Notes

Chemotherapeutic Nitroheterocycles. 2.[1a,b] 2-(5-Nitro-2-furyl)pyrimidines with Basic Substituents

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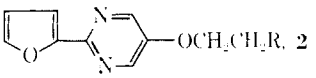
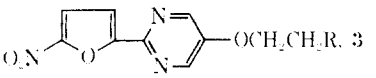
It was shown in a previous paper[1a] that 5-substituted 2-(5-nitro-2-furyl)pyrimidines possess a high *in vitro* activity against *Trichomonas vaginalis* and an *in vivo* activity could be demonstrated. A continuous search for derivatives with better biological potency led us to the syntheses of derivatives with basically substituted side chains in position 5 of the pyrimidine nucleus. This paper refers to the synthesis and biological evaluation of the new nitrofurylpyrimidines **3**.

Chemistry.—The compounds were synthesized by reaction of 2-(2-furyl)-5-(2-chloroethoxy)pyrimidine (**1a**) or of the tosylate of 2-(2-furyl)-5-(2-hydroxyethoxy)pyrimidine (**1b**) with excess secondary amine in EtOH and subsequent nitration of the 2-(2-furyl)-5-(2-aminoethoxy)pyrimidine derivatives (**2**) with HNO_3–H_2SO_4 according to Scheme I.

The compounds were isolated as free bases; only in the case that no crystalline material could be obtained the HCl or HSO_4 salts were prepared. All synthesized intermediates **2** and nitro compounds **3** are summarized in Table I. The analytical data and physical measurements (uv, ir, nmr, or titrations) are in accordance with the given structures and were determined for all compounds.

TABLE I





Compd	R	Cryst solvent	Mp, °C	Yield, %	Formula	Analysis	Cryst solvent	Mp, °C	Yield, %	Formula	Analysis
a	NMe_2	*a*	81–83	57	$C_{12}H_{15}N_3O_2$	*b*	EtOH	147–148	37	$C_{12}H_{14}N_4O_4$	N
b	NEt_2	*a*	47–49	51	$C_{14}H_{19}N_3O_2$	C, H, N	EtOH	137–141	40	$C_{14}H_{18}N_4O_4$	C, H, N
c	N-(*n*-Bu)$_2$	*i*-PrOH	168–173	44	$C_{18}H_{28}ClN_3O_2$[c]	C, H, Cl, N	*i*-PrOH–H_2O	83–85	45	$C_{18}H_{26}N_4O_4$	C, H, N
d		Petroleum ether–C_6H_6	91–92	83	$C_{14}H_{17}N_3O_2$	C, H, N	EtOH–2-methoxyethanol	165–167	54	$C_{14}H_{18}N_4O_8S$[d]	C, H, N, S
e		*a*	91–92	66	$C_{15}H_{19}N_3O_2$	*b*	EtOH	135–136	36	$C_{15}H_{18}N_4O_4$	C, H, N
f		*a*	83–84	75	$C_{16}H_{21}N_3O_2$	*b*	EtOH	144–145	57	$C_{16}H_{20}N_4O_4$	C, H, N
g		*a*	78–79	60	$C_{16}H_{21}N_3O_2$	*b*	EtOH	134–136	31	$C_{16}H_{24}N_4O_8S$[d]	C, H, N, S
h		Petroleum ether–C_6H_6	109–112	69	$C_{18}H_{23}N_3O_2$	*b*	MeOH	252 dec	51	$C_{18}H_{23}ClN_4O_4$[e]	C, H, N, Cl
i		Petroleum ether–C_6H_6	94–95	75	$C_{14}H_{17}N_3O_3$	*b*	MeOH–H_2O	200–201	48	$C_{14}H_{18}N_4O_9S$[d]	C, H, N, S
j		Petroleum ether–C_6H_6	76–80	64	$C_{15}H_{20}N_4O_2$	*b*	EtOH	144–145	39	$C_{15}H_{19}N_3O_4$	C, H, N
k		Petroleum ether–C_6H_6	73–74	53	$C_{17}H_{24}N_4O_2$	*b*	MeOH	257 dec	22	$C_{17}H_{25}Cl_2N_5O_4$[e]	C, H, N, Cl

[a] Crude material, which was used without purification. [b] These compounds were used without analytical measurements and were characterized by their nitration products **3**. [c] Hydrochloride. [d] Hydrogen sulfate. [e] Dihydrochloride.

Biological Results.—The compounds were screened *in vitro* against Gram-positive and Gram-negative bacteria, fungi, and protozoa. The activity against a selection of microorganisms is shown in Table II. It can be seen that only in a few cases does a pronounced activity occur against Gram-positive and Gram-negative bacteria and in selected cases a slight activity against *Candida albicans*. But the activity against *T. vaginalis* is impressive; all compounds show a better activity than metronidazole which has a MIC of

(1) (a) Paper 1: R. Albrecht, K. Gutsche, H.-J. Kessler, and E. Schroder; *J. Med. Chem.*, **13**, 733 (1970); (b) a preliminary report of part of this work has been presented at the 6th International Congress of Chemotherapy, Tokyo, Aug. 1969; (c) to whom inquiries should be addressed.

SCHEME I

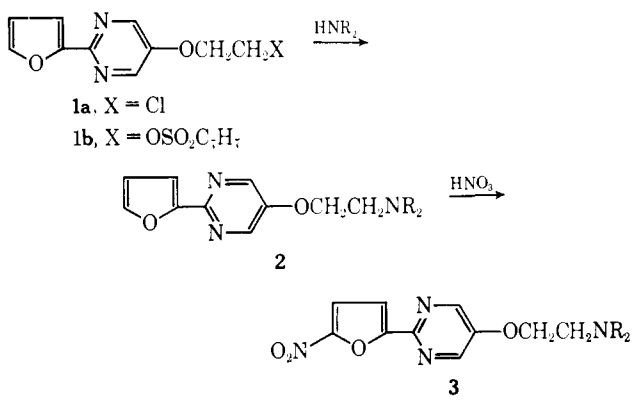


TABLE II

In Vitro ANTIMICROBIAL DATA (TUBE DILUTION TEST; MIC VALUES IN μg/ml)

Compd	*S. aureus*[a]	*E. coli*[b]	*P. vulgaris*[c]	*K. pneumoniae*[d]	*C. albicans*	*T. vaginalis*
2a	12	1.6	6.2	3.1	100	0.39
2b	25	6.2		12		0.19
2c						0.78
2d	25	12	25	25		0.19
2e	25	3.1		12	25	0.39
2f		3.1		25		0.19
2g	50	6.2	50	50		0.78
2h	50	12				0.19
2i	12	1.6	50	25		0.78
2j	3.1	1.6	12	6.2	100	0.78
2k	25	12				0.10
Metronidazole						1.6

[a] *Staphylococcus aureus.* [b] *Escherichia coli.* [c] *Proteus vulgaris.* [d] *Klebsiella pneumoniae.*

1.6 μg/ml in our test. The most active compound *in vitro* is 2-(5-nitro-2-furyl)-5-(2-*N*-*n*-propylpiperazinoethoxy)pyrimidine dihydrochloride (**3k**) with an MIC of 0.10 μg/ml. Some of the compounds were investigated *in vivo* against a subcutaneous *T. vaginalis* infection in mice and proved to be active by oral application. Preliminary results indicate that *in vivo* activity of 2-(5-nitro-2-furyl)-5-(2-pyrrolidinoethoxy)-pyrimidine (**3d**) is comparable to metronidazole.

Experimental Section[2]

2-(2-Furyl)-5-(2-*p*-toluenesulfonyloxyethoxy)pyrimidine (1b).—2-(2-Furyl)-5-(2-hydroxyethoxy)pyrimidine (10.3 g, 50 mmol) was dissolved in 100 ml of pyridine, 9.53 g (50 mmol) of *p*-TsCl was added and the mixture was stirred for 1,5 hr. The solution was poured into H_2O, the insoluble product was filtered and recrystd from PhMe, mp 154–155°; yield 8.6 g (48%). *Anal.* ($C_{17}H_{16}N_2O_5S$) N, S.

2-(2-Furyl)-5-(2-diethylaminoethoxy)pyrimidine (2b).—2-(2-Furyl)-5-(2-chloroethoxy)pyrimidine (7.85 g, 38.3 mmol) and 10.42 g (0.142 mol) of Et_2NH was heated in 80 ml EtOH at 70–80° for 18 hr. The solvent and excess amine were removed by distillation, the residue was mixed with H_2O and extracted with CH_2Cl_2. The solution was dried (K_2CO_3) and CH_2Cl_2 was removed, yielding a crystalline compound, mp 47–49°; yield 5.1 g (51%). *Anal.* ($C_{14}H_{19}N_3O_2$) C, H, N.

2-(5-Nitro-2-furyl)-5-(2-diethylaminoethoxy)pyrimidine (3b)—2-(2-Furyl)-5-(2-diethylaminoethoxy)pyrimidine (5.0 g, 19.1 mmol) was suspended in 25 ml of concd H_2SO_4 and 1.5 ml of HNO_3 (d = 1.48) was added dropwise at 5°. After stirring for 0.5 hr the mixture was poured on ice, the aq solution was made alkaline with aq NH_3 and the solid product was filtered, washed with H_2O, and recrystallized from EtOH, mp 137–141°; yield 2.0 g (34%). *Anal.* ($C_{14}H_{18}N_4O_4$) C, H, N.

2-(2-Furyl)-5-(2-di-*n*-butylaminoethoxy)pyrimidine·HCl.—2-(2-Furyl)-5-(2-*p*-toluenesulfonyloxyethoxy)pyrimidine (2.08 g, 5.77 mmol) and 2.33 g (18.1 mmol) of *n*-Bu_2NH in 60 ml of EtOH was refluxed for 20 hr. EtOH and excessive Bu_2NH were removed by distillation, the residue was dissolved in H_2O and the aq solution was extracted with CH_2Cl_2. The solution was dried (Na_2SO_4) and the solvent removed. The residue was dissolved in *i*-PrOH–Et_2O and HCl in Et_2O was added. The solid hydrochloride was filtered off and recrystd from *i*-PrOH, mp 168–173°; yield 0.90 g (44%). *Anal.* ($C_{18}H_{28}ClN_3O_2$) C, H, Cl, N.

2-(5-Nitro-2-furyl)-5-(2-di-*n*-butylaminoethoxy)pyrimidine (3c).—2-(2-Furyl)-5-(2-di-*n*-butylaminoethoxy)pyrimidine·HCl (0.90 g, 2.54 mmol) was suspended in 3 ml of concd H_2SO_4 and 0.255 ml of HNO_3 (d = 1.48) was added at 5°. After stirring for 0.5 hr the mixture was poured onto ice, the resulting aq mixture was neutralized with concd NH_3 and the insoluble material recrystallized from *i*-PrOH–H_2O, mp 83–85°; yield 413 mg (45%). *Anal.* ($C_{18}H_{26}N_4O_4$) C, H, N.

(2) Melting points are uncorrected and taken on a Tottoli melting point apparatus (Fa. W. Büchi, Switzerland). Where analytical results are indicated only by symbols of the elements or functions, values found for those elements or functions were within ±0.4% of the calculated values.

Reassignment of the Absolute Configuration of 3-Acetoxyquinuclidine Methiodide and the Absolute Configuration of Receptor-Bound Acetylcholine

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The resolution and absolute configurations of (+)- and (−)-3-acetoxyquinuclidine methiodide have recently been reported.[1] It was noted that only one of the optical enantiomers is a substrate of acetylcholinesterase (AChE) and is a muscarinic agonist.[1] This enantiomer was assigned the (*S*) configuration by the method of asymmetric sulfoxide synthesis[2] as applied to (+)-3-quinuclidinol. This assignment led to the conclusion that the bridgehead carbon atom of the biologically active enantiomer occupies a position equivalent to the methyl substituent of (*S*)-(+)-β-methylacetylcholine (I), the enantiomer which is a ubstrate of AChE and possesses muscarinic activity equivalent to that of acetylcholine (ACh).[1] In the meantime, the crystal structures of the α- and β-methyl-ACh isomers have been analyzed by Chothia and Pauling,[3,4] and their conformation was discussed in relation to hydrolysis by AChE.[5] The results led us to question the configurational assignment of (+)-3-quinuclidinol[1] and after reexamination of the experimental data it is evident that the dextrorotatory enantiomer possesses the (*S*) rather than the (*R*) configuration. It follows that the previous analysis of results[1] requires reinterpretation.

According to the rules governing asymmetric sulfoxide synthesis,[2] alcohols corresponding to stereo-

(1) J. B. Robinson, B. Belleau, and B. Cox, *J. Med. Chem.*, **12**, 848 (1969).

(2) M. M. Green, M. Axelrod, and M. Mislow, *J. Amer. Chem. Soc.*, **88**, 861 (1966).

(3) C. Chothia and P. Pauling, *Chem. Commun.*, 626 (1969).

(4) C. Chothia and P. Pauling, *ibid.*, 746 (1969).

(5) C. Chothia and P. Pauling, *Nature*, **223**, 919 (1969).