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The reaction of 7-acetoxyquinoline with trifluorosulfonate esters of primary alcohols in methylene chloride or acetonitrile, followed by acid hydrolysis, provides a general synthesis of 1-substituted-7-hydroxyquinolines, whose phenolate anions are fluorescent.

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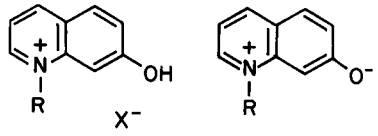
The intense fluorescence of the phenolate anion of the 1-methyl-7-hydroxyquinolinium cation (**1b**) has proved very useful in biochemical assays for acetylcholinesterase, since it is the cleavage product of the non-fluorescent 7-acetoxy and 7-carbamoyl ester analogs of acetylcholine (2-4). The protonated form (**1a**) is also non-fluorescent; the pK_a of the phenol is 5.8 (5).



1a **1b**

The 1-substituted-7-hydroxyquinolinium system should therefore be useful as a fluorescent probe for *p*H changes, particularly in biological membranes, since the 1-substituents can, in principle, be lipophilic long-chain alkyl groups. Prior to this study, the only known compound in this group was the 1-methyl derivative (2). Further, it was clear that steric hindrance at quinoline nitrogen (6-8) markedly decreased the rate of quaternization with alkyl iodides and bromides as the size of the alkyl group increased in the series *i*-propyl (9), *n*-butyl (10,11), *n*-dodecyl (12). In this paper, we report a convenient method for the synthesis of 1-*n*-alkyl-7-hydroxyquinolinium salts using the trifluoromethylsulfonate (triflate) esters obtained from the corresponding *n*-alkyl alcohols. The method was extended to the more complex alcohols, ethyl glycollate and 1,2:3,4-di-*o*-isopropylidenegalactose, and so would seem to be a general method for synthesizing 1-substituted quinolines from available triflates of primary alcohols.

The preparative scheme for the preparation of 1-substituted 7-hydroxyquinolinium triflates **5** is shown in Chart 1. For synthesis of the 1-(*n*-alkyl) derivatives, the triflate ester **3** was generated in methylene chloride at -20° by treatment of the appropriate normal alcohol with trifluoromethanesulfonic anhydride in the presence of finely divided anhydrous potassium carbonate. The methylene chloride solution was used directly, after removal of inorganic salts, as the reaction medium for the quaternization of added 7-acetoxyquinoline (**2**). The reflux temperature of this solvent provided convenient reaction times with minimal side reactions. Removal of the acetoxy group was readily accomplished with 0.5*N* hydrochloric acid in aqueous methanol. The synthesis of 1-carboethoxymethyl and 1-(6-deoxy-D-galactopyranosyl)-7-hydroxyquinolinium triflate esters was accomplished by isolation of the corresponding triflate esters and subsequent quaternization reaction with 7-acetoxyquinoline.

Chart 1

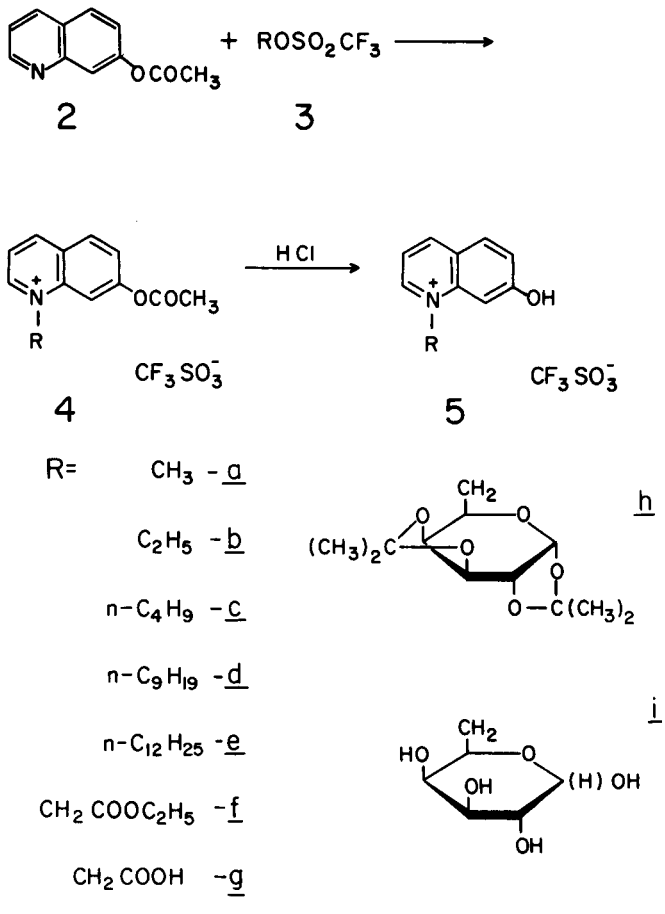


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Table I

Properties of 1-(*n*-Alkyl)-7-hydroxyquinolinium Triflates

Compound No.	R	M.p., °C	Yield %	m/e Peak M^+ Ion	NMR	Formula	Analyses (%) Calcd./Found C	H	N	F	S
5a	CH_3	135	49	160	4.4 (3H, s)	$C_{11}H_{10}F_3NO_4S$	42.72 42.63	3.24 3.23	4.53 4.52	18.45 18.39	10.36 10.38
5b	C_2H_5	129	54	174	1.85 (3H, t), 5.02 (2H, bm)	$C_{12}H_{12}F_3NO_4S$	44.58 44.52	3.72 3.71	4.33 4.34	17.65 17.68	9.91 9.93
5c	n-C_4H_9	118	62	202	0.9 (3H, t), 1.3 (2H, m), 1.8 (2H, m), 4.7 (2H, t)	$C_{14}H_{16}F_3NO_4S$	47.86 47.77	4.56 4.55	3.99 4.00	16.24 16.20	9.12 9.10
5d	n-C_9H_{19}	124	64	272	0.8 (3H, m), 1.0-1.7 (12H, bm), 1.8-2.4 (2H, bm), 4.6-5.2 (2H, bm)	$C_{19}H_{26}F_3NO_4S$	54.16 54.08	6.18 6.16	3.33 3.32	13.54 13.52	7.60 7.56
5e	n-$C_{12}H_{25}$	110	68	314	0.9 (3H, m), 1.1-1.6 (18H, bm), 1.7-2.4 (2H, bm), 4.7-5.2 (2H, bm)	$C_{22}H_{32}F_3NO_4S$	57.02 56.96	6.91 6.90	3.02 3.01	12.31 12.33	6.91 6.90

Attempts to *N*-alkylate 7-hydroxyquinoline directly with the triflate esters yielded a mixture of *N*- and *O*-alkyl products, in contrast to the unique *N*-alkylation reported by Prince (2). Pure *N*-substituted compounds were obtained only by using 7-acetoxyquinoline (**2**) as starting material.

All the compounds showed absorbance and fluorescence excitation/emission spectra identical to that reported for 1-methyl-7-hydroxyquinolinium iodide (**2**) in the phenolate form. The protonated phenol forms were non-fluorescent and had spectra identical to that of the 1-methyl compound **1**. The pK_a value for the phenol/phenolate equilibrium was in the range of 5.5-5.8 for all the compounds. Within the limits of size and hydro- and lipophilicity covered in this group of compounds, the structure of the 1-substituent has very little effect on the pK_a of 1-substituted-7-hydroxyquinolinium ions.

EXPERIMENTAL

Nmr spectra were obtained from Varian T-60 or XL-100-15 instruments with tetramethylsilane (TMS) or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as standard. Ir spectra were recorded on a Perkin-Elmer 412 instrument. Mass spectra were obtained from Hitachi Perkin-Elmer Model RMH-2. The fluorescence spectra and pK_a data were obtained on an Aminco Bowman spectrofluorimeter equipped with xenon lamp source. The uv/vis absorbance spectra were obtained with a Beckman DB-G spectrophotometer. Tlc analyses were performed on silica gel G (Analtech) using chloroform:benzene:methanol (1:1:1) and benzene:methanol (9:1) and reversed phase KC-18 HPTLC plates (Whatman) using water:ethanol:acetic acid (10:90:1). Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York. Melting points were taken on a Kofler micro hotstage.

Reagent grade methylene chloride was purified by washing with 5% sodium carbonate solution, followed by distilled water, dried over anhydrous calcium chloride, distilled and stored over 4A molecular sieves. Trifluoromethanesulfonic anhydride (Aldrich) and acetic anhydride were freshly distilled prior to use. Ethyl glycollate (Eastman) was twice distilled, the fraction boiling at 160-162° collected and stored over molecular sieves. Reagent grade *n*-butyl, *n*-nonyl and *n*-dodecyl alcohols (Aldrich) were stirred overnight over anhydrous potassium carbonate and decanted prior to use. 7-Hydroxyquinoline was synthesized from *m*-aminophenol, glycercol, 70% sulfuric acid and arsenic acid according to the procedure of Bradford, Elliot and Rowe (13).

7-Acetoxyquinoline (**2**).

7-Hydroxyquinoline (4 g., 0.028 mole) and acetic anhydride (10.2 g., 0.1 mole) were heated to reflux and distilled at atmospheric pressure to remove acetic acid and excess anhydride, then *in vacuo* to 90° for removal of other volatile impurities. A dark brown oily product was obtained. This was taken up in ether, dried with anhydrous sodium sulfate and filtered. Addition of petroleum ether and careful cooling of the solution gave feathery crystals of 7-acetoxyquinoline (3.7 g., 71%, m.p. 62-63°); ir (potassium bromide): 3100, 1720 cm^{-1}; nmr (DMSO-d_6): δ 2.38 (3H, s), 7.41 (H_3, m; J_{3-4}, 8.2 Hz), 7.57 (H_8, m, J_{5-8}, 0.5 Hz), 7.80 (H_6, bm, J_{6-8}, 2.2 Hz), 8.07 (H_5, m, J_{5-6}, 9.0 Hz), 8.43 (H_4, m, J_{2-4}, 2.1 Hz), 8.96 (H_2, dd, J_{2-3}, 4.6 Hz).

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.59; H, 4.81; N, 7.49. Found: C, 70.56; H, 4.80; N, 7.50.

1-Alkyl-7-hydroxyquinolinium Triflates (**5a** to **5e**).

Triflate esters were prepared by slowly adding over 1 hour 0.01 mole of trifluoromethanesulfonic anhydride in 25 ml. of methylene chloride to 0.01 mole of the hydroxy compound in 50 ml. of methylene chloride containing 0.1 mole of anhydrous

potassium carbonate at -20° with stirring. The mixture was stirred for another 6 hours, then filtered. To this solution was added 1.87 g. (0.01 mole) of 7-acetoxyquinoline under anhydrous conditions. The reaction mixture was refluxed for 16 hours, the solvent removed *in vacuo*, and the dark residue was taken up on 0.5 *N* hydrochloric acid in 30% aqueous methanol. This solution was refluxed 2 hours, treated with charcoal, filtered and the solvent removed *in vacuo*. The product was then recrystallized 3 times from the methanol/ether, at which point a single spot was obtained by tlc. This method was used for the methyl, ethyl, *n*-butyl, *n*-nonyl and *n*-dodecyl compounds. For the methyl compound, purified methyl triflate was used with equal success.

All of the 1-(*n*-alkyl) derivatives had characteristics infrared spectra centered around (potassium bromide): 3100-3200 (s), 1620-1625 (s), 1575-1580 (s), 1530-1535 (m), 1445-1460 (m), 1200-1280 (s), 1130-1140 (s), 835-840 (m), 725-735 (m), and 625-630 (m) cm^{-1}. The nmr spectra of these compounds had characteristic chemical shifts for the quinoline ring protons centered around δ 7.4, 7.5, 7.8, 8.2, 8.9 and 9.0, with the following values for the coupling constants (values in Hz): H_2-H_3, 5.0-5.5; H_2-H_4, 1.8-2.3; H_3-H_4, 7.5-8.5; H_5-H_6, 8.8-9.5; H_6-H_8, 1.9-2.3; H_5-H_8, <0.5.

Physical properties of the 1-(*n*-alkyl) derivatives are given in Table I. Nmr values of δ peculiar to each compound are given; for compounds **5a-c**, the solvent was DMSO-d_6, while for **5d,e** it was deuteriochloroform.

1-Carboethoxymethyl-7-hydroxyquinolinium Triflates (**5f**).

Carboethoxymethyl triflate (**3f**) was synthesized from ethyl glycollate (0.03 mole) and trifluoromethanesulfonic anhydride (0.03 mole), as described for the alkyl triflates, and isolated by recrystallization from 100 ml. of dried hexane at -25°, yield 70%, m.p. 22-23°. The nmr and ir spectra were identical to those reported (14). This compound (0.01 mole) was reacted with 7-acetoxyquinoline in dry methylene chloride (30 ml.) under reflux for 16 hours. After removal of the solvent *in vacuo*, the product was washed with a minimal volume of ether, then dissolved in 30 ml. 0.5 *N* hydrochloric acid and refluxed for 2 hours. After treatment with charcoal, the crude product was recovered by removal of the solvent and purified by recrystallization from water to give a 66% yield of 1-carboethoxymethyl-7-hydroxyquinolinium triflate, m.p. 208°; nmr (DMSO-d_6): δ 1.06 (3H, t), 2.42 (2H, 2), 5.6 (2H, bd), 7.45 (H_8, bm), 7.68 (H_3, bm J_{3-4}, 8.4 Hz), 7.92 (H_6, m, J_{6-8}, 2.1 Hz), 8.35 (H_5, d, J_{5-6}, 9.3 Hz), 9.15 (H_4, m, J_{2-4}, 2.1 Hz), 9.28 (H_2, m, J_{2-3}, 5.7 Hz; ir (potassium bromide): 3100, 1727, 1285 cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}F_3NO_4S$: C, 44.58; H, 3.72; F, 17.65; N, 4.33; S, 9.91. Found: C, 44.51; H, 3.71; F, 17.60; N, 4.32; S, 9.93.

1-Carboxymethyl-7-hydroxyquinolinium Chloride (**5g**).

The triflate salt **5f** (1 g., 2.7 mmoles) was dissolved in 30 ml. 5 *N* hydrochloric acid and the solution refluxed 16 hours. The product obtained after solvent removal was dissolved in 25 ml. of water, treated with charcoal. After removal of the solvent, the product was recrystallized from methanol/ether to give purified 1-carboxymethyl-7-hydroxyquinolinium chloride in 62% yield, m.p. 230°; nmr (DMSO-d_6): δ 5.9 (2H, bd), 7.55 (H_8, bm), 7.75 (H_3, m, J_{3-4}, 8.6 Hz); 7.97 (H_6, m, J_{6-8}, 2.2 Hz); 8.40 (H_5, d, J_{5-6}, 9.5 Hz); 9.25 (H_4, m, J_{2-4}, 2.0 Hz); 9.4 (H_2, m, J_{2-3}, 5.5 Hz); ir (potassium bromide): 3300-2600, 1715, 875 cm^{-1}; ms: m/e 204 (M^+), 160, 159, 145.

Anal. Calcd. for $C_{11}H_{10}ClNO_3$: C, 55.11; H, 4.17; N, 5.84; Cl, 14.82. Found: C, 55.22; H, 4.16; N, 5.86; Cl, 14.85.

1-(6-Deoxy-α-D-galactopyranosyl)-7-hydroxyquinolinium Triflate (**5i**).

The triflate ester of 1,2:3,4-di-*O*-isopropylidene-α-D-galactose was synthesized from 0.01 mole of the hydroxyl-protected hexose and 0.01 mole of trifluoromethanesulfonic anhydride, as described for the alkyl triflates, and twice recrystallized at -20° from petroleum ether, m.p. 50°, yield 68%. The product is labile to heat and moisture and is stable for an extended period only when kept dry at -20°; nmr (perdeuterio-1,1,1-trichloroethane): δ 1.49 (3H, s), 1.58 (3H, s), 1.68 (2x 3H, s), 4.1 (H_5; J_{5-6}, 2.5 Hz; J_{5-6}, 7.5 Hz), 4.23 (H_2; J_{2-3}, 2.0 Hz), 4.31 (H_3; J_{3-4}, 5.0 Hz), 4.48 (H_6 H_6'; $J_{6-6'}$, 12.0 Hz), 4.60 (H_4; J_{4-5}, 1.2 Hz), 5.44 (H_1; J_{1-2}, 5.0 Hz).

This compound (0.01 mole) and 7-acetoxyquinoline (0.01 mole) was refluxed in dry acetonitrile 16 hours. The product, 1-(1,2:3,4-di-*O*-isopropylidene-6-deoxy-α-D-galactopyranosyl)-7-acetoxyquinoline (**4h**) could not be crystallized. It was washed with ether and then dissolved in 50 ml. of 10% aqueous trifluoroacetic acid and refluxed 1 hour. The solvent was removed at 80° *in vacuo*, and the residue was dissolved in 50 ml. of water, treated with charcoal, and recovered by *in vacuo* evaporation. Extraction of the residue with water-saturated ethyl acetate at reflux yielded a solution which, under slow evaporation, yielded fine white crystals, m.p. 125°. These crystals were identified as pure 1-(6-deoxy-α-D-galactopyranosyl)-7-hydroxyquinolinium triflate (**5i**); nmr (perdeuteriomethanol): δ 3.33 (2H, H_6, H_6', bm, $J_{6-6'}$, 12.5 Hz), 3.63 (H_4, m, J_{4-5}, 2.0 Hz), 4.08 (H_2, m, J_{2-3}, 2.0 Hz), 4.20 (H_3, m, J_{3-4}, 6.0 Hz), 4.35 (H_5, bm, J_{5-6}, 2.8 Hz; $J_{5-6'}$, 8.0 Hz), 5.15 (H_1, J_{1-2}, 5.5 Hz), 7.50 (H_3, m, J_{3-4}, 8.3 Hz), 7.68 (H_8, bm), 7.85 (H_6, m, J_{6-8}, 2.2 Hz), 8.30 (H_5, d J_{5-6}, 9.2 Hz), .901 (H_4, bm, J_{2-4}, 2.0 Hz), 9.10 (H_2, bm, J_{2-3}, 5.4 Hz); ir (potassium bromide): 3000-3600, 1720, 1200-1300 cm^{-1}; ms: m/e 308 (M^+).

Anal. Calcd. for $C_{16}H_{18}F_3NSO_9$: C, 42.01; H, 3.94; F, 12.47; N, 3.06; S, 7.00. Found: C, 42.07; H, 3.95; F, 12.43; N, 3.06; S, 6.98.

The crystalline material was obtained in only about 5% yield. A crude product, comprising about 95% of **5i**, as estimated by thin layer chromatography on reversed phase K_{C-18} plates, was obtained by lyophilization of the charcoal-treated aqueous solution as a light brown, hygroscopic, amorphous powder.

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