Imidazo[4,5-*f*]quinolines III: Antibacterial 7-Methyl-9-(substituted Arylamino)imidazo[4,5-*f*]quinolines

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Abstract □ A series of 7-methyl-9-(substituted arylamino)imidazo-[4,5-*f*]quinolines was prepared and screened against four varieties of bacteria. The compounds possessed antibacterial activity against both Gram-positive and Gram-negative organisms.

Keyphrases □ Imidazo[4,5-*f*]quinolines, substituted—synthesized, screened for antibacterial activity □ Antibacterial activity—various substituted imidazo[4,5-*f*]quinolines screened □ Structure–activity relationships—various substituted imidazo[4,5-*f*]quinolines screened for antibacterial activity

Synthesis and biological evaluation of a series of 9-(substituted amino)imidazo[4,5-*f*]quinolines (1, 2) as anthelmintic agents against the tapeworm *Hymenolepis nana* led to the screening of these compounds for antibacterial properties. Several 7-methyl-9-(substituted arylamino)imidazo[4,5-*f*]quinolines (2) were particularly effective against *Haemophilis vaginalis*. Accordingly, a series of these compounds was prepared to explore this activity further.

DISCUSSION

Chemistry—All but two of the compounds listed in Table I were prepared by treating 9-chloro-7-methylimidazo[4,5-*f*]quinoline (II) (3) with the appropriate anilines as previously described (2) (Scheme I). Most prerequisite anilines were purchased. However, the anilines for VI, XII–XIV, and XX were obtained by the catalytic reduction of the corresponding nitro compounds. Compounds VIII and X were obtained by the acid hydrolysis of VII and IX, respectively. With the exception of VI, all products were obtained as the hydrochloride salts.

Biological Screening and Results—Compounds III–XXIII were screened *in vitro* against *Staphylococcus aureus* (Mi-12)[1], *Escherichia coli* (Es-2)[1], *Corynebacterium liquefaciens* (Co-11)[1], and *Haemophilis vaginalis* (He-127)[1].

Screening data for the compounds are listed in Table I, along with data for nitrofurazone[2] for comparison. These compounds possess activity against Gram-positive and Gram-negative organisms.

EXPERIMENTAL

Synthesis—The anilines for VI and XX were prepared by catalytic reduction of 9-nitroanthracene and 2-chloro-4-nitrophenol, respectively, which were purchased. The prerequisite amines for XII, XIII, and XIV were obtained from 4-pyrrolidinonitrobenzene (4), 4-morpholinonitrobenzene (4), and 3-chloro-4-morpholinonitrobenzene (5), respectively, which were synthesized by literature procedures.

Melting points[3] were taken in open capillary tubes and are uncorrected. IR spectra (mineral oil mull) and NMR spectra)dimethyl sulfoxide-d_6) were consistent with the assigned structures. The physical constants of all final products are listed in Table I, and analytical data are listed in Table II.

3-Chloro-4-morpholinoaniline—A 500-ml reduction bottle was charged with 3-chloro-4-morpholinonitrobenzene (5) (19.5 g, 0.08 mole) and absolute ethanol. Raney active nickel catalyst (2.5 ml in water) was added, and the mixture was shaken under hydrogen at 40 psi until absorption was complete. The catalyst was removed by filtration, and the filtrate was concentrated to 80 ml under reduced pressure. The residue was chilled and filtered to yield 10.8 g, mp 93–97°. The filtrate was concentrated to 10 ml, chilled, and filtered to yield 3.2 g, mp 92–93°. The total yield was 14.0 g (82%). A small sample (1.0 g) was recrystallized from absolute ethanol to yield 0.5 g, mp 97–100°.

Anal.—Calc. for $C_{10}H_{13}ClN_2O$: C, 56.47; H, 6.16; N, 13.17. Found: C, 56.43; H, 6.05; N, 13.19.

7-Methyl-9-(substituted Arylamino)imidazo[4,5-*f*]quinolines (III–XXIII)—All of these compounds, except VIII and X, were prepared by the procedure of Spencer *et al.* (2).

9-(4-Aminoanilino)-7-methylimidazo[4,5-*f*]quinoline Hydrochloride (VIII)—A solution of VII (20.0 g, 0.05 mole) in concentrated hydrochloric acid was heated under reflux for 30 min. A clear yellow solution formed after about 15 min; in another 5 min, crystals began to separate. After cooling, the product was filtered, washed with hydrochloric acid and then with methanol, and air dried to give 20 g of yellow crystals. These crystals contained a variable amount of hydrogen chloride even after drying *in vacuo*.

The product was converted to the monohydrochloride by the following procedure. A solution of the material in water (200 ml) was made alkaline with ammonium hydroxide. The yellow precipitate was filtered, washed with water, and suspended in water (300 ml). One equivalent (4.2 ml) of concentrated hydrochloric acid was added, and the mixture was heated on the steam bath (solution incomplete) and then kept overnight at room temperature. The product was filtered, washed with absolute ethanol, and air dried to give 12 g of VIII. Drying at 100° *in vacuo* removes the water, but it is rapidly reabsorbed on exposure to the atmosphere.

Compound XI was hydrolyzed in a similar manner to give X directly with no additional workup required.

Biological Testing—Compounds III–XXIII were screened *in vitro* against three varieties of bacteria, *S. aureus*, *E. coli*, and *C. liquefaciens*, according to procedures previously described (6). In addition, the compounds were tested against *H. vaginalis* by the following method. The inoculum of *H. vaginalis* was prepared by growing the organism for 18–20 hr at 37° in brain–heart infusion broth[4] with 0.1% agar and 10% calf serum added. The culture was adjusted in fresh medium to an optical density of 0.4 in a spectrometer[5] set at 440 nm. Cotton-plugged tubes containing 2 ml of the growth medium, 5% calf serum, and diluted test compound were inoculated with 0.2 ml of the adjusted culture. After the inoculum was added, the tubes were incubated without being shaken for 24 hr at 37° and then observed for turbidity.

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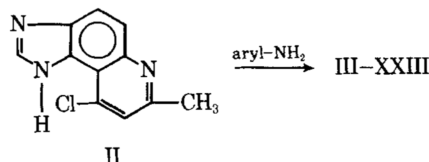
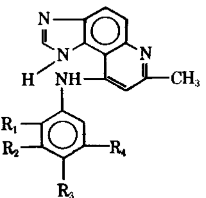


Scheme I

[1] The Norwich Pharmacal Co. strain number.
[2] Furacin, Eaton Laboratories Division, Morton-Norwich Products.
[3] Mel-Temp melting-point apparatus.
[4] Difco.
[5] Bausch and Lomb Spectronic 20.

Table I—7-Methyl-9-(substituted Arylamino)imidazo[4,5-*f*]quinolines



Compound	R_1	R_2	R_3	R_4	Melting Point	Yield, %	Recrystallization Solvent	MIC[a], µg/ml *H. vaginalis*	MIC[a], µg/ml *S. aureus*	MIC[a], µg/ml *E. coli*	MIC[a], µg/ml *C. liquefaciens*
III	H	H	C_2H_5	H	327–332°	100	2-Propanol	6.25	3.1	6.25	3.1
IV	H	H	CH_2CH_2OH	H	302–308°	81	Water	25.0	100	50	100
V	H	H	$C_{12}H_{25}$-*n*	H	216–220°	80	Dimethylformamide	25.0	>50	>50	50
VI	2,3-benzo		H	5,6-benzo	192–198°	74	Methanol	50.0	25	50	25
VII	H	H	$NHCOCH_3$	H	381–383°	81	Methanol	12.5	>50	50	>50
VIII	H	H	NH_2	H	>350°	65	Water	12.5	100	25	100
IX	H	H	$N(CH_3)COCH_3$	H	315–317°	48	Methanol	62.5	500	125	125
X	H	H	$NHCH_3$	H	<330° dec.	86	Methanol	6.25	50	50	25
XI	H	H	$N(CH_3)CH_2CH_2OH$	H	299–303°	100	Methanol–ether	25	100	100	50
XII	H	H	N (pyrrolidino ring)	H	364–372°	93	Methanol–ether	12.5	3.1	6.25	1.5
XIII	H	H	N O (morpholino ring)	H	351–353°	99	Methanol–ether	25.0	50	100	100
XIV	H	Cl	N O (morpholino ring)	H	322–327°	100	Methanol–ether	12.5	12.5	12.5	50
XV	H	H	Cl	H	Gradual decomposition	29	Methanol	6.25	6.25	3.1	1.5
XVI	H	Cl	H	H	351–353°	88	Methanol	12.5	6.25	3.1	6.25
XVII	H	H	F	H	341–345°	57	Absolute ethanol	3.1	25	12.5	25
XVIII	H	H	OH	H	393–395°	48	Methanol	6.25	50	50	25
XIX	H	OH	H	H	396–398°	89	Absolute ethanol	1.5	25	25	25
XX	H	Cl	OH	H	387° dec.	97	Methanol–ether	6.25	>50	25	3.1
XXI	OCH_3	H	H	$COCH_3$	>400°	69	Methanol	15.5	500	250	>1000
XXII	H	H	COC_6H_5	H	348–350°	90	Methanol	50	12.5	100	50
XXIII	H	H	$COOC_2H_5$	H	275–280°	60	Absolute ethanol	25	12.5	12.5	12.5
Nitrofurazone								0.75	12.5	3.1	25

[a] MIC = minimal inhibitory concentration, which is the lowest concentration of a compound that prevents visible growth after 24-hr incubation at 37°.

Table II—Elemental Analysis Data for III-XXIII

Compound	Formula	Calc./Found, % C	H	N
III	$C_{19}H_{18}N_4 \cdot HCl$	67.34/66.94	5.65/5.56	16.54/16.48
IV	$C_{19}H_{18}N_4O \cdot HCl$	64.31/64.12	5.40/5.23	15.79/15.80
V	$C_{29}H_{38}N_4 \cdot HCl \cdot 0.25\ H_2O$	72.02/72.05	8.23/8.32	11.59/11.70
VI	$C_{25}H_{18}N_4 \cdot 0.5\ H_2O$	78.30/78.53	4.99/4.71	14.61/14.73
VII	$C_{19}H_{17}N_5O \cdot HCl$	62.04/61.66	4.93/4.69	19.04/19.06
VIII	$C_{17}H_{15}N_5 \cdot HCl \cdot 0.5\ H_2O$	60.98/60.99	5.12/5.04	20.92/20.99
IX	$C_{20}H_{19}N_5O \cdot HCl \cdot 1.5\ H_2O$	58.75/58.97	5.67/5.32	17.13/17.33
X	$C_{18}H_{17}N_5 \cdot 2\ HCl \cdot H_2O$	54.83/55.17	5.37/5.25	17.76/17.71
XI	$C_{20}H_{21}N_5O \cdot HCl \cdot 0.5\ H_2O$	61.13/61.48	5.90/5.92	17.83/17.81
XII	$C_{21}H_{21}N_5 \cdot HCl$	66.39/65.99	5.84/5.85	18.44/18.17
XIII	$C_{21}H_{21}N_5O \cdot HCl$	63.71/63.59	5.60/5.70	17.69/17.43
XIV	$C_{21}H_{20}ClN_5O \cdot HCl \cdot 3\ H_2O$	52.07/52.19	5.62/5.39	14.46/14.42
XV	$C_{17}H_{13}ClN_4 \cdot HCl \cdot 1.25\ H_2O$	55.67/55.83	4.26/4.31	15.28/15.20
XVI	$C_{17}H_{13}ClN_4 \cdot HCl$	59.14/59.32	4.09/4.08	16.23/16.04
XVII	$C_{17}H_{13}FN_4 \cdot HCl$	62.10/62.50	4.29/4.32	17.04/17.15
XVIII	$C_{17}H_{14}N_4O \cdot HCl \cdot 0.5\ H_2O$	60.81/60.55	4.80/5.11	16.69/16.71
XIX	$C_{17}H_{14}N_4O \cdot HCl$	62.48/62.18	4.63/4.65	17.15/16.87
XX	$C_{17}H_{13}ClN_4O \cdot HCl$	56.52/56.25	3.91/3.91	15.51/15.29
XXI	$C_{20}H_{18}N_4O_2 \cdot HCl \cdot 0.5\ H_2O$	61.30/61.26	5.14/5.02	14.64/14.26
XXII	$C_{24}H_{18}N_4O \cdot HCl$	69.48/69.08	4.62/4.68	13.51/13.58
XXIII	$C_{20}H_{18}N_4O_2 \cdot HCl$	62.74/62.56	5.00/4.88	14.64/14.75

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New Compounds: Synthesis of D-Arabinofuranosylurea Derivatives

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Abstract □ Procedures are described for the preparation of a series of D-arabinofuranosylurea derivatives.

Keyphrases □ D-Arabinofuranosylurea derivatives—synthesis described □ Ureas, D-arabinofuranosyl—synthesis described

The structural resemblance of D-arabinofuranosylurea derivatives to nucleosides possessing cytotoxic activity such as cytarabine (1) suggested the synthesis of a series of these urea derivatives.

Oxidation of the pyrimidine base in 2′,3′,5′-tri-(*O*-acetyl)uridine or its N^3-methyl derivative (2) with permanganate, ozone, or osmium tetroxide gave, apart from unchanged starting material, urea or methylurea and poor yields of compounds whose structures were not established unambiguously.

Ureidoglycosides have been formed by an acid-catalyzed reaction between monosaccharides and urea (3). Normally, this reaction would result in the formation of ureidopyranosides. For the preparation of ureidofuranosides, protected furanose derivatives are required so that pyranosides are not formed under acidic reaction conditions. 2′,3′,5′-Tri-(*O*-benzyl)-D-arabinofuranose and a variety of ureas (Table I) were used. This particular derivative offered the advantage that the benzyl groups could be removed by catalytic hydrogenolysis (4) to give the required D-arabinofuranosylureas. The urea derivatives were obtained by heating the benzylated sugar, appropriate urea, and acetone (or acetone–water) with sulfuric acid or perchloric acid as a catalyst (5).

EXPERIMENTAL

Chemical-ionization mass spectra[1], with isobutane as the reagent gas, and NMR spectra were obtained[2]. Chemical shift data were measured relative to tetramethylsilane as an internal standard and are given in parts per million. Evaporations were conducted under diminished pressure at a bath temperature below 50°. Column chromatography was carried out on silica gel (60–200 mesh).

N^3-Methyl -2′,3′,5′-tri- (*O*-acetyl)uridine—2′,3′,5′-Tri-(*O*-ace-

[1] DuPont 21-490F mass spectrograph.
[2] Varian T-60 instrument.