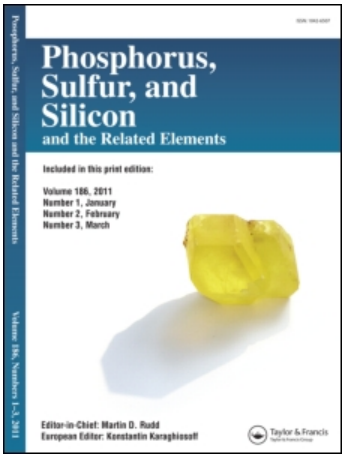

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-MERCAPTO-1H-IMIDAZO[4,5-f]QUINOLINE DERIVATIVES

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-MERCAPTO-1H-IMIDAZO[4,5-f]QUINOLINE DERIVATIVES

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5,6-Diaminoquinoline (Ic) which was prepared from 6-nitroquinoline (Ia) by successive amination and reduction, upon condensation with carbondisulphide in alkaline medium yielded 2-mercapto-1H-imidazo[4,5-f]quinoline (IIa). This on treatment with alkyl, aralkyl and acid halides gave the corresponding thioethers (II b–i) and thioesters (II j,k) respectively. Their structures were established by elemental analysis and spectral data (I.R., P.M.R., ^{13}C N.M.R. and mass). The biological activity of some of the compounds was evaluated.

INTRODUCTION

Various quinoline derivatives exhibit antimalarial activity.[1] Many imidazo[4,5-f]quinoline derivatives are reported to exhibit microsomal,[2] anthelmintic,[3] anti-parasitic, antimicrobial,[4] and antihistaminic activities.[5] A good number of 2-aryl- or 2-mercaptooxazolo[4,5-c]quinoline derivatives have been synthesised in our laboratories, which were evaluated as optical brighteners[6] and microbicidal agents.[7] We wish now to report the synthesis of the hitherto unknown 2-mercapto-1H-imidazo[4,5-f]quinoline derivatives with a view to evaluate their biological activity.

RESULTS AND DISCUSSION

6-Nitroquinoline (Ia) was prepared[8] by the condensation of p-nitroacetanilide with glycerol in the presence of arsenic pentoxide and conc. sulphuric acid. Amination[9] of Ia with hydroxylamine hydrochloride in methanol-KOH afforded 5-amino-6-nitroquinoline (Ib) which was later reduced to 5,6-diaminoquinoline (Ic) using Raney-nickel in the presence of hydrazine hydrate. The reaction of (Ic) with carbondisulphide in methanolic potassium hydroxide gave 2-mercapto-1H-imidazo[4,5-f]quinoline (IIa).

The IR spectrum of IIa shows absorption bands at 3450 – 3100 (broad, NH), 2560 – 2550 (weak, S–H), 1200 (C=S) and 1675 cm^{-1} ($\rangle$C=N) which are assignable to the vibrations of the mercapto imidazole system.

Reaction of (IIa) with various alkyl, aralkyl and acid halides in methanol

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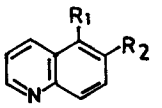

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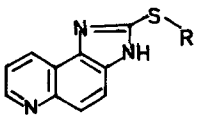


II

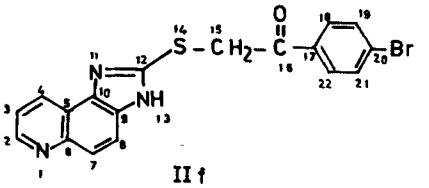
a, $R_1 = H$: $R_2 = NO_2$

b, $R_1 = NH_2$, $R_2 = NO_2$

c, $R_1 = R_2 = NH_2$

a, R = H

b–K, R = alkyl/aralkyl/acyl



II f

containing dimethylformamide under anhydrous conditions[10] yielded the respective thioethers (II b–i) and thioesters (II j,k) (Table I). All compounds (II b–k) show strong IR bands at 1600 ± 10, 1570 ± 10, 1490 ± 10 and $1325 \pm 10\,cm^{-1}$, which are due aromatic ring stretchings. A band around $660–680\,cm^{-1}$ is due to the C—S—C function[11] and additional bands around $1680 \pm 10\,cm^{-1}$ are due to the thiolesters (II j,k). The PMR spectrum of IIf in $CDCl_3$ (chemical shifts in δ-ppm downfield from TMS) displayed a two protons singlet at 5.0 δ assignable to a —S—CH_2— group and a complex multiplet at 7.6–9.25 δ for the NH and nine aromatic protons.

The structure of IIf was further confirmed by a ^{13}C NMR spectrum. The chemical shift values are obtained from a spin decoupled spectrum. By making use of the splitting pattern of the off-resonance spectrum, the values are assigned as shown below: (δ-ppm)

Singlets at 195.35 for C-16; 148.25 for C-6, C-12; 147.42 for C-10; 137.12 for C-9; 131.81 for C-17; 128.39 for C-5; and 125.85 for C-20. Doublets at 150.71 for C-18, C-22; 132.94 for C-2, C-4; 132.39 for C-19, C-21; 125.81 for C-3 and 123.59 for C-7, C-8; and triplet at 41 for C-15. Compared with the reported values of the imidazole system,[12] the chemical shifts of C-9, C-10 and C-12 however, show varying degrees of downfield shifts (~1.2 to 9.3 ppm), which may be attributed to the decreased electron densities at these carbon atoms owing to a fairly strong intramolecular hydrogen bonding between —N—H and carbonyl oxygen.

The mass spectrum of IIf shows peaks at m/z 398 ($M^{+\cdot}$, 29%), 214 (100), 201 (42), 200 (19), 198 (2), 186 (6), 184 (5), 174 (4), 173 (26), 169 (9), 168 (2) and 155 (18).

BIOLOGICAL TESTINGS

Compounds II d, h, k were evaluated against bacteria such as *Bacillus megaterium* (gram positive) and *Proteus vulgaris* (gram negative) by using filter paper disc technique[13] and also against fungi such as *Drechslera spicifera* and *Fusarium*

TABLE I

Characterization data of 2-substituted mercapto-1H-imidazo[4,5-f]quinolines

†Compound	R	m.p. °C	Yield %	Molecular formula	†Found (cal) % N	S
IIa	—H	>300	60	$C_{10}H_7N_3S$	21.00 (20.89)	16.00 (15.92)
IIb	$-CH_2-CH_2-CH_3$	139	40	$C_{13}H_{13}N_3S$	17.3 (17.28)	13.2 (13.16)
IIc	$-(CH_2)_3-CH_3$	135	45	$C_{14}H_{15}N_3S$	16.37 (16.34)	12.47 (12.45)
IId	$-CH_2-\overset{O}{\overset{\|}{C}}-C_6H_5$	104	60	$C_{18}H_{13}N_3OS$	13.19 (13.16)	10.4 (10.04)
IIe	$-CH_2-\overset{O}{\overset{\|}{C}}-C_6H_4-Cl$ (p)	155	57	$C_{18}H_{12}ClN_3OS$	12.00 (11.88)	9.15 (9.05)
IIf	$-CH_2-\overset{O}{\overset{\|}{C}}-C_6H_4Br$ (p)	141	70	$C_{18}H_{12}BrN_3OS$	10.65 (10.55)	8.45 (8.04)
IIg	$-CH_2-\overset{O}{\overset{\|}{C}}-C_6H_4-NO_2$ (p)	150(dec)	63	$C_{18}H_{12}N_4O_3S$	15.4 (15.38)	8.81 (8.79)
IIh	$-CH_2-\overset{O}{\overset{\|}{C}}-C_6H_4-OCH_3$ (p)	206	57	$C_{19}H_{15}N_3O_2S$	12.13 (12.03)	9.2 (9.17)
IIi	$-CH_2-\overset{O}{\overset{\|}{C}}-NH-C_6H_4-CH_3$ (m)	290	55	$C_{19}H_{16}N_4OS$	16.19 (16.09)	9.2 (9.19)
IIj	$-\overset{O}{\overset{\|}{C}}-CH_3$	180	55	$C_{12}H_9N_3OS$	17.3 (17.28)	13.19 (13.16)
IIk	$-\overset{O}{\overset{\|}{C}}-C_6H_5$	104	56	$C_{12}H_{11}N_3OS$	13.8 (13.77)	10.5 (10.49)

† Solvents used for crystallisation were: benzene for IIb to f; methanol for II a, j, k; and ethanol for II g to i.

‡ Satisfactory C and H analyses were obtained for all compounds.

soloni by employing glass slide humid chamber technique.[14] Results of the activity are presented in Table II. Compound IIh showed strong inhibition against *B. megaterium* and IId and h showed moderate inhibition against *P. vulgaris* at the dose level of 600 μg/ml., whereas IId, and IIh showed 100% inhibition, and IIk showed 59.6% inhibition of spore germination in *F. soloni* at the concentration of 600 μg/ml.

TABLE II

Antimicrobial activity of the compounds (II d,h,k)

Compound	Conc. μg/ml	Antibacterial activity†		Antifungal activity‡	
		B. megaterium	*P. vulgaris*	*D. spicifera*	*F. soloni*
IId	400	—	—	35.15	59.25
	600	—	1.0	91.83	100.00
IIh	400	0.5	—	62.76	100.00
	600	3.4	1.0	86.03	100.00
IIk	400	—	—	16.56	26.66
	600	—	0.3	57.41	59.61

† Inihibition zone (in mm).
‡ Spore germination inhibition (percentage).

EXPERIMENTAL PROCEDURE

Melting points are uncorrected. IR spectra in KBr (ν_{max} in cm^{-1}) were scanned on Perkin Elmer Model-137 spectrophotometer. PMR and ^{13}C NMR spectra were run in $CDCl_3$ on a Varian 60 MHz spectrometer operating at 60 MHz and in DMSO-d_6 solvent on XL-100 NMR spectrometer operating at 22.50 MHz respectively and the chemical shifts were recorded in δ-ppm using TMS as an internal standard. The mass spectrum was recorded on a VG-Micro mass 7070H instrument at 70 eV.

5,6-Diaminoquinoline (Ic). Raney nickel (0.5 g) was added to a solution of 5-amino-6-nitroquinoline[9] (Ib) (2 g, 0.01 mole) in methanol (100 ml), followed by dropwise addition of hydrazine hydrate (2 ml). The mixture was refluxed for 1 hour, until the colour changed from yellow to dark green. It was cooled and filtered. The solid which separated upon concentration was recrystallized from ethyl alcohol (yellow needles) (1.2 g; 71% yield) m.p. 148°C. (Found C, 68.1; H, 5.42; N, 26.82%. $C_9H_9N_3$ requires C, 67.9; H, 5.6; N, 26.4%). IR in cm^{-1}. 3410 – 3215 (broad, N–H), 1640 (C=N) and 680, 650 (aromatic).

2-Mercapto-1H-imidazo[4,5-f]quinoline (IIa). A mixture of Ic (0.05 mole), carbondisulphide (30 ml), KOH (0.05 mole), methanol (40 ml) and water (10 ml) was refluxed for 24 hours. It was cooled and acidified with dil. HCl. The separated solid was recrystallized from methanol (yield 60%), m.p. >300°C (Table I).

Reaction of IIa with alkyl, aralkyl and acid halides: General procedure. Compound IIa (0.01 mole) was dissolved in dry methanol (20 ml) containing anhydrous dimethylformamide (20 ml) and appropriate alkyl halides (0.01 mole) or aralkyl halides (0.01 mole) or acid halides (0.01 mole). The reaction mixture was refluxed for 3–4 hours at 80–90°C, then cooled, filtered, dried and recrystallized from a suitable solvent to give the corresponding thioethers (II b–i) and thioesters (II j,k) (Table I) respectively.

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