4-HYDROXYBENZAZOLES: PREPARATION AND ANTIBACTERIAL ACTIVITIES

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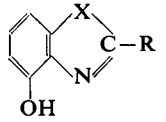
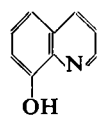
In a previous communication, the preparations and investigation of metal-chelating molecules as potential antibacterial agents were described[1]. As a continuation of these studies, a number of 4-hydroxybenzazoles (I; X = N or O, R = alkyl; X = S; R = NH_2) which may be regarded as analogues of the active, metal-reagent oxine (II), have been prepared and their antibacterial activity examined*.



(I)



(II)

It is known that variation in the alkyl substituent at the 2 position of benziminazole causes only slight variation of the basic strength of the derivatives[2]. Hence a study of the 2-alkyl-4-hydroxybenziminazoles seemed to offer the opportunity of modifying the lipoid solubility of the compounds by altering the size of the alkyl group without an attendant change in the electron donating capacity of the basic nitrogen atom. Such a study is of interest, because a relation between lipoid solubility and activity independent of the degree of metal-chelation is indicated in the "aza-quinolines"[3]. It also seemed reasonable to separately alter the electron availability of the basic nitrogen atom by replacement of the N (1) atom of the 4-hydroxybenziminazoles by O and S atoms by preparing suitably substituted benzoxazoles and benzthiazoles.

Preparation of the compounds. The 2-alkyl derivatives of 4-methoxybenziminazole were prepared by heating the appropriate aliphatic acid with 2:3-diaminoanisole in the presence of 4N hydrochloric acid, according to the general procedure of Phillips[4]. An 85 per cent. yield of the 2-benzyl derivative was obtained by heating together equimolecular proportions of *diamine* and phenylacetic acid, in the presence of 10 per cent. hydrochloric acid in a sealed tube for 40 minutes at 180 to 185° C.[5]

Since iminazole is not reduced in the presence of constant boiling hydriodic acid and red phosphorus[6], this reagent was used to demethylate the 2-alkyl-4-methoxybenziminazoles, by heating at 130 to 140° C. for one hour. The corresponding hydroiodides of the hydroxy derivatives (I; X = NH, R = alkyl) were obtained in yields of 85 to 95 per cent. by this process.

2-Alkyl-4-hydroxybenzoxazoles (I; X = O, R = H, Me, Et, or CH_2Ph)

*During the course of this work, Erlenmeyer and colleagues, *Helv. chim. Acta*, 1952, **35**, 1736, examined 4-hydroxybenziminazole, benzthiazole, and benzoxazole for antibacterial activity.

were prepared by condensing 2-aminoresorcinol hydrochloride with the appropriate acid, amide, or cyanide.

In attempting to prepare 2-amino-4-methoxybenzthiazole by ring closure of *o*-methoxyphenylthiourea with sulphuryl chloride, 2-amino-7-chloro-4-methoxybenzthiazole was obtained.

Experimental

Chemical

Microanalyses were made by Mr. G. S. Crouch, School of Pharmacy, University of London. Equivalent weights, except those of the benzoxazoles, were determined by titration with 0·2 N perchloric acid in acetic acid. It was found that the titration of benzoxazoles and picrates of benziminazoles with perchloric acid was not quantitative under the conditions employed. Details of new compounds are given in Table I.

Preparation of 2-alkyl-4-methoxybenziminazoles. 2:3-Diaminoanisole (5·52 g., 0·04 mole), dissolved in 4 N hydrochloric acid (40 ml.), was refluxed with the appropriate aliphatic acid (0·2 mole) under an atmosphere of nitrogen for 40 minutes. The cooled, neutralised (10 per cent. solution of ammonia) solution was extracted with ethyl acetate. 2-Alkyl-4-methoxybenziminazole derivatives were obtained from the ethyl acetate extract by evaporation of the solvent under reduced pressure. Ether was added to those residues which were not crystalline, and the side of the flask scratched with a glass rod to effect crystallisation.

Demethylation of 2-alkyl-4-methoxybenziminazoles. The methoxy derivative (2 g.) was heated with hydriodic acid (10 ml.) sp. gr. 1·7 and red phosphorus (0·2 g.) for 1 hour at 130 to 140° C. After cooling, the crystallised hydriodide of the corresponding hydroxybenziminazole was filtered off and the free base precipitated with ammonia solution.

Preparation of 2-ethyl- and 2-benzyl-4-hydroxybenzoxazoles. (I; X = O; R = Et or CH_2Ph respectively). 2-Aminoresorcinol hydrochloride (0·02 mole) was heated with either propio- or phenylaceto-nitrile (0·02 mole) in a sealed tube for 1 hour at 180 to 185° C. After cooling, the residues were recrystallised from 50 per cent. aqueous ethanol to give the respective 2-alkyl-4-hydroxybenzoxazoles.

4-Hydroxybenzoxazole. (I; X = O, R = H) was prepared by refluxing 2-aminoresorcinol hydrochloride (3·24 g.) with formic acid (10 ml.) for one hour. After distilling off the excess acid, the residue was sublimed, 200 to 215° C./1·5 mm., and the sublimate recrystallised from 30 per cent. aqueous ethanol.

4-Hydroxy-2-methylbenzoxazole. (I; X = O, R = Me) sublimed on heating a mixture of 2-aminoresorcinol hydrochloride (3·24 g.) and acetamide (1·3 g.) at 120° C./1 mm.

2-Amino-7-chloro-4-methoxybenzthiazole was formed on slowly adding sulphuryl chloride (10·0 g.; 0·075 mole) to a solution of *o*-methoxyphenylthiourea (9·1 g., 0·05 mole) in chlorobenzene (40 ml.), the temperature of which was maintained between 40 to 50° C. The evolution of hydrogen chloride was complete within five minutes, after which time the reaction mixture was cooled and the chlorobenzene decanted

TABLE I

4-HYDROXY- AND 4-METHOXYBENZAZOLES

Compound	M.pt. °C.	Physical form	Found			Formula	Required			Yield per cent.	Equivalent	
			C	H	N		C	H	N		Found	Required
12. 4-Methoxy-2-methylbenziminazole	163	grey-white prisms (*a*)	66·0	6·0	17·3	$C_9H_{10}N_2O$	66·0	6·2	17·3	60	163	162
13. 2-Ethyl-4-methoxybenziminazole	132	grey prisms (*a*)	68·05	6·9	15·9	$C_{10}H_{12}N_2O$	68·2	6·8	15·9	53	176	176
14. 4-Methoxy-2-propylbenziminazole	128	brown prisms (*a*)	68·9	7·2	14·7	$C_{11}H_{14}N_2O$	69·5	7·4	14·8	48	192	190
15. 2-Benzyl-4-methoxybenziminazole	173	grey prisms (*a*)	76·0	5·8	11·8	$C_{14}H_{14}N_2O$	75·6	5·9	11·8	85	239	238
1. 4-Hydroxybenziminazole	194	white prisms (*a*)	62·5	4·50	20·7	$C_7H_6N_2O$	62·75	4·5	20·9	87	135	134
2. 4-Hydroxy-2-methylbenziminazole	211 (decomp.)	white prisms (*a*)	64·2	5·4	19·0	$C_8H_8N_2O$	64·9	5·4	18·9	88	149	148
3. 2-Ethyl-4-hydroxybenziminazole	156	white prisms (*a*)	66·2	5·9	17·2	$C_9H_{10}N_2O$	66·7	6·2	17·3	89	163	162
4. 4-Hydroxy-2-propylbenziminazole	140	grey prisms (*a*)	68·5	6·8	15·9	$C_{10}H_{12}N_2O$	68·2	6·8	15·9	85	174	176
5. 2-Benzyl-4-hydroxybenziminazole	191	silver prisms (*a*)	74·9	5·45	12·55	$C_{14}H_{12}N_2O$	75·0	5·35	12·5	93	222	224
6. 4-Hydroxybenzoxazole	190 (*b*)	silver plates (*c*)	62·7	3·9	10·5	$C_7H_5NO_2$	62·2	3·7	10·4	58		
7. 4-Hydroxy-2-methylbenzoxazole	147·5	white plates (*c*)	64·65	4·8	9·3	$C_8H_7NO_2$	64·45	4·7	9·4	73		
8. 2-Ethyl-4-hydroxybenoxazole	87·5	white plates (*c*)	66·8	5·6	8·7	$C_9H_9NO_2$	66·2	5·5	8·6	65		
9. 2-Benzyl-4-hydroxybenzoxazole	189	grey plates (*c*)	75·0	4·85	6·1	$C_{14}H_{11}NO_2$	74·7	4·9	6·2	75		
10. 2-Amino-7-chloro-4-hydroxybenzthiazole	227	needles (*d*)	41·6	2·6	13·9	$C_7H_5N_2ClOS$	41·9	2·5	13·95	50	201	200·6

(*a*) Solvent, ethyl acetate. (*b*) Lit. m. pt. 181° C[7]. (*c*) Solvent, aqueous ethanol. (*d*) Solvent, ethanol.

All the hydroxy compounds in Table I showed a positive reaction with cupric and ferric ions at a concentration of 0·5 per cent. in 70 per cent. aqueous ethanol. 2-Ethyl-and 2-methyl-4-hydroxybenzoxazoles gave precipitates with 0·05 N silver nitrate in 0·05 N nitric acid solution.

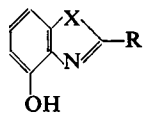
from the viscous residue of benzthiazole hydrochloride. Ether was added and the *hydrochloride* separated by filtration. 2-Amino-7-chloro-4-methoxybenzthiazole, m.pt. 202 to 203° C. (C, 44·8; H, 3·4; N, 12·9. Calc. for $C_8H_8N_2ClOS$: C, 44·8; H, 3·3; N, 13·05 per cent.) and not the expected 2-amino-4-methoxybenzthiazole was obtained on neutralising the hydrochloride with ammonia and recrystallising the base obtained from ethanol. The identity of the isolated compound was proved by a mixed m.pt. and a comparison of its infra-red spectrum with that of a sample of 2-amino-7-chloro-4-methoxybenzthiazole kindly supplied by Professor H. Erlenmeyer[7].

The corresponding hydroxy compound was obtained by demethylating with hydriodic acid as described under hydroxybenziminazoles.

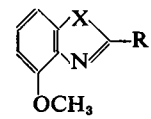
Other materials. 2:3-Diaminoanisole was prepared according to Lane and Williams[8]. 2-Aminoresorcinol, m.pt. 160·5° C. (decomp.), lit. m.pt. 159 to 160° C.[9], was obtained on hydrogenating 2-nitroresorcinol at 5 atm. in the presence of Raney nickel. *o-Methoxyphenylthiourea*, m.pt. 154·5° C., lit. m.pt. 156° C.[10], was prepared by a method similar to the one described for the preparation of *p*-tolylthiourea[11].

TABLE II

ANTIBACTERIAL ACTIVITIES OF 4-HYDROXY- AND 4-METHOXYBENZAZOLES



(III)



(IV)

Cpd. No.	Derivative (III)	M.I.C. in reciprocal molar concentrations against*					
		Staph. aureus	*B. subtilis*	*Bact. coli*	*Proteus vulgaris*	*Sh. sonnei*	*Myco. phlei*
1	X = N; R = H	1600	—	—	6400	—	—
2	X = N; R = Me	—	—	—	1600	—	—
3	X = N; R = Et	—	—	—	3200	—	—
4	X = N; R = Pr^n	—	—	—	3200	—	1600
5	X = N; R = CH_2Ph	—	3200	1600	12,800	1600	6400
6	X = O; R = H	—	—	—	1600	—	
7	X = O; R = Me	—	—	—	—	—	
8	X = O; R = Et	—	—	—	1600	—	
9	X = O; R = CH_2Ph	—	—	—	—	—	
10	X = S; R = NH_2 (7-Chlorine atom)	—	1600	1600	3200	1600	
	(IV)						
11	X = N; R = H	—	—	—	—	—	
12	X = N; R = Me	—	—	—	1600	—	
13	X = N; R = Et	—	—	—	1600	—	
14	X = N; R = Pr^n	—	—	—	1600	—	
15	X = N; R = CH_2Ph	—	—	—	1600	—	
16	X = S; R = NH_2 (7-Chlorine atom)	—	—	1600	3200	—	

— Signifies growth at M/1600.

* All these compounds are inactive at M/1600 concentration against *Str. pyogenes*.

Bacteriology

Minimum inhibitory concentrations of the compounds described were determined in a similar manner to that used previously[1]. The results are summarised in Table II.

Despite the metal chelating properties of the compounds, the low order of their antibacterial properties precludes any attempted correlation of chelation and antibacterial action in the present series.

Summary

1. 2-Alkyl-4-hydroxybenzazoles have been prepared as potential antibacterial agents acting through the chelation of metal ions.

2. All the 4-hydroxybenzazoles listed show chelation phenomena with cupric and ferric ions: 2-ethyl- and 2-methyl-4-hydroxybenzoxazole precipitate silver ions in dilute acid solution.

3. None of the compounds prepared possessed significant antibacterial activity.

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