

and will serve to illustrate the use of the model. The axial plane is (010), $2V$ is $48^\circ (+)$, and X is almost normal to (001), so that sections parallel to this face give a nearly centred obtuse bisectrix figure, as is immediately apparent from the model. The emergence of the optic axes, and thus the type of interference figure, on a {110} face may be made out very clearly by shifting the framework (while preserving the correct orientation with the aid of the squares marked on the baseboard) so that the axes project through the face. The extinction directions on the face may be determined by means of the sighting protractor G . This consists of a thin glass plate marked with two double arrows at right angles, and thinner radial lines at intervals of 10° . At the centre of the plate and at right angles to it is cemented a short length of thin brass tubing. The model is supported on the floor by means of a stand and clamp, with the face in question horizontal and uppermost. A thick sheet of mica is laid across the face, and on top of this is placed the protractor, which is then moved until, on looking from above, the origin of the indicatrix axes is seen to be in line with the axis of the brass tube and the double arrows bisect the projected angles between the optic axes. By the law of Biot and Fresnel the arrows then represent the extinction directions on the face. With a carefully constructed model this method gives the correct extinction angle to within about 5° . A rougher but more convenient method is simply to view the optic axes through the face, along a direction normal to it as nearly as can be judged, and find the positions at which a rod laid across the face bisects the projected angles between these axes.

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Mode of Action of Acridine Antibacterials

Two years ago, it was shown¹ that, in a series of 107 acridines, marked antibacterial activity was, for

opened up a fruitful field of investigation, with the result that antibacterial properties ascribable to this metal-chelating effect have been demonstrated in several other heterocyclic series that bear a hydroxyl-group *ana* to a ring-nitrogen².

The enhanced activity of 5-amino-1-hydroxy-acridine is a further example of this phenomenon, but two of its isomerides seemed to form exceptions to the cationic rule. Using an approximate correction to derive the pK_a value in water from the pK_a value as determined in 50 per cent alcohol, it appeared that 5-amino-2-(and -3-)hydroxyacridines were sufficiently well ionized (71 and 98 per cent respectively) to command a greater antibacterial activity than was actually found. Re-examination of all four hydroxy derivatives of 5-aminoacridine has shown, rather surprisingly, that they produce a high proportion of zwitterions at pH 7.3, an effect not previously reported for simple phenolic amines. The use of a Hilger absorptiometer has permitted determination of the pK_a values directly in water³, thus dispensing with the correction which is inapplicable when zwitterionic species are present. The corrected figures are given in the accompanying table (Nos. 22-25; the numbering of the previous paper¹ is retained for ease of reference). It is seen that the new values fall into line with those obtained from the other acridines and add further support to the correlations already found.

The synthesis of 1:5- and 4:5-diaminoacridines (Nos. 2a and 4a) completes the set of amino-derivatives of the important antibacterial, 5-aminoacridine. These showed antibacterial activity of the intensity expected from their high degree of ionization.

The inclusion of 2-dimethylaminoacridine (47a) provides the first tertiary mono-aminoacridine for the series. The lowered response to Gram-negative organisms (compared with the corresponding primary amine) forms the third example of such an effect in this series (the others being 2:8-bisdimethylaminoacridine and 2-dimethylamino-7-aminoacridine). This suggests that hydrogen bonding may make a contribution to the action of the primary amines on these bacteria.

No.	-acridine	Highest dilution completely inhibiting growth after 48 hr. at 37° C. (Medium: 10 per cent serum broth, pH 7.3)					Sum of inhibitory indices	pK_a in water at 20° C.	Per cent ionized as cation at pH 7.3
		<i>Cl. welchii</i>	<i>Strept. pyog.</i>	<i>Staph. aur.</i>	<i>B. coli</i>	<i>Proteus</i>			
2a	1:5-Diamino-	5	5	4	4	4	22	9.3	99
4a	4:5-Diamino-	5	5	3	3	2	18	11.0	100
22	5-Amino-1-hydroxy-	5	5	3	3	3	19	7.1	39
23	5-Amino-2-hydroxy-	2	4	0	0	0	6	6.6	17
24	5-Amino-3-hydroxy-	4	6	2	0	0	12	7.7	72
25	5-Amino-4-hydroxy-	3	3	1	0	0	7	5.6	2
47a	2-Dimethyl-amino-	5	5	3	2	0	15	8.3	91

Key to dilutions: 0 signifies growth at 1:5,000; 1 signifies inhibition at 1:5,000; 2 signifies inhibition at 1:10,000; 3 signifies inhibition at 1:20,000; 4 signifies inhibition at 1:40,000; 5 signifies inhibition at 1:80,000; 6 signifies inhibition at 1:160,000.

the most part, confined to those substances which exist mainly in the form of cation at pH 7.3. Apparent exceptions to this rule have since been examined more closely and some important gaps in the series closed.

1-Hydroxyacridine, which possesses antibacterial activity greatly in excess of what could be predicted from its feeble ionization, has been shown to owe this biological effect to an entirely different chemical property, namely, to its ability to combine with metabolically important trace metals. This has

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¹ Albert, Rubbo, Goldacre, Davey and Stone, *Brit. J. Exp. Path.*, **26**, 160 (1945).

² Albert, Rubbo, Goldacre and Balfour, *Brit. J. Exp. Path.*, **28**, 69 (1947).

³ Albert and Goldacre, *J. Chem. Soc.*, 706 (1946).