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Synthesis of 4-Substituted Aminoquinoline-3-carboxylates as Potential Antimicrobial Agents

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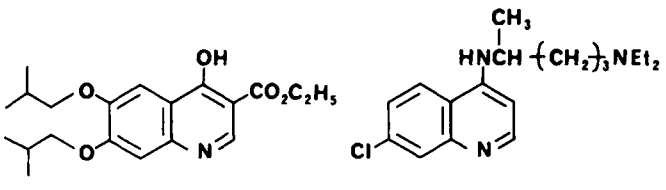
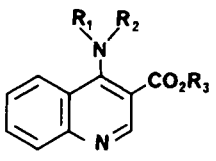
Abstract □ A series of 4-substituted aminoquinoline-3-carboxylates was prepared and evaluated for antimicrobial activity. Four of the compounds (VIII, XIII, XV, and XXIII) exhibited low activity against *Staphylococcus aureus*.

Keyphrases □ 4-Substituted aminoquinoline-3-carboxylates—synthesis, antimicrobial activity □ Antimicrobial agents—potential, 4-substituted aminoquinoline-3-carboxylates

The structural similarity between the coccidiostat buquinolate (I) (1) and the antimalarial 4-aminoquinolines (*e.g.*, chloroquin; II) (2) raised the question as to whether combination of the major functional groups of each class might lead to useful agents. This work sought to determine if the quinoline-3-carboxylate moiety of the coccidiostats could be successfully combined with 4-amino substituents, some of which have shown promise in antimalarial quinolines. A series of 4-aminoquinoline-3-carboxylates (III) was necessary, and a search of the literature revealed that these compounds had not previously been synthesized. To determine if antibacterial properties were associated with this new substituent pattern, the synthesis of several examples was undertaken.





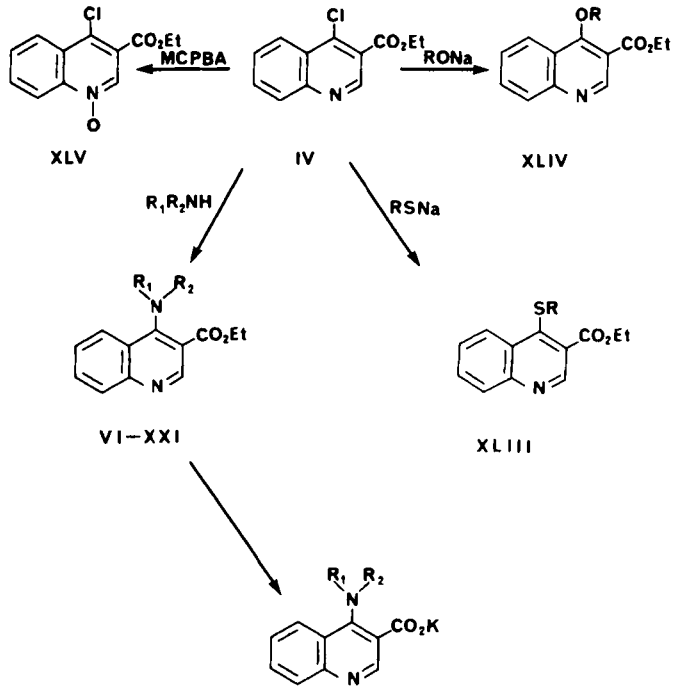
III

R_1, R_2 = H, alkyl, aralkyl
R_3 = K, C_2H_5

RESULTS AND DISCUSSION

Ethyl 4-chloroquinoline-3-carboxylate, IV (3), was the key intermediate from which the target compounds were prepared (Scheme I). The immediate precursor to IV, ethyl 4-hydroxyquinoline-3-carboxylate V, was prepared in satisfactory yield by the method of Gould and Jacobs (4) as modified by Price and Roberts (5) and by Riegel *et al.* (6). The importance of short reaction times in the preparation of V was noted (7); yields of V decrease for reaction times exceeding 30 min. Reaction of V with phosphorus oxychloride smoothly led to IV (3).

Nucleophilic displacement of the 4-chloro substituent occurred in high yield after a few hours in refluxing toluene; several cases were noted where the reaction started while still at room temperature. The relative ease of displace-



Scheme I

0022-3549/84/0800-1141$01.00/0

Table I—Properties of 4-Aminoquinoline-3-carboxylates (III)[a]

Compound	R_1	R_2	R_3	Yield, %	mp, °C	MIC Against *Staph. aureus*, ppm
VI	H	H	C_2H_5	76	205–207	
VII[b]	C_2H_5	C_2H_5	C_2H_5	96	oil	
VIII[c]	n-C_3H_7	n-C_3H_7	C_2H_5	30	oil	62.5
IX	H	C_2H_5	C_2H_5	69	65–68	
X	H	n-C_3H_7	C_2H_5	85	63–65	
XI	H	$CH_2CH{=}CH_2$	C_2H_5	83	79–81	
XII	H	$CH_2C{\equiv}CH$	C_2H_5	68	115.0–117.5	
XIII[d]	H	C_6H_5	C_2H_5	60	102.5–104.5	50
XIV	H	$CH_2C_6H_5$	C_2H_5	84	98.5–100.5	
XV	H	CH_2-p-C_6H_4Cl	C_2H_5	68	124–126	25
XVI	H	CH_2-p-$C_6H_4NO_2$	C_2H_5	49	133–135	
XVII	$-CH_2CH_2CH_2CH_2-$		C_2H_5	68	75.5–78.0	
XVIII	$-CH_2CH_2CH_2CH_2CH_2-$		C_2H_5	95	oil	
XIX[e]	$-CH_2CH_2-O-CH_2CH_2-$		C_2H_5	91	oil	
XX	$-CH{=}CH-N{=}CH-$		C_2H_5	72	115.5–117.0	
XXI	$-CH_2CH_2NHCH_2CH_2-$		C_2H_5	76	120.0–121.5	
XXII	C_2H_5	C_2H_5 HCl Salt	C_2H_5	34	145–147	
XXIII	n-C_3H_7	n-C_3H_7 HCl Salt	C_2H_5	75	95–98	50
XXIV[f]	H	$CH_2CH_2CH_2N(CH_3)_2$ HCl Salt	C_2H_5	77	219–220	
XXV	$-CH_2CH_2CH_2CH_2CH_2-$	HCl Salt	C_2H_5	78	174.5–176.0	
XXVI[g]	$-CH_2CH_2OCH_2CH_2-$	HCl Salt	C_2H_5	67	204.5–206.0	
XXVII[g]	H	H	K	97	>350	
XXVIII[h]	C_2H_5	C_2H_5	K	66	258–260	
XXIX[i]	n-C_3H_7	n-C_3H_7	K	29	174–176	
XXX[h]	H	C_2H_5	K	90	275–277	
XXXI[h]	H	n-C_3H_7	K	94	250.0–252.5	
XXXII[j]	H	$CH_2CH{=}CH_2$	K	87	249.5–251.5	
XXXIII[k]	H	$CH_2C{\equiv}CH$	K	93	340 (dec.)	
XXXIV[l]	H	$CH_2CH_2CH_2N(CH_3)_2$	K	72	78–83	
XXXV[h]	H	C_6H_5	K	71	331–332	
XXXVI[m]	H	$CH_2C_6H_5$	K	71	293.5–295.0	
XXXVII[n]	H	CH_2-p-C_6H_4Cl	K	94	278.0–279.5	
XXXVIII[o]	$-CH_2CH_2CH_2CH_2-$		K		>250	
XXXIX[p,q]	$-CH_2CH_2CH_2CH_2CH_2-$		K	83	274–277	
XL[p]	$-CH_2CH_2OCH_2CH_2-$		K	82	>330	
XLI[o]	$-CH{=}CHN{=}CH-$		K			
XLII[n]	$-CH_2CH_2NHCH_2CH_2-$		K	74	210–213	
XLIII	C-4	$SCH_2C_6H_5$	C_2H_5	51	34–36	
XLIV[r]	C-4	OC_2H_5	C_2H_5	53	34–36	
XLV	C-4 N-oxide	Cl	C_2H_5	49	102–104 bp 125–128 (0.01 mm Hg)	
V[s]	C-4	OH	C_2H_5			
IV[t]	C-4	Cl	C_2H_5		44–46 bp 133–135 (0.5 mm Hg)	

[a] In all cases the spectral data agreed with the structure illustrated. Compounds VI–XLIII and XLV underwent elemental analyses for C, H, and N; XLIII and XLV were also analyzed for S and Cl, respectively. Unless otherwise noted, the values were within ±0.4% of the theoretical values. [b] Calc. for C, 70.56; N, 10.29. Found: C, 69.88; N, 10.91. [c] Calc. for N, 9.33; found, 10.20. [d] See Ref. 11; lit. mp 99–100°C. [e] Seven attempts were made to determine microanalytical data for this oil after evaporative distillation and vigorous pumping at high vacuum. All determinations of carbon were erratic, for unknown reasons. The spectroscopic evidence was excellent. [f] Calc. for C, 54.55; found, 54.00. [g] 0.25 H_2O. [h] 1.0 H_2O. [i] Microanalyses were done on the benzylisothiuronium salt. [j] 1.25 H_2O. [k] 1.75 H_2O. [l] 3.5 H_2O. Calc. for H, 6.73; found, 7.20. [m] 2.25 H_2O. [n] 2.0 H_2O. [o] Deliquescent. [p] 1.5 H_2O. [q] Calc. for N, 8.60; found, 9.24. [r] See Ref. 10; lit. mp 32–34°C. [s] See Ref. 6; lit. mp 269–270°C. [t] See Ref. 3; lit. mp 46–47°C, bp 128–129°C (0.2 mm Hg).

ment is presumably due to the activating effect of the carboxylic ester adjacent to the reaction center. A similar effect has been observed for halogen displacement of 3-nitro-4-chloroquinolines (8). Table I lists the ethyl 4-aminoquinoline-3-carboxylates obtained in this manner. Preparation of VI required a slight modification. When the normal reaction conditions were employed with a constant, steady stream of ammonia passing through the reaction solution, no VI was obtained; however, when the reaction was carried out in liquid ammonia at 115–130°C a good yield of VI resulted.

Several of the amino esters were viscous oils which could not be purified either by evaporative distillation or by chromatography. These compounds were converted to the corresponding hydrochloride salts (XXII–XXVI) which, in some cases, could be purified by crystallization. Some of the salts, notably XXV and XXVI, were hygroscopic and did not give satisfactory microanalysis results after several attempts.

Ester hydrolysis using an equivalent amount or a slight excess of potassium hydroxide in ethanol afforded salts XXVII–XLII (Table I). The potassium carboxylates were hygroscopic, making acquisition of microanalytical data difficult. In the extreme cases of XXXVIII and XLI, the compounds were deliquescent. The remaining salts were also hygroscopic, but most could be equilibrated with atmospheric moisture to yield a hydrate of constant, although often nonstoichiometric, composition. The method of Donleavy (9) for preparation of solid derivatives of waxy fatty acids was helpful in some cases. Formation of the pseudouronium salt of the quinoline carboxylates in some instances gave nonhygroscopic salts suitable for microanalysis, but this method was by no means applicable to each compound. Structural assignments were confirmed by ^{1}H-NMR and IR spectrometry, and each ester showed one spot on TLC.

Nucleophilic displacement of the halogen in IV also readily occurred when IV was treated with a sodium thiolate to give XLIII and with ethoxide anion to give XLIV (10). In addition, the *N*-oxide XLV was prepared by treating IV with *m*-chloroperoxybenzoic acid.

Each compound was tested in an *in vitro* assay against a range of microorganisms to determine a general activity profile. The organisms used were *Escherichia coli* ATCC 23540, *Salmonella choleraesuis* ATCC 13312, *Streptococcus faecalis* ATCC 19433, *Staphylococcus aureus* (Smith) Merck 2949, *Pseudomonas aeruginosa* PS-44, *Proteus mirabilis* PR-91, and *Clostridium perfringens* ATCC 3624. Dimethyl sulfoxide was used to aid the dissolution of test compounds in Mueller-Hinton broth at 50 ppm. Inoculated broths, prepared with a semiautomated dispenser and inoculator[1], were incubated for 18 h at 37°C, then examined and assigned a general rating of active, slightly active, or inactive. Measurement of the minimum inhibitory concentrations (MIC) was accomplished by the same method using successive twofold dilutions of the test compound, starting at a concentration of 62.5 ppm.

The target compounds showed no remarkable *in vitro* antibacterial activity, although small amounts of growth inhibition by several members of the series

[1] Model MIC 2000; Dynatech.

was observed. Four of the active compounds (X, XVIII, XXV, and XLIII) were slightly active against *C. perfringens* with minimum inhibitory concentrations of ≥62.5 ppm. Another subgroup of four compounds showed general activity against *Staph. aureus*.

The four compounds active against *Staph. aureus* were examined further by measurement of the MIC values (Table I). Since XXIII is the salt of VIII, it is not surprising that both species have the same order of activity. However, the presence of XIII and XV, which bear no structural relationship to the tertiary amines VIII and XXIII, makes it difficult to draw a structural relationship with the *in vitro* antimicrobial activity.

EXPERIMENTAL SECTION[2]

Ethyl 4-Aminoquinoline-3-carboxylate (VI)—A solution of 23.5 g (0.1 mol) of IV, 250 mL of toluene, and 21 mL (1.0 mol) of liquid ammonia was scaled in a high-pressure reaction vessel, then heated at 120–125°C for 4 h. The vessel was cooled, opened, and the ammonia was allowed to evaporate. The residue was suction-filtered, and the solid was partitioned between chloroform and water. The organic phase was dried (Na_2SO_4), and the solvent was removed under reduced pressure to give 17.4 g of white needles. Recrystallization from ethyl acetate afforded 14.9 g (69%) of VI as white needles, mp 205.0–207.5°C. IR (KBr): 1669 cm^{-1} (C=O); ^{1}H-NMR (Me_2SO-d_6): δ 8.90 (s, 1, quinoline C-2 H), 7.33–8.50 (m, 6, ArH and NH), 4.33 (q, 2, J = 7 Hz, OCH_2), and 1.36 ppm (t, 3, J = 7 Hz, CH_3).

General Procedure for Preparation of Ethyl 4-Alkylamino- and Ethyl 4-Aralkylaminoquinoline-3-carboxylates (VII–XXI)—The general method is illustrated by the synthesis of VII. A solution of 5.89 g (25 mmol) of IV and 9.17 g (125 mmol) of diethylamine in 50 mL of toluene was stirred and heated at reflux for 35 h. The mixture was cooled to room temperature and the salt was removed by filtration. The solvent was removed under reduced pressure to give 7.5 g of a cloudy oil, which was chromatographed on silica gel (5 × 40 cm, ether) to give 6.59 g (96%) of VII as a clear yellow oil. IR ($CHCl_3$): 1698 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 8.90 (s, 1, C-2 H), 7.25–8.22 (m, 4, ArH), 4.43 (q, 2, J = 7 Hz, OCH_2), 3.43 (q, 4, J = 7 Hz, CH_2NCH_2), 1.41 (t, 3, J = 7 Hz, ester CH_3), and 1.15 ppm (t, 6, J = 7 Hz, aminoethyl CH_3).

General Procedure for Preparation of Hydrochloride Salts (XXII–XXVI)—The general method is illustrated by the synthesis of XXII. To a stirred solution of 15.2 g (55.8 mmol) of VII in 250 mL of ether was added 200 mL of dry, ethereal hydrogen chloride. The resulting mixture was filtered, and the solid was recrystallized several times from dichloromethane–ether and then from ethyl acetate. The solid was sublimed to give 5.83 g (34%) of XXII as a fine yellow powder, mp 145–147°C. IR ($CHCl_3$): 1712 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 8.93 (s, 1, C-2 H), 7.61–8.72 (m, 4, ArH), 4.50 (q, 2, J = 7 Hz, OCH_2), 3.87 (q, 4, J = 7 Hz, CH_2NCH_2), 1.47 (t, 3, J = 7 Hz, ester CH_3), and 1.40 ppm (t, 6, J = 7 Hz, aminoethyl CH_3).

General Procedure for Preparation of Potassium Salts (XXVII–XLII)—The general method is illustrated by the synthesis of XXVIII. A solution of 14.9 g (54.8 mmol) of VII and 5.37 g (82.2 mmol) of potassium hydroxide in 150 mL of ethanol was stirred and heated at reflux for 4 h. The mixture was cooled to room temperature, and the solid material was removed by filtration. The solvent was removed under reduced pressure to give 16.9 g of a tan solid. Recrystallization from ethyl acetate–acetone afforded 10.9 g (70%) of XXVIII as fine needles, mp 258–260°C; ^{1}H-NMR (Me_2SO-d_6): δ 8.76 (s, 1, C-2 H), 7.30–8.43 (m, 4, ArH), 3.61 (s, 2, H_2O), 3.33 (q, 4, J = 7 Hz, CH_2NCH_2), and 1.06 ppm (t, 6, J = 7 Hz, CH_3).

[2] Boiling and melting points are uncorrected. Melting points were measured with a Thomas-Hoover Unimelt capillary melting point apparatus. IR spectra were measured with a Perkin-Elmer model 137 spectrophotometer. NMR spectra were measured with a Varian 56/60D or a Hitachi Perkin-Elmer R-24B spectrometer in the stated solvent using tetramethylsilane as internal standard. Microanalyses were performed by the Analytical Department, Diamond Shamrock Corp.

Ethyl 4-Benzylthioquinoline-3-carboxylate (XLIII)—A mixture of 1.65 g (72 mg-atoms) of sodium and 75 mL of absolute ethanol was stirred at room temperature under an argon atmosphere. To the resulting solution of sodium ethoxide was added, over a period of 10 min, a solution of 8.7 g (70 mmol) of benzylmercaptan in 50 mL of absolute ethanol. The mixture was stirred at room temperature for 25 min, and then a solution of 16.5 g (70 mmol) of IV in 75 mL of absolute ethanol was added. The stirring was continued at room temperature for 27 h. The mixture was poured into 150 mL of water, the phases were separated, and the aqueous phase was extracted with ether (3 × 150 mL). The organic phases were combined, washed with water and then with brine, and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a solid-oil mixture. The oil was decanted, and the solid was recrystallized from hexane to afford 11.4 g (51%) of XLIII as pale yellow prisms, mp 34–36°C. IR ($CHCl_3$): 1724 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 8.97 (s, 1, C-2 H), 7.33–8.62 (m, 4, ArH quinoline), 7.05 (s, 5, ArH), 4.43 (q, 2, J = 7 Hz, OCH_2), 4.12 (s, 2, SCH_2), and 1.42 ppm (t, 3, J = 7 Hz, CH_3).

Ethyl 4-Ethoxyquinoline-3-carboxylate (XLIV)—The method of Markees (10) was employed with slight modification. Dimethylformamide was not used as cosolvent, and the entire reaction was allowed to take place at room temperature rather than for a brief period at reflux. This gave a 53% yield of XLIV as colorless needles, mp 34–36°C, bp 125–128°C (0.1 mm Hg) [lit. (10) mp 32–34°C, bp 160–162°C (1.4 mm Hg)].

Ethyl 4-Chloroquinoline-3-carboxylate-*N*-oxide (XLV)—A solution of 22.3 g (0.11 mol) of *m*-chloroperoxybenzoic acid and 23.5 g (0.1 mol) of IV in 350 mL of dichloromethane was stirred in an ice bath for 1 h, then at room temperature for 66 h. The solution was then stirred with 50 mL of 10% Na_2HSO_3 until a negative starch–iodide test was observed. The phases were separated, and the organic phase was washed with 7.5% $NaHCO_3$ and then brine, and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave 22.2 g of an orange solid, which was recrystallized from ether to give 12.4 g (49%) of XLV as pale yellow plates, mp 102–104°C. IR ($CHCl_3$): 1739 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 7.55–9.00 (m, 5, ArH), 4.50 (q, 2, J = 7 Hz, OCH_2), and 1.47 ppm (t, 3, J = 7 Hz, CH_3).

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