Secondary Mechanisms of Antifungal Action of Substituted 8-Quinolinols. 3. 5,7,8-Substituted Quinolines†

Herman Gershon,* Maynard W. McNeil, Raulo Parmegiani, and Patricia K. Godfrey

Boyce Thompson Institute for Plant Research, Yonkers, New York 10701. *Received June 24, 1971*

It was previously shown that the antifungal activity of 5- and 5,7-halogeno-8-quinolinols was generally greater than that of 8-quinolinol.[1] A subsequent study of a related series of 8-methoxyquinolines, where chelation as a mechanism of fungitoxicity is of no significance, indicated that they were markedly less active than the parent 8-quinolinols. With the exception of the 5,7-dichloro, 5,7-dibromo, and 5,7-diiodo derivatives, the substituted 8-methoxyquinolines were more fungitoxic than 8-methoxyquinoline.[2] A further study of the antifungal activity of monosubstituted quinolines where the 8 position was occupied by H revealed that the analogous pairs of quinolines and 8-methoxyquinolines were quite similar in fungitoxicity. Although of a lower order of activity, both the substituted quinolines and 8-methoxyquinolines paralleled the corresponding substituted 8-quinolinols in fungitoxicity.[3] Based on these results, it was concluded that substituted 8-quinolinols possess a secondary mechanism of antifungal action in addition to chelation.

It was also shown that fungal inhibition was enhanced by placing F meta to Cl in the 5 or 7 positions, and, conversely, antifungal activity was depressed by NO_2 meta to 5-Cl.[2] Thus it appeared that this secondary mechanism of antifungal action can be altered by strategically placed substituents.

The present work is concerned with a study of the 5,7-dihalogenoquinolines. It was of interest to determine whether they would be as inactive as the corresponding 8-methoxyquinolines and to confirm, if possible, the earlier observation that F meta to another halogen atom in the 5 or 7 position of the quinoline ring caused increased antifungal activity.

The preparation of 5,7-difluoro-, 5,7-dichloro-, 5,7-dibromo-, and 5,7-diiodoquinolines was undertaken for this study. Since the 8-nitro and 8-aminoquinolines were easily accessible, they were also prepared and tested for antifungal activity.

The 5,7-dihalogenoquinolines (I) were prepared from 3,5-difluoro-,[4] 3,5-dichloro-,‡ 3,5-dibromo,[5] and 3,5-diiodoanilines,[6] respectively, by the Skraup reaction according to the modification of Palmer.[7] The substituted quinolines were then nitrated to yield the respective 8-nitroquinolines (II). 5,7-Difluoro-8-nitroquinoline (IIb) was prepared from the dichloro analog IIc by treatment with KF in DMF. The dimethoxy analog IIf was similarly prepared from IIc using MeO^- as the nucleophile.[8] The preparation of 5,7-dichloro- (IIIc) and 5,7-dibromo-8-aminoquinolines (IIId) was achieved by the method of Hurdis,[9,§] by using SO_2Cl_2 and Br_2 in AcOH, respectively. The difluoro- (IIIb), diiodo- (IIIe), and dimethoxy-8-aminoquinolines (IIIf)[8] were obtained from the respective 8-nitroquinolines by reduction with $SnCl_2$ and HCl.

The compounds were tested for antifungal activity in shake culture against the spores of 5 fungi, *Aspergillus niger*, *Trichoderma viride*, *Aspergillus oryzae*, *Myrothecium verrucaria*, and *Trichophyton mentagrophytes* by the method of Gershon and Parmegiani.[11] Table I contains a summary of the results.

The antifungal activity of quinoline (Ia), as herein reported, is in fairly good agreement with that of the earlier work,[3] indicating that the assay is reproducible. Thus, it is reasonable to make comparisons of the data obtained during this period of time. The dichloro-, dibromo-, and diiodoquinolines (Ic-Ie) were inactive in this test system, and the results parallel those obtained for the corresponding 8-methoxy derivatives.[2] 5,7-Difluoroquinoline (Ib) is considerably more toxic than the parent compound, quinoline (Ia). This is consistent with the concept expressed previously that F meta to another halogen atom in the quinoline ring enhances fungitoxicity.[3] The antifungal activity of 8-nitroquinoline (IIa) is somewhat greater than that of quinoline (Ia) but, again, the dichloro-, dibromo-, and diiodo-8-nitroquinolines (IIc-IIe), like the corresponding quinolines, are completely inactive under the conditions of these tests. On the other hand, 5,7-difluoro-8-nitroquinoline (IIb) is much more fungitoxic than 5,7-difluoroquinoline (Ib). The reason for this is unclear. The fungitoxicities of IIb and 8-quinolinol[1] are within the same order of magnitude. In the group of 8-aminoquinolines (III), the parent compound, IIIa, showed some toxicity to all 5 organisms. The 5,7-disubstituted derivatives (IIIb-IIIf) were inhibitory to only 3 organisms each, but they were more toxic toward the susceptible organisms than IIIa.

Experimental Section#

5,7-Difluoroquinoline (Ib). A mixt of 3,5-difluoroaniline** (36 g, 0.28 mole), sodium *m*-nitrobenzenesulfonate (63 g, 0.28 mole), glycerol (50 ml), and H_2SO_4 (200 ml, 70% w/w) was heated under reflux for 4 hr. It was then cooled, made alk with 10% NaOH, and steam distd. The dist was extd with Et_2O which was then evapd, leaving a residue of 36 g (78%) of product, mp 76–77.5°. An analytical sample was crystd from pentane, mp 77–78°. *Anal.* ($C_9H_5F_2N$) C, H, F, N.

5,7-Difluoro-8-nitroquinoline (IIb). A soln of 5,7-dichloro-8-nitroquinoline (IIc)[10] (32 g, 0.13 mole) and KF (31 g, 0.53 mole) in DMF (250 ml, distd over P_2O_5) was heated under reflux for 9 hr. The material was poured into 1000 ml of H_2O, and the pptd product was filtered off, washed with H_2O, and dried at 70° overnight. The crude material was sublimed, and 18 g (65%) of compd was obtd, mp 140–144°. An analytical sample was produced after several recrystns from Me_2CO–hexane, mp 142–144°. *Anal.* ($C_9H_4F_2N_2O_2$) C, H, F, N.

8-Amino-5,7-difluoroquinoline (IIIb). To a soln of 77 g (0.34 mole) of $SnCl_2 \cdot 2H_2O$ in a mixt of 100 g of HCl and 100 g of EtOH was added 20 g (0.095 mole) of IIb in small portions with stirring. After completion of addn of the nitro compd, stirring was contd for an addl 0.5 hr. The material was refrigerated overnight, after which the insol product was removed by filtration, slurried in 200 ml of H_2O, and made alk with KOH. After cooling in an ice bath, the amine was obtd by filtration and crystd from aq EtOH: yield, 12.5 g (73%); mp 80–95°. An analytical sample was prepd by several recrystns from hexane: mp 99–101°. *Anal.* ($C_9H_6F_2N_2$) C, H, F, N.

5,7-Diiodoquinoline (Ie). The title compd was prepd in 62% yield from 3,5-diiodoaniline[6] by the method described for the prepn of Ib: mp 133–134° dec (lit.[6] mp 132°). *Anal.* ($C_9H_5I_2N$) C, H, I, N.

5,7-Diiodo-8-nitroquinoline (IIe). Diiodoquinoline (Ie) (29 g, 0.076 mole) was added in small portions with stirring to a mixt of 60 ml of fuming HNO_3 in 60 ml of H_2SO_4. The temp of the reaction was kept between 20 and 25° by means of a water bath. After completion of addn of the quinoline, stirring was contd for an addl 2 hr.

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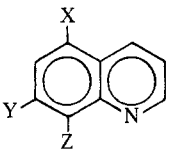
‡Commercially available.

§ The preparation of IIIc and IIId from 8-aminoquinoline was reported by Elderfield and Claflin.[10]

#Melting points were taken in a Mel-Temp melting point apparatus and are uncorrected.

**Prepd in nearly quant yield from 1,3-difluoronitrobenzene by hydrogenation at 3 atm over PtO_2. The NO_2 compd was obtd according to the procedure of Finger, *et al.*[4]

Table I. Minimal Antifungal Activity of Substituted Quinolines (millimoles per liter)



Compd	X	Y	Z	*A. niger* S[a]	*A. niger* C	*T. viride* S	*T. viride* C	*A. oryzae* S	*A. oryzae* C	*M. verrucaria* S	*M. verrucaria* C	*T. mentagrophytes* S	*T. mentagrophytes* C
Ia	H	H	H	7.0	NA[b]	3.9	NA	NA		5.4	NA	2.3	7.8
Ib	F	F	H	4.3	NA	1.8	2.4	NA		3.6	NA	1.8	2.4
Ic	Cl	Cl	H	NA		NA		NA		NA		NA	
Id	Br	Br	H	NA		NA		NA		NA		NA	
Ie	I	I	H	NA		NA		NA		NA		NA	
IIa	H	H	NO_2	4.6	NA	2.2	NA	5.2	NA	NA		2.0	NA
IIb	F	F	NO_2	0.29	NA	0.11	4.6	0.57	NA	0.23	0.29	0.11	0.11
IIc	Cl	Cl	NO_2	NA		NA		NA		NA		NA	
IId	Br	Br	NO_2	NA		NA		NA		NA		NA	
IIe	I	I	NO_2	NA		NA		NA		NA		NA	
IIf	CH_3O	CH_3O	NO_2	NA		NA		NA		NA		NA	
IIIa	H	H	NH_2	6.3	NA	3.8	3.8	NA		4.2	5.2	2.1	3.5
IIIb	F	F	NH_2	NA		1.1	NA	NA		1.1	NA	0.83	NA
IIIc	Cl	Cl	NH_2	NA		0.094	NA	NA		0.094	2.1	0.26	0.28
IIId	Br	Br	NH_2	NA		1.0	NA	NA		2.6	NA	0.33	2.0
IIIe	I	I	NH_2	NA		1.5	NA	NA		NA		0.15	0.25
IIIf	CH_3O	CH_3O	NH_2	NA		1.7	1.7	NA		3.3	3.3	0.11	0.11

[a] S = fungistatic, C = fungicidal. [b] NA = not active below 1000 ppm, highest level tested.

The mixt was poured onto ice, and 31 g (95%) of product was obtd by filtration, washing with H_2O, and drying at 70° overnight: mp 168–171°. An analytical sample was crystd from MeOH–DMF: mp 170–172°. *Anal.* ($C_9H_4I_2N_2O_2$) C, H, I, N.

8-Amino-5,7-diiodoquinoline (IIIe) was prepd in 41% yield from IIe in a manner similar to that for the prepn of IIb: mp 120–132° dec. An analytical sample was prepd by several recrystns from MeOH; mp 143–144° dec. *Anal.* ($C_9H_6I_2N_2$) C, H, I, N.

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Heterocyclic Compounds. 4.† Synthesis and Antiinflammatory Activity of Some Substituted Thienopyrimidones

M. S. Manhas,* S. D. Sharma, and S. G. Amin

Department of Chemistry and Chemical Engineering, Stevens Institute of Technology, Hoboken, New Jersey 07030.

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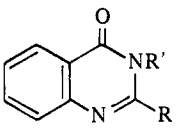
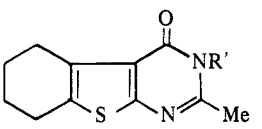
Substituted quinazolines (I) have attracted attention because of their biological activity.[1] This communication describes the preparation of a number of derivatives of 2-methyl-3-aryl-4-oxo-5,6-tetramethylenethieno[2,3-*d*]-pyrimidines (II) which are closely related to I.

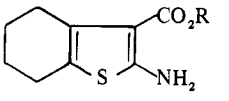


I

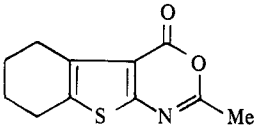


II

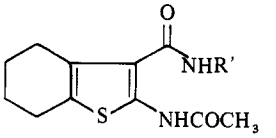
The thienopyrimidones II described here were prepared from 2-amino-3-carbethoxy-4,5-tetramethylenethiophenes (III) which are easily made.[2] Alkaline hydrolysis of III afforded the *o*-aminocarboxylic acid IV in 70% yield. Refluxing IV with Ac_2O provided the lactone V[3] which on heating with equiv proportions of appropriate arylamines gave the 3-aryl substituted pyrimidones of the general structure II (Table I). It was observed that the yields of the



III, R = Et
IV, R = H



V



VI

pyrimidones (II) were good when aniline or a para-substituted aniline was used as the amine component; the ortho- or meta-substituted anilines gave mixtures of the cyclic compounds II and the open chain amides VI.

†Part 3 was submitted for publication.