute ether. The base is obtained by careful neutralization of an aqueous solution of the hydrobromide with dilute alkali. The best method for obtaining the chloromethylquinoline is the one described recently by Mosher.[7]

The bromomethylquinolines are much more reactive and difficult to handle than the chloromethylquinolines. Although this high reactivity has been reported by previous workers,[2–5] Johnson and Hamilton[8] have found that 4-bromomethylcarbostyril[9] and 4-(α-chloroethyl)-quinoline resisted attempts at hydrolysis. The bromomethylquinolines could not be recrystallized without a great loss except by dissolving them in a hydrocarbon solvent at room temperature and cooling the solution to a sub-zero temperature. The higher melting points of the bromomethylquinolines could be obtained only by insertion of the capillary tube into the bath at a temperature just below that determined by previous trials. In the case of both the chloro and bromo compounds, continued heating would cause solidification in the capillary tube, due, presumably, to the formation of the quaternary compounds of poly-N-methylenequinolinium halides.

The substances summarized in Table I were prepared from the corresponding quinolinemethanols by the same methods as are described in the Experimental part for 6-bromomethyl- and 6-chloromethylquinoline. Since 8-chloromethylquinoline has been prepared previously only by halogen exchange from 8-bromomethylquinoline, its formation from 8-quinolinemethanol was included. Howitz and Nother[4] reported a melting point of 56° for 8-chloromethylquinoline.

TABLE I

HALOMETHYLQUINOLINES XCH_2– 

Substituent	Yield, %	M.p., °C.	Empirical formula	Halogen, % Calcd.	Found
5-CH_2Cl	67	88–89.5	$C_{10}H_8ClN$	19.96	19.99
5-CH_2Br	64	75.5–76.5	$C_{10}H_8BrN$	35.98	35.48
7-CH_2Cl	76	53–54	$C_{10}H_8ClN$	19.96	20.48
8-CH_2Cl	70	53.5–54.5[a]	$C_{10}H_8ClN$	19.96	20.06
7-CH_2Br	36	69.5–70.5	$C_{10}H_8BrN$	35.98	35.35
3-CH_2Cl	63	33–34	$C_{10}H_8ClN$	19.96	19.87
4-Cl-3-CH_2Cl	74	121–122	$C_{10}H_7Cl_2N$	33.34	33.57

[a] Melting point reported by ref. 4 is 56°.

Experimental[10]

6-Quinolinemethanol.—This substance was prepared from methyl 6-quinolinecarboxylate by reduction with lithium aluminum hydride according to published procedure.[6]

The hydrobromide was prepared by the action of hydrogen bromide upon a benzene solution of 6-quinolinemethanol and was recrystallized from absolute ethyl alcohol; m.p. 199° dec.

Anal. Calcd. for $C_{10}H_{10}BrNO$: Br, 33.29. Found: Br, 33.29.

The methiodide was prepared by the action of 0.5 g. of methyl iodide upon 0.5 g. of 6-quinolinemethanol dissolved in 5 ml. of absolute ether. The pale yellow solid was recrystallized from absolute ethyl alcohol; m.p. 168.5° dec.

Anal. Calcd. for $C_{11}H_{12}INO$: I, 42.13. Found: I, 42.59.

6-Chloromethylquinoline.—6-Quinolinemethanol (2.5 g., 0.016 mole) was dissolved in 75 ml. of dry benzene and the solution was saturated with hydrogen chloride. The precipitated hydrochloride was removed by filtration, dried and treated with 7.5 ml. of purified thionyl chloride contained in a 200-ml. round-bottomed flask. After the initial reaction had subsided, the solution was refluxed for one hour, then cooled and 125 ml. of dry benzene was added. After the white solid was collected and dried, it was dissolved in 25 ml. of ice-water and neutralized with 1 *N* sodium hy-

(1) Taken mainly from a thesis submitted by J. M. S. to the Faculty of the Graduate School, Indiana University, in partial fulfillment of the requirements for the M. A. degree, February, 1954.

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(10) Microanalyses were performed by Miss Joanna Dickey of this Laboratory.

droxide. The dry, crude 6-chloromethylquinoline was dissolved in 35 ml. of hot ligroin (b.p. 63–93°) and the solution was cooled to −15°. A yield of 2.3 g. (83%) of short white needles was obtained, m.p. 70.5–71°.

Anal. Calcd. for $C_{10}H_8ClN$: Cl, 19.96. Found: Cl, 19.86.

The hydrochloride was prepared and recrystallized from absolute ethyl alcohol; m.p. 183.5–184.5°.

Anal. Calcd. for $C_{10}H_9Cl_2N$: Cl, 33.28. Found: Cl, 33.51.

6-Bromomethylquinoline.—A stream of dry hydrogen bromide was directed at the surface of a solution of 5 g. (0.031 mole) of 6-quinolinemethanol dissolved in 75 ml. of glacial acetic acid, which was contained in a 500-ml. flask, until a gain in weight of 15 g. was attained. The temperature rose to 40°. The solution was heated on a steam-bath at 70° for 20 minutes, then cooled and the solution was diluted with 300 ml. of dry ether. The solid was collected on a filter and was washed with dry ether. The yield of the crude hydrobromide was 9 g. (95%). The crude solid was dissolved in 125 ml. of water, cooled to 10° and carefully neutralized with 1 *N* sodium hydroxide. The solid was filtered immediately and dried in a desiccator. The dried solid was dissolved in 150 ml. of ligroin (b.p. 63–93°) at room temperature, filtered and the clear solution was cooled in a Dry Ice–acetone-bath. The yield of slightly yellow short needles was 4.7 g. (68%), m.p. 74–75°. This substance is a strong irritant and a lachrymator.

Anal. Calcd. for C_9H_8BrN: Br, 35.98. Found: Br, 35.73.

6-Quinolineacetonitrile.—A solution of 3 g. (0.017 mole) of 6-chloromethylquinoline and 1.2 g. (0.0185 mole) of potassium cyanide in 150 ml. of absolute ethyl alcohol was refluxed for ten hours then the alcohol was removed by evaporation in a vacuum and the residue extracted with three 50-ml. portions of ether. The ether was allowed to evaporate leaving an oil which congealed after standing overnight. The crude solid was extracted with two 75-ml. portions of ligroin (b.p. 63–93°), the solution was treated with Norite, filtered and evaporated to about 75 ml. After cooling to −15° and recrystallization a second time, a yield of 0.8 g. (28%) of white platelets was obtained, m.p. 80–81.5°.

Anal. Calcd. for $C_{11}H_8N_2$: N, 16.66. Found: N, 16.86.

6-Quinolineacetic Acid.—A mixture of 0.7 g. of 6-quinolineacetonitrile and 10 ml. of 10% sodium hydroxide was refluxed for 25 minutes then diluted with 10 ml. of water. The cold solution was extracted with 10 ml. of benzene. The aqueous layer was heated to boiling, then it was made slightly acidic (*p*H 4–5) with acetic acid. After cooling in ice-water for one hour, the white granular solid was collected on a filter, washed and dried. The yield was 0.64 g. (78%); it melted with decomposition at 220°. After solution in dilute alkali and reprecipitation, the melting point was raised to 225° dec.

Anal. Calcd. for $C_{11}H_9NO_2$: N, 7.48. Found: N, 7.62.

Ethyl 6-Quinolylmethyl Ether.—Sodium (0.5 g., 0.022 mole) was dissolved in 40 ml. of absolute ethyl alcohol, 3 g. (0.017 mole) of 6-chloromethylquinoline was added and the solution was refluxed for three hours. After the solution was filtered, the volume was reduced to about 12–15 ml., then four drops of water was added and the solution filtered again. After removal of the alcohol, the residue was vacuum distilled at 0.4 mm. yielding 2.4 g. (76%) of the ether which came over at 101–102°. The liquid was redistilled at 0.05 mm., b.p. 82–83°.

Anal. Calcd. for $C_{12}H_{13}NO$: N, 7.48. Found: N, 7.71.

4-(6-Quinolyl)-2-butanone.—To a cooled solution of 0.68 g. (0.03 mole) of sodium in 80 ml. of absolute ethyl alcohol was added 3.66 g. (0.036 mole) of ethyl acetoacetate. After the solution was stirred for a few minutes, a solution of 5 g. (0.028 mole) of 6-chloromethylquinoline in 25 ml. of absolute alcohol was added and the mixture heated on a steam-bath for three hours. At the end of this time, most of the alcohol was removed by distillation then 100 ml. of water was added and the aqueous portion extracted with two 100-ml. portions of ether. The ether layer was extracted with three 100-ml. portions of 0.5 *N* hydrochloric acid, then the acid solution was neutralized with 10% sodium hydroxide and the alkaline solution extracted with three 100-ml. portions of ether. After evaporation of the ether, the oil was refluxed with 50 ml. of 5% sodium hydroxide then acidified while hot with dilute sulfuric acid. After cooling, the solution was made slightly alkaline, extracted with three 100-ml. portions of ether and the latter dried with magnesium sulfate. After removal of the ether, a viscous yellow oil remained which congealed after standing for several days. The crude solid was recrystallized from 200 ml. of petroleum ether (b.p. 30–60°) by cooling the solution in Dry Ice–acetone. The yield of long white needles was 1.5 g. (28%), m.p. 56–57°.

Anal. Calcd. for $C_{13}H_{13}NO$: N, 7.03. Found: N, 7.06.

The 2,4-dinitrophenylhydrazone was prepared in the customary manner and recrystallized from a 1:1 solution of ethyl alcohol–pyridine as yellow platelets, m.p. 197–198.5°.

Anal. Calcd. for $C_{19}H_{17}N_5O_4$: N, 18.46. Found: N, 18.62.

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11-Deoxycorticosterone. The Aqueous Sulfuric Acid Hydrolysis of 21-Diazoprogesterone

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Reichstein and von Euw[3] have studied 21-diazoprogesterone (II) and some of its transformation products, and have established the constitution of II in part by the action of aqueous sulfuric acid which converts it into 11-deoxycorticosterone (III). Yields and experimental details were not furnished. It was of interest, therefore, to reinvestigate this hydrolysis as a possible method for the preparation of III. It was gratifying to have available a more recent, improved synthesis whereby 3-oxo-Δ^4-etiocholenic acid (I)[4,5] may be converted in two steps and in good yield to 21-diazoprogesterone (II).[6]

Preliminary hydrolyses of II according to the directions of Steiger and Reichstein[7] yielded oils which were only weakly reducing with ammoniacal silver oxide. It was found, however, that by increasing considerably the temperature and time of reaction, an oily product was obtained which gave a strong reducing test with this reagent, and which on chromatography on silicic acid gave pure, crystalline 11-deoxycorticosterone (III) in 62% yield, considerably above our expectations.

Experimental

11-Deoxycorticosterone (III).—A mixture of 680 mg. (2.0 mmoles) of 21-diazoprogesterone (II), 20 ml. of pure dioxane and 7.6 ml. of 2 *N* sulfuric acid was maintained at 75° for four hours. The material was then extracted with 300 ml. of ether, the ether extract washed with two 100-ml. portions of 5% potassium carbonate, and dried over anhydrous magnesium sulfate. The filtered extract was concentrated *in vacuo* at 55° and the small amount of residual dioxane aspirated on a steam-bath by means of a current of

(1) In partial fulfillment of requirements for the degree of Master of Science.

(2) Communications should be addressed to the senior author.

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(5) We are indebted to Dr. A. C. Shabica, Ciba Pharmaceutical Products, Inc., Summit, N. J., for supplying us with methyl 3β-hydroxy-Δ^5-etiocholenate from which this acid was prepared.

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