quired 24 hours at 0° followed by 48 ± 12 hours at room temperature for complete reaction. With isoamyl bromide the reaction was run at 0° for 12 hours and then for 4 days at room temperature; only then was a negative Beilstein test obtained. Isobutyl bromide after 24 hours at 0° and 96 hours at room temperature gave only 37% of the theoretical amount of silver bromide and *ca.* a 40% recovery of isobutyl bromide (which was, however, not quite pure).

The reaction time can be shortened considerably by running the reaction at 0° for 3 hours, then at room temperature for 5 hours and, finally, refluxing until a negative Beilstein test is obtained (*ca.* 4 hours of refluxing for iodides and 18 hours for straight chain bromides). However, the product is then a more complex mixture and the sulfuric acid treatment[7] is necessary to ensure that pure nitroparaffin is obtained; the yields are generally about 15–20% lower.

Spectrophotometric Determination of Nitrite Esters.—Since the lower molecular weight nitrites cannot be separated quantitatively from the reaction solvent it was necessary to devise a method for their determination in ether solution. The absorption spectrum of nitrite esters extends further into the visible than that of any other component of the reaction mixture; at 410 mμ the nitroparaffins, alkyl nitrates, alkyl halides, alcohols and carbonyl compounds do not interfere and, therefore, photometric readings were taken at this wave length on the ether solutions obtained by filtering out the silver salts. The amounts of each nitrite were determined from a calibration curve set up by using known concentrations of that particular alkyl nitrite. The accuracy of the method as checked by means of known mixtures of nitrite and nitroparaffin appears to be good to within 2%. Furthermore, the spectrophotometric technique was applied in the *n*-octyl iodide case. Here the amount of nitrite ester found spectrophotometrically was 14% while, upon rectification, 11% of pure 1-octyl nitrite was isolated.

The primary nitrite esters needed as reference compounds were synthesized by the excellent procedure of Chretien and Longi[19] in which a 40% aqueous solution of $Al_2(SO_4)_3 \cdot 18H_2O$ is added to a cold mixture of saturated aqueous sodium nitrite and the alcohol. After a few hours yields ranging from 70–80% were obtained in all cases (*cf.* Table IV).

TABLE IV

ALKYL NITRITES

Nitrite	B.p. °C.	B.p. Mm.	$n^{20}D$	Lit. value B.p. °C.	Lit. value B.p. Mm.	Lit. value $n^{20}D$	Ref.
n-Butyl	78		1.3762	75		1.3760	*b*
n-Hexyl	64	76	1.3990	50	48	1.3977/23°	*c*
n-Heptyl	41	5	1.4063	58	20	1.4060	*d*
n-Octyl	56	9	1.4127	55	8	1.4129	*e*
Isobutyl	66[a]		1.3702[a]	67		1.3715/22°	*f*
Isoamyl	51	115	1.3870	99		1.3871	*g*

[a] Isobutyl nitrite prepared from isobutyl alcohol and nitrosyl chloride has identical b.p. and $n^{20}D$. [b] W. A. Noyes, THIS JOURNAL, **55**, 3883 (1933). [c] L. M. Soffer, E. W. Parrotta and J. D. Domenico, *ibid.*, **74**, 5301 (1952). [d] Ref. 10. [e] J. C. Krantz, U. S. Patent 2,161,358; *C.A.*, **33**, 7495 (1939). [f] J. W. Brühl, *Z. physik. Chem.*, 16, 214 (1895). [g] Ref. 19.

(19) A. Chretien and Y. Longi, *Compt. rend.*, **220**, 746 (1945).

WEST LAFAYETTE, INDIANA

NOTES

Some Derivatives of 8-Methylquinoline[1]

BY WILLIAM E. BLANKENSTEIN AND JULIUS D. CAPPS

RECEIVED JULY 20, 1953

This investigation was conducted as part of a general study concerned with the synthesis and establishment of molecular structures of various previously unreported derivatives of quinoline. Although pertinent information pertaining to the chemistry of 6-bromo-8-methylquinoline and 6-chloro-8-methylquinoline[2] has been reported previously, many of the properties of 8-methylquinoline and its derivatives are as yet not recorded.

Since 6-methyl-5-nitroquinoline[3] results from the nitration of 6-methylquinoline and since 5-nitroquinoline is obtained along with 8-nitroquinoline during the nitration of quinoline, it is not surprising that Noelting and Trautmann[4] reported the preparation of 8-methyl-5-nitroquinoline (I) from 8-methylquinoline by direct nitration. It now appears that 2-chloro-8-methyl-5-nitroquinoline (VI) (m.p. 118–119°) also results from the nitration of 2-chloro-8-methylquinoline (III), but the product differs from that (m.p. 232°) described by Fischer[5] as resulting from the nitration of III. Furthermore Fischer[5] reported that the reduction of his mononitro derivative of III gave a product melting at 148° and possessing amine characteristics; whereas the substance obtained by us on reduction of VI with hydrogen in the presence of Raney nickel melts at 109–110°. The structure of VI as obtained by us was verified by an alternate synthesis from I *via* 1,8-dimethyl-5-nitro-2-quinolone (V).

The acid-catalyzed hydrolysis of VI gave the corresponding 2-hydroxyquinoline; but when 2-hydroxy-8-methylquinoline (IV) was nitrated, a mixture of products resulted from which only a small quantity of 2-hydroxy-8-methyl-5-nitroquinoline (VII) could be isolated. Some 20–30% of the mixture was shown to be 2-hydroxy-8-methyl-6-nitroquinoline (IX). The identity of IX was established by an unambiguous synthesis from 8-methyl-6-nitroquinoline *via* 1,8-dimethyl-6-nitro-2-quinolone and 2-chloro-8-methyl-6-nitroquinoline (VIII).

Hydrogen in the presence of Raney nickel reduces I, VI and VII to the corresponding amines. These amines were converted into arsonic acids, acetamido and benzamido derivatives by resorting to conditions previously reported for effecting such changes.[6]

(1) Presented in part before the Southeastern Regional Meeting of The American Chemical Society, Wilson Dam, Alabama, October, 1951. Condensed in part from a thesis presented by William E. Blankenstein to the Graduate School of the Alabama Polytechnic Institute in partial fulfillment of the requirements for the degree of Master of Science.

(2) T. A. Irving, J. L. Greene, Jr., J. G. Peterson and J. D. Capps, THIS JOURNAL, **72**, 4069 (1950).

(3) M. T. Bogert and H. L. Fisher, *ibid.*, **34**, 1570 (1912).

(4) E. Noelting and E. Trautmann, *Ber.*, **23**, 3654 (1890).

(5) O. Fischer, *ibid.*, **35**, 3674 (1902).

(6) H. Diaz de Arce, J. L. Greene, Jr., and J. D. Capps, THIS JOURNAL, **72**, 2971 (1950).

Experimental[7]

2-Hydroxy-8-methylquinoline (IV).[5,8,9]—III was hydrolyzed with 25% by volume (sulfuric acid–water solution) at 175–180° to give IV; yield almost the theoretical, m.p. 219–220°. See also reports of work by Fischer[5] and Spath.[8,9]

2-Chloro-8-methyl-5-nitroquinoline (VI). (A).—V was treated with dimethyl sulfate at 120–125°, and the resulting salt was subjected to alkaline ferricyanide oxidation to give VI; yield 0.5 g. (8.8%), m.p. 118–119°.

Anal. Calcd. for $C_{10}H_7ClN_2O_2$: Cl, 15.92; N, 12.59. Found: Cl, 15.83; N, 12.42.

(B).—A solution of nitric acid (35 ml., sp. gr. 1.42) in sulfuric acid (96 ml., sp. gr. 1.84) was added dropwise with constant stirring to III (70 g.) contained in sulfuric acid (273 ml., sp. gr. 1.84); the temperature was maintained below 0° during the addition. The flask and its contents were removed from the cooling bath and kept in the atmosphere of the laboratory for 12 hours prior to pouring the contents into cracked ice and water mixture (2000 ml.). The resulting solid was separated by filtration, washed with water and purified by recrystallizing from 95% ethanol subsequent to treating with decolorizing carbon; yield 60 g. (67%), m.p. 118–119°. A mixture of VIA and VIB also melted at 118–119°.

Anal. Calcd. for $C_{10}H_7ClN_2O_2$: Cl, 15.92; N, 12.59. Found: Cl, 16.08; N, 12.71.

2-Hydroxy-8-methyl-5-nitroquinoline (VII).—Refluxing of a solution of VI (35 g.) in 50% by volume aqueous sulfuric acid for 20 minutes followed by pouring of the resulting solution into 250 ml. of ice and water mixture gave solid VII. The solid was separated by filtration, washed with water and purified by crystallizing from 95% ethanol subsequent to a decolorizing carbon treatment; yield, almost the theoretical, m.p. 289.5–290.5°.

Anal. Calcd. for $C_{10}H_8N_2O_3$: N, 14.04. Found: N, 13.96.

2-Chloro-8-methyl-6-nitroquinoline (VIII) (A).—IX (0.28 g.), as obtained by the nitration of 2-hydroxy-8-methylquinoline, 0.3 ml. of phosphorus oxychloride and phosphorus pentachloride (1.4 g.) were heated together under reflux in an oil-bath maintained at 135° for two hours prior to pouring into water accompanied by stirring. Recrystallization from 95% ethanol gave a substance melting at 170–171°. A mixture of this substance with VIII as obtained from 8-methyl-6-nitroquinoline melted at 172–173°.

(B).—8-Methyl-6-nitroquinoline[10] (20.5 g.) and dimethyl sulfate (50 ml.) were heated together under reflux in an oil-bath maintained at 145° for 1.75 hours prior to cooling to room temperature. Water (110 ml.) was added and the system extracted three times with diethyl ether (30, 15, 15 ml.). The water-rich phase was mixed with a solution of potassium ferricyanide (134 g.) in water (1240 ml.), and heat was applied until the temperature of the resulting solution was 65°. A solution of KOH (19 g. in 62 ml. of water) was added dropwise and with mechanical stirring, at such a rate as to maintain the temperature of the reacting mixture at 65–70°. Stirring was continued for an additional hour, while the system spontaneously cooled, before filtering and washing the solid residue with water. After drying under reduced pressure at 25° this orange-yellow solid (1,8-dimethyl-6-nitro-2-quinolone) melted at 150–152° with decomposition.

Crude 1,8-dimethyl-6-nitro-2-quinolone (17.4 g.), phosphorus oxychloride (47.5 ml.) and phosphorus pentachloride (19 g.) were heated together under reflux in an oil-bath maintained at 140° for two hours. After pouring into a cracked ice and water mixture while stirring, solid VIII formed. VIII was purified, after washing it with water, by dissolving it in 95% ethanol (hot), applying an activated charcoal treatment and allowing to crystallize; m.p. 172–173°.

Anal. Calcd. for $C_{10}H_7ClN_2O$: N, 12.59. Found: N, 12.66.

2-Hydroxy-8-methyl-6-nitroquinoline (IX).—A solution of VIII in 50% by volume sulfuric acid–water solution was refluxed for one hour and poured into cold water that was being stirred. The solid that formed was separated by filtration and washed with water prior to purifying by repeated recrystallization from glacial acetic acid; m.p. 323–324.5° (uncor.).

Anal. Calcd. for $C_{10}H_8N_2O_3$: N, 13.65. Found: N, 13.68.

Nitration of IV.—A solution of IV (9.0 g.) in sulfuric acid (35.2 ml., sp. gr. 1.84) was added dropwise at 0 to 5° to a solution of nitric acid (4.5 ml., sp. gr. 1.42) in sulfuric acid (13 ml., sp. gr. 1.84), which was stirred mechanically. After removing the reaction mixture from the cooling bath and leaving it for 12 hours in the atmosphere of the laboratory, its temperature was slowly increased to 65° and maintained for five minutes. The solid that formed upon pouring the reaction mixture, with stirring, into cracked ice and water mixture (1000 ml.) was separated by filtration, washed with water, dried and dissolved in boiling glacial acetic acid. A solid formed upon cooling that melted at 323–324° after repeated recrystallization from glacial acetic acid; a mixture of this solid with IX also melted at 323–324°.

That portion of the nitration product that was most soluble in cold glacial acetic acid was recovered by adding water to the acetic acid solution (filtrate). Saturated aqueous sodium acetate was added in portions to a solution of the resulting solid in aqueous sulfuric acid to effect the formation of solid fractions containing different concentrations of VII. A small quantity of relatively pure VII was finally isolated after several fractional precipitations from aqueous sulfuric acid.

5-Amino-8-methylquinoline (X),[4] **5-Acetamido-8-methylquinoline (XIII) and 5-Benzamido-8-methylquinoline (XIV).**—VI (7.1 g.) was dissolved in absolute ethanol and reduced at 50° in the presence of Raney nickel catalyst with hydrogen at 40 p.s.i. to give X (recovered first as its hydrochloride); 60% yield, m.p. 144–145° from water–ethanol solution.

Anal. Calcd. for $C_{10}H_{10}N_2$: N, 17.71. Found: N, 17.59.

X was acetylated under conditions similar to those used by de Arce, Greene and Capps[6] for the acetylation of 5-amino-8-bromo-6-methylquinoline; poor yield, m.p. 189–190° from ethanol–water solution.

Anal. Calcd. for $C_{12}H_{12}N_2O$: N, 13.99. Found: N, 13.93.

X was benzoylated under conditions similar to those recorded by de Arce, Greene and Capps[6] for the benzoylation of 5-amino-8-bromo-6-methylquinoline; yield 40%, m.p. 252–252.5°.

Anal. Calcd. for $C_{17}H_{14}N_2O$: N, 10.68. Found: N, 10.51.

5-Amino-2-chloro-8-methylquinoline (XI), 5-Acetamido-2-chloro-8-methylquinoline (XVI) and 5-Benzamido-2-chloro-8-methylquinoline (XVII).—VII (2.9 g.) was dissolved in reagent grade acetone and reduced at 50° in the presence of Raney nickel catalyst with hydrogen at 40 p.s.i. to give XI; yield 54%, m.p. 109–110° from 95% ethanol.

Anal. Calcd. for $C_{10}H_9ClN_2$: Cl, 18.41; N, 14.54. Found: Cl, 18.40; N, 14.37.

XI was acetylated under conditions similar to those used by de Arce, Greene and Capps[6] for the acetylation of 5-amino-8-bromo-6-methylquinoline; 55% yield, m.p. 234–236° from 95% ethanol.

Anal. Calcd. for $C_{12}H_{11}ClN_2O$: Cl, 15.11; N, 11.94. Found: Cl, 14.91; N, 12.02.

The conditions recorded by de Arce, Greene and Capps[6] for the benzoylation of 5-amino-8-bromo-6-methylquinoline were used during the benzoylation of XI; yield 52%, m.p. 272–274°.

Anal. Calcd. for $C_{17}H_{13}ClN_2O$: Cl, 11.95; N, 9.44. Found: Cl, 12.09; N, 9.39.

5-Amino-2-hydroxy-8-methylquinoline (XII), 5-Acetamido-2-hydroxy-8-methylquinoline (XIX) and 5-Benzamido-2-hydroxy-8-methylquinoline (XX).—XIII (3.0 g.) was dissolved in reagent grade acetone and reduced at 50° in the presence of Raney nickel catalyst with hydrogen at 40 p.s.i. to give XII (recovered first as its hydrochloride); yield 77%, m.p. 203–204° from 95% ethanol.

Anal. Calcd. for $C_{10}H_{10}N_2O$: N, 16.04. Found: N, 16.09.

(7) Melting points not corrected.

(8) E. Spath, *Monatsh.*, **40**, 15 (1919).

(9) E. Spath, *ibid.*, **40**, 90 (1919).

(10) W. C. Hutchinson and W. O. Kermack, *J. Chem. Soc.*, 681 (1947).

XII was acetylated under conditions similar to those recorded by de Arce, Greene and Capps[6] for the acetylation of 5-amino-8-bromo-6-methylquinoline; yield 67%, m.p. >330° (uncor.) from 95% ethanol.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: N, 12.96. Found: N, 13.11.

XII was benzoylated under conditions similar to those used by de Arce, Greene and Capps[6] for the benzoylation of 5-amino-8-bromo-6-methylquinoline; yield 42%, m.p. > 315°.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: N, 10.07. Found: N, 10.00.

8-Methyl-5-quinolinearsonic Acid (XV), 2-Chloro-8-methyl-5-quinolinearsonic Acid (XVIII) and 2-Hydroxy-8-methyl-5-quinolinearsonic Acid (XXI).—The hydrochlorides of X (12.0 g.), XI (9.0 g.) and XII (10.0 g.) were diazotized and converted into arsonic acids according to the procedure reported by Capps and Hamilton[11] for changing certain 2-chloroaminoquinolines into 2-chloroquinolinearsonic acids. XV, XVIII and XXI resulted in yields of 12.8, 11.9 and 14.8%, respectively. XV melted at 224–226° while XVIII and XXI melted above 315° (uncor.).

Anal. Calcd. for $C_{10}H_{10}AsNO_3$: As, 28.05; N, 5.27. Found: As, 27.92; N, 5.09. Calcd. for $C_{10}H_9AsClNO_3$: As, 24.84; N, 4.65. Found: As, 24.69; N, 4.75. Calcd. for $C_{10}H_{10}AsNO_4 \cdot H_2O$: As, 24.87; N, 4.65. Found: As, 24.79; N, 4.67.

(11) J. D. Capps and C. S. Hamilton, THIS JOURNAL, **60**, 2105 (1938).

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Seroflocculating Steroids. I. Ethyl 3β-Chloro-Δ¹¹-cholenate[1]

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RECEIVED APRIL 2, 1954

During the course of our study of the relationship of steroids[2] to immunological phenomena associated with injury, we have had the occasion to investigate the seroflocculating reagents described by Penn and his associates.[3] These reagents[4] cause flocculation in a high percentage of the sera of patients with cancer and other diseases.

Our investigation of the flocculating reaction led us to prepare ethyl 3β-chloro-Δ¹¹-cholenate (I) which in preliminary testing we have found to be a very satisfactory flocculating reagent. The compound is crystalline and stable under ordinary conditions. We will discuss in detail elsewhere implications of general significance in this field suggested to us by this finding.

Treatment of ethyl 3α-hydroxy-Δ¹¹-cholenate (II) with phosphorus pentachloride in chloroform at 0° yielded ethyl 3β-chloro-Δ¹¹-cholenate (I), which could be quantitatively hydrogenated to ethyl 3β-chlorocholanate (III). The latter was found to be identical by melting point comparison with the product of reaction between ethyl lithocholate and phosphorus pentachloride.

(1) Aided in part by a grant from the United States Public Health Service.

(2) D. H. Sprunt, A. D. Dulaney and R. P. Conger, *Cancer Research*, **2**, 282 (1951).

(3) H. S. Penn, *J. Natl. Cancer Inst.*, **12**, 1389 (1952); A. H. Dowdy, H. S. Penn, G. Hall and A. Bellamy, *Proc. Am. Assoc. for Cancer Research*, **1**, 12 (1954).

(4) We wish to thank Drs. Dowdy and Penn and their group for their coöperation in making available to us procedures for preparing and testing both the liver and desoxycholic acid-derived flocculating reagents which they designate as "antigens."

Testing data on I and current studies on related compounds with flocculating activity will be reported in forthcoming publications.

Experimental[5,6]

Ethyl 3α-Hydroxy-Δ¹¹-cholenate (II).—3α-Hydroxy-Δ¹¹-cholenic acid[7,8] was esterified with absolute ethanol essentially according to the method used by Kendall and his associates for the preparation of the methyl ester.[9] However, whereas esterification with methanol is complete in less than an hour, with ethanol 27% of unreacted acid was recovered even after 22 hours. The ethyl ester did not crystallize from aqueous ethanol, but separated satisfactorily from purified Skellysolve F as colorless needles melting at 81–82°, $[\alpha]^{26}D$ + 30° (*c* 2.01, chf.). *Anal.* Calcd. for $C_{26}H_{42}O_3$: C, 77.56; H, 10.52. Found: C, 77.3; H, 10.6.

Ethyl 3β-Chloro-Δ¹¹-cholenate (I).[10]—To a stirred solution of 500 mg. of II in 28 ml. of chloroform, in a flask equipped with a drying tube and immersed in an ice-bath maintained at 0°, 800 mg. of powdered calcium carbonate and, in two portions with a 20-minute interval, 1.2 g. of phosphorus pentachloride were added. Stirring was continued for 100 minutes at 0°. The reaction product was poured into 200 ml. of 5% sodium bicarbonate solution containing ice, and ether was added. The resulting mixture was stirred until the ice had melted, transferred to a separatory funnel and shaken thoroughly. The organic layer, which still retained a small amount of an insoluble, colorless, inorganic solid, was washed with water, dried (Drierite), filtered and evaporated (reduced pressure) to a colorless residual oil. This oil dissolved in the minimum amount of warm methanol, on refrigeration for 2 hours yielded 380 mg. (73%) of colorless crystals m.p. 69–73°. Two recrystallizations from methanol gave thin plates melting at 74–76°, $[\alpha]^{26}D$ + 25° (*c* 2.05, chf.). *Anal.* Calcd. for $C_{26}H_{41}O_2Cl$: C, 74.16; H, 9.82; Cl, 8.42. Found: C, 74.3; H, 9.8; Cl, 8.8.

Catalytic Hydrogenation.—I in acetic acid solution and the presence of Adams catalyst absorbed 1.03 moles of hydrogen within 20 minutes. After removal of catalyst and solvent, two crystallizations of the product from methanol gave colorless, feathery crystals, m.p. 59–60.5°, which did not depress the melting point of ethyl 3β-chlorocholanate (III) prepared from ethyl lithocholate[11,12] by the same method as used for the unsaturated derivative, crystallizing in methanol as colorless needles, m.p. 59–61.5°, $[\alpha]^{26}D$ +18.5° (*c* 1.27, chf.). *Anal.* Calcd. for $C_{26}H_{43}O_2Cl$: C, 73.81; H, 10.24; Cl, 8.38. Found: C, 73.5; H, 10.5; Cl, 8.2.

(5) Microanalyses by the Microchemical Laboratory of New York University.

(6) Melting points were taken on an electrically heated micro hot-stage and are uncorrected.

(7) J. Press and T. Reichstein, *Helv. Chim. Acta*, **25**, 878 (1942); B. F. McKenzie, W. F. McGuckin and E. C. Kendall, *J. Biol. Chem.*, **162**, 555 (1946).

(8) Generously supplied by Merck and Co. through the kindness of Dr. Max Tishler.

(9) L. L. Engle, V. R. Mattox, B. F. McKenzie, W. F. McGuckin and E. C. Kendall, *J. Biol. Chem.*, **162**, 565 (1946).

(10) Although a double bond shift is considered unlikely under the conditions of this reaction, experiments are under way to confirm the position of unsaturation.

(11) F. Reindel and K. Niederländer, *Ber.*, **68**, 1969 (1935).

(12) We are indebted to Ciba Pharmaceutical Products, Inc., and Dr. H. B. MacPhillamy for a supply of lithocholic acid.

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The Preparation of Sarcosine and Methyl α-Methylamino-β-(3-indolyl)-propionate

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RECEIVED FEBRUARY 15, 1954

The preparation of methyl α-methylamino-β-(3-indolyl)-propionate was undertaken since a supply of this ester was required as an intermediate.