J. Lein, *Proc. Soc. Exp. Biol. Med.*, **107**, 455 (1961).
(7) R. Raap and R. G. Micetich, *J. Med. Chem.*, **11**, 70 (1968).
(8) W. E. Bachmann and W. S. Struve, *Org. React.*, **1**, 38 (1960).
(9) C. D. Hurd and R. I. Mori, *J. Amer. Chem. Soc.*, **77**, 5359 (1955).
(10) L. Wolff, *Justus Liebigs Ann. Chem.*, **333**, 1 (1904).
(11) R. Raap and R. G. Micetich, *Can. J. Chem.*, **46**, 1057 (1968).
(12) J. Plucker III and E. D. Amstutz, *J. Amer. Chem. Soc.*, **62**, 1512 (1940).
(13) R. G. Micetich, *Can. J. Chem.*, **48**, 2006 (1970).
(14) F. F. Blicke and F. Leonard, *J. Amer. Chem. Soc.*, **68**, 1934 (1946).
(15) L. Horner and E. H. Winkelmann, "Newer Methods of Preparative Organic Chemistry," Vol III, Academic Press, N. Y., 1964, p 151.
(16) E. Campaigne and B. F. Tullar, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 921.
(17) E. Campaigne and W. M. LeSuer, *J. Amer. Chem. Soc.*, **70**, 1555 (1948).
(18) J. H. Ford, G. C. Prescott, and D. R. Colingsworth, *ibid.*, **72**, 2109 (1950).
(19) Phrix-Werke A-G, German Patent 892,136 (Oct 5, 1953); *Chem. Abstr.*, **52**, 13801 (1958).
(20) R. Raap and J. Howard, *Can. J. Chem.*, **47**, 813 (1969).
(21) R. Raap, *ibid.*, **46**, 2255 (1968).
(22) R. Morey and H. Schenkel, *Helv. Chim. Acta*, **33**, 405 (1950).
(23) E. R. H. Jones, F. A. Robinson, and M. N. Strachen, *J. Amer. Chem. Soc.*, **68**, 87 (1946).
(24) H. A. Smith, J. B. Conley, and W. H. King, *ibid.*, **73**, 4633 (1951).
(25) R. G. Jones, M. J. Mann, and K. C. McLaughlin, *J. Org. Chem.*, **19**, 1428 (1954).
(26) T. Curtius and W. Klaveln, *J. Prakt. Chem.*, **125**, 498 (1930).
(27) C. Ainsworth and R. G. Jones, *J. Amer. Chem. Soc.*, **77**, 621 (1955).

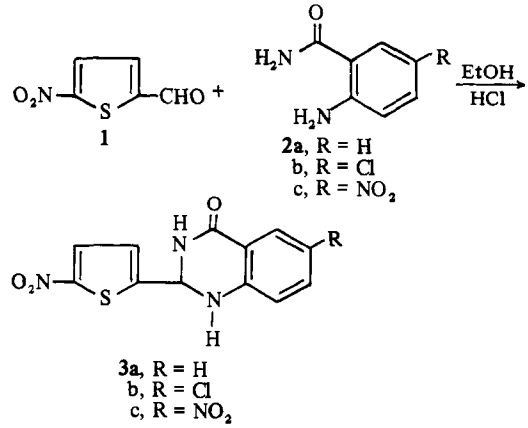
Antibacterial 2,3-Dihydro-2-(5-nitro-2-thienyl)-quinazolin-4(1*H*)-ones

Robert J. Alaimo*
Chemistry Division

and H. Eric Russell

Chemotherapy Division, Research and Development Department, The Norwich Pharmacal Company, Norwich, New York 13815.
Received September 18, 1971

The anthelmintic activity of a series of 2-(5-nitro-2-thienyl)quinazolines has recently been reported.[1] During the course of this research, three 2,3-dihydro-2-(5-nitro-2-thienyl)quinazolin-4(1*H*)-one derivatives were prepared as intermediates. These 2,3-dihydroquinazolin-4(1*H*)-ones have shown significant activity against organisms implicated in bacterial vaginitis.



Chemistry. The general synthetic method for the preparation of the compounds **3a**, **3b**, and **3c** involves the reaction of 5-nitro-2-thiophenecarboxaldehyde with a suitably substituted anthranilamide in acidic EtOH.

Table I

Bacterial strain	MIC, μg/ml[a] 3a	3b	3c	nitrofurazone
Staphylococcus aureus	>50	>50	>50	12
Streptococcus faecalis	>50	–	–	25
Corynebacterium liquefaciens	50	25	50	25
Escherichia coli Es-2	1.5	12.5	12.5	3
E. coli Es-L	50	>50	>50	12
Salmonella typhosa	12.5	50	>50	6
Hemophilus vaginalis	0.4	6	1.5	0.8

[a]Minimal inhibitory concentration is the lowest concentration of compound that prevents visible growth after 24 hr of incubation.

Table II

Compound	Concentration, μg/ml	Medium with serum–mucin	Medium without serum–mucin
3a	0.5	1.2×10^3	1.3×10^{3b}
3b	1	8.1×10^4	7.8×10^4
3c	1	7.5×10^4	3.0×10^3
Nitrofurazone[a]	0.5	6.1×10^5	7.9×10^5
Control		5.2×10^7	6.6×10^7

[a]For comparison. [b]Compounds were considered active when they produced a 3 log reduction in the viable *Hemophilus vaginalis* concentration both in the presence and the absence of serum and mucin after 6-hr incubation at 37°.

Biological Method. The compounds in Table I were screened for bacteriostatic activity by methods reported previously.[2] However, since *Hemophilus vaginalis* requires more fastidious growth conditions than the other microorganisms tested, the composition of the growth medium was altered. The compounds were also tested for bactericidal activity in a medium with serum and mucin added. Both tests are described in the Experimental Section and the results are shown in Table II.

Biological Results. *In vitro* testing results indicate that the most active compound is 2,3-dihydro-2-(5-nitro-2-thienyl)quinazolin-4(1*H*)-one (**3a**). It is more active than the reference standard nitrofurazone, in the serum–mucin bactericidal test. It also has MIC's comparable to nitrofurazone against *H. vaginalis* and *Escherichia coli*, organisms usually implicated in bacterial vaginitis.

Experimental Section†

Bacteriostatic Test. Brain–heart infusion broth (Difco) with 0.1% agar added was heated to expel residual O_2 and then cooled to 40°. Calf serum was added at a 10% concentration. A 0.3-ml aliquot of a 24-hr culture was added to 5 ml of complete medium and after incubation for 18–20 hr at 37°, the culture was adjusted in fresh complete medium to 40% transmittance in a Spectronic 20 colorimeter at a setting of 440 nm. Calf serum was also added to the medium after diluting the test compound. The inoculum, 0.2 ml of the diluted culture, was added to 2-ml vol of the previously diluted compound. Tubes were incubated at 37° for 24 hr and the lowest compound concentration with no visible growth was considered the minimal inhibitory concentration (MIC).

Bactericidal Test. Appropriate concentrations of the compounds were added to 2 test tubes. Serum and mucin at 25% and 1%, respectively, were added to 1 tube and to the other tube serum at 5% and H_2O equivalent to the addition made to the first tube. Equal amounts of double strength Casman's broth were then added to each tube. Finally, a 16-hr broth culture of *Hemophilus vaginalis* was centrifuged and resuspended in Casman's broth to an O.D. of 0.3 at 620 nm is a Spectronic 20 colorimeter. Approximately 1×10^8 cells (0.1 ml) were added to each tube. Tubes, containing a

†Melting points were determined in open capillary tubes using a Mel-Temp melting point apparatus and are uncorrected. Microanalytical results obtained for the elements indicated were within ±0.4% of the theoretical value.

final volume of 2 ml, were incubated at 37° in a shaking water bath. Standard bacterial plate counts of each tube were made and plates incubated in an atm of 10% CO_2 for 48 hr when the viable plate count was determined.

2,3-Dihydro-2-(5-nitro-2-thienyl)quinazolin-4(1*H*)-one (3a) and 6-chloro-2,3-dihydro-2-(5-nitro-2-thienyl)quinazolin-4(1*H*)-one (3b) were prepared as reported previously.[1]

2,3-Dihydro-6-nitro-2-(5-nitro-2-thienyl)quinazolin-4(1*H*)-one (3c). A mixt of 2-amino-5-nitrobenzamide (2.3 g, 0.012 mole) and 5-nitro-2-thiophenecarboxaldehyde (2.0 g, 0.012 mole) in 40 ml of EtOH was treated with 1 ml of concd HCl. The reaction mixt was boiled under reflux with stirring for 2 hr. After chilling overnight in the refrigerator, the mixt was filtered to give a yellow solid (2 g, 52%).

Dissolving the crude compound in hot EtOH–DMF (charcoal) and diluting with H_2O until turbidity persisted provided analytically pure material which melted at 210–211°. *Anal.* ($C_{12}H_8N_4O_5S$) C, H, N.

Acknowledgments. The authors are grateful to Mr. James Sheffer, Mr. Charles Depew, Mr. Carlos Whitney, and Mr. Patrick Moynihan for their technical assistance. Microanalyses were performed by Mr. Marvin Tefft and Mr. Grant Gustin.

References

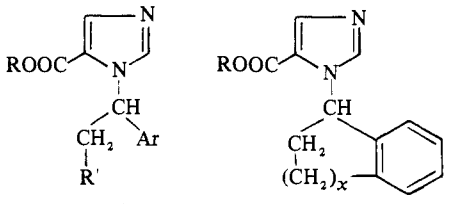
(1) R. J. Alaimo and C. J. Hatton, *J. Med. Chem.*, 15, 108 (1972).
(2) R. Freedman and R. E. Chamberlain, *Antimicrob. Ag. Chemother.*, 502 (1967).

DL-1-(α-Methylbenzyl)-2-methylimidazole-5-carboxylate Esters. Synthesis and Pharmacological Properties

Erik F. Godefroi* and J. Th. J. Platje

Department of Organic Chemistry, The University of Technology, Eindhoven, The Netherlands. *Received September 24, 1971*

Certain 1-substituted imidazole-5-carboxylic acid esters have, in the past, been shown to display significant biological activity. For example 1-arylalkylimidazole-5-carboxylate esters of type I induce a potent and short-acting hypnosis in the rat;[1a,b] cyclized variants of I, such as II, exhibit significant antimycotic activity against dermatophytes.[2a,b]

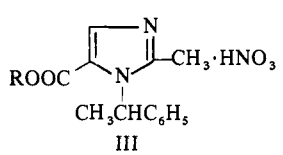


I II

R = alkyl; substituted alkyl
R' = H, CH_3, C_2H_5
x = 1, 2

These compounds were made essentially according to Jones;[3] this method precluded the preparation of 2-alkylimidazole homologs. The conceivable metabolic vulnerability of this position prompted preparation of a few 2-Me analogs (III). The synthesis and gross pharmacological properties of **8** and **9** are now reported.

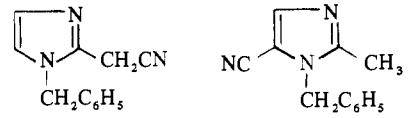
Chemistry. Efforts to synthesize 2-β-aminoethylimidazole



III

8, R = CH_3
9, R = C_2H_5

("isohistamine") had led Jones[4] to base his approach on the reaction of 1-benzyl-2-chloromethylimidazole with KCN in absolute EtOH. Recent work by Roe, *et al.*,[5] proves beyond a doubt that Jones' purported 1-benzyl-2-cyanomethylimidazole (**1**) was, in fact, 1-benzyl-2-methylimidazole-5-carbonitrile (**2**). Such anomalous substitution patterns are not uncommon in heterocyclic chemistry.†

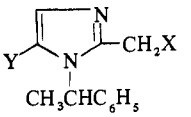


1 2

With these considerations in mind, **4** was made as follows. Reaction of α-methylbenzyl chloride with the Na salt of imidazole in DMF‡ followed by hydroxymethylation of the crude reaction mixture afforded **3**; this was converted to the chloromethyl hydrochloride **4** by means of $SOCl_2$. The original Jones procedure for preparing "**1**" (*i. e.*, **2**) called for the use of KCN–absolute EtOH. We chose to treat **4** with 2 equiv of NaCN in "80% acetone," thereby avoiding alcoholysis of **4**. The reaction was carried out at room temp. Upon ir examination of the crude reaction mixture the presence of 2 nitriles was apparent. Separation of these components was facile and practical, as they differed in basicity. The main product (47%), isolated as the HCl salt, was identified as **5**; *ca.* 10% of the desired nitrile **6** was obtained as base from the mother liquor. Characterization of **5** and **6** was predicated upon analytical and spectral data (see Experimental Section).

Hydrolysis of **6** to **7** was monitored by the rate of NH_3 evolution. This was slow under ordinary hydrolytic conditions (5 *N* NaOH; alcoholic KOH); more vigorous conditions (KOH–ethylene glycol) made the reaction proceed more rapidly but the yield of **7** was unsatisfactory (*ca.* 50%). Recourse was eventually taken to a 2-step procedure. Treatment of nitrile **6** with MeOH–HCl gave (presumably) the corresponding Me ester and/or the imino ether. Subsequent basic hydrolysis then gave acid **7** in very good yield.

Compd **7** was converted to the corresponding acid chloride by means of $SOCl_2$. Esters **8** and **9** were then obtained by methanolysis and ethanolysis of the acid chloride. They were isolated and tested as nitrate salts.



3, X = OH; Y = H
4, X = Cl, Y = H (·HCl)
5, X = CN; Y = H (·HCl)
6, X = H; Y = CN
7, X = H; Y = COOH

Pharmacology.§ Compds **8** and **9** were tested on mice for behavioral effects, anticonvulsant properties, and lethality. Results are summarized in Table I. The compounds in question resemble pharmacologically the general anaesthetics, as doses causing loss of righting reflex lie close to those effecting loss of corneal and spinal reflexes. No convulsions were noted upon high-level administration of the compounds. At nonhypnotic doses, **8** (75 mg/kg ip) and **9** (100 mg/kg ip) slightly potentiated the hypnotic effect of sodium phenobarbital.[7]

Experimental Section

Melting points were taken on a Fisher-Johns block and are uncorrected. Analytical samples had ir and nmr spectra compatible

†See literature citations of ref 5.

‡Reaction conditions were analogous to the benzylation of imidazole.[6]

§Pharmacological data were kindly furnished by Dr. V. Claassen, Department of Pharmacology, N. V. Philips-Duphar, Weesp, The Netherlands.