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The antiseptic action of ethoxyquinolin, chitenin and H-acid.

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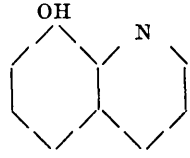
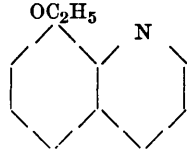
In 1911 Morgenroth and his collaborators[1] found that when hydrocuprein, a quinine derivative, was changed to ethyl hydrocuprein the substance acquired specific pneumococcicidal powers, both in vitro and in vivo. However, many clinicians have found that in the treatment of lobar pneumonia ethyl hydrocuprein is too toxic and that changes in the optic nerve and sometimes permanent blindness may result from its use.

Two years ago Pankow and Hirschfelder[2] investigated two parallel series of simple aromatic substances, hydroxy compounds and the corresponding ethoxy compounds, in order to determine whether in these simple compounds also, the introduction of an ethoxy group would yield increased pneumococcicidal action. The experiments showed, however, that this is not the case. In the series reported in this paper we have tested the action of 8-oxyquinolin sulphate



and 8-ethoxyquinolin sulphate



* This research has been performed with the aid of funds from the research fund granted the Graduate School by the Board of Regents of the University of Minnesota.

1 Morgenroth, J., and collaborators, *Berl. Klin.* 1911, lxxi, 501; *Ibid. Ztschr. f. Immunitatsforchung, etc.*, 1912, xv, 610; 1920, xxix, 217.

2 Hirschfelder, A. D., and Pankow, L. J., PROC. SOC. EXPER. BIOL. AND MED., *N. Y.*, 1922, xix, 64.

A few loopfuls of pneumococcus suspension were added to the solution of the substance in 0.9 per cent. NaCl, and after the desired interval transpired to rabbit blood agar plates and incubated 24 hours. We find that, like the aromatic compounds, there is practically no difference in the action of the two compounds upon the pneumococcus. A ten-minute exposure to 1/5000 solution in 0.9 NaCl kills the cocci. The streptococcus is less sensitive requiring a 1/1000 solution, but no difference is observable between the two compounds.

An attempt was made to produce a quinine derivative having a toxicitiy less than quinine. Chitenin, which differs from quinine in having a —COOH group in place of the vinyl —CH=CH_2 group in the side chain was prepared by oxidizing quinine according to the method of Skraup.[3] We have found that this substance is from three to four times less toxic than quinine on subcutaneous injection (minimum lethal dose of Chitenin=2.2^G to 4.2^G per Kg. rat; minimum lethal dose of quinine=0.7^G per Kg. rat).

The antiseptic actions of ethylhydrocuprein, quinine and Chitenin are shown in the following table:

TABLE

+ = growth
— = no growth

Pneumococcus (3 separate tests made)

Ethylhydrocuprein, HCL.....	1/10,000	sol. 5 min.	—	10 min.	—	1/5000	sol. 5 min.	—		
			—		—			—		
Quinine, HCL.....	1/1000	sol. 5 min.	—	10 min.	—	1/500	sol. 5 min.	—		
			+		—			—		
Chitenin, HCL.....	1/200	sol. 5 min.	+	10 min.	+	1%	sol. 5 min.	+		
			+		—			—		
		10 min.	+							
			—							
Chitenin, Na salt.....	1/500	sol. 10 min.	+	30 min.	+					
			+		—					
H acid.....	1/500	sol. 5 min.	—;	1/1000	30 min.	+	(24 hrs.	—)		
			—							

Streptococcus

Ethylhydrocuprein, HCL.....	1/1000	5 min.	—	10 min.	—	1/2000	5 min.	+		
			+		—;			+		
			++		—			+		
		10 min.	+	1/5000	10 min.	++				
			+;			+—				
			—			+				

[3] Skraup, Zd., *Annalen der Chemie*, 1879, cxcix, 344.

Quinine, HCL..... 1% 5 min. $\begin{matrix}-\\+\\+\end{matrix}$ 10 min. $\begin{matrix}-\\-\\-\end{matrix}$; $\frac{1}{1000}$ 10 min. $\begin{matrix}+\\+\\+\end{matrix}$ 30 min. $\begin{matrix}-\\-\\-\end{matrix}$

Chitenin, HCL..... 1% 5 min. $\begin{matrix}+\\+\\-\end{matrix}$ 10 min. $\begin{matrix}-\\-\\-\end{matrix}$; $\frac{1}{1000}$ 5 min. $\begin{matrix}+\\+\\+\end{matrix}$ 10 min. $\begin{matrix}?\\+\\+\end{matrix}$ 30 min. $\begin{matrix}-\\-\\-\end{matrix}$

Chitenin, Na salt..... $\frac{1}{500}$ 10 min. + 30 min. +

H acid..... $\frac{1}{200}$ 30 min. + (24 hrs. —; $\frac{1}{1000}$ 24 hrs. +)

Staphylococcus

Quinine, HCL..... $\frac{1}{200}$ 5 min. +, 10 min. —; $\frac{1}{1000}$ 30 min. +

Chitenin, HCL..... $\frac{1}{50}$ 5 min. +, 10 min.?, 30 min. —

H acid..... $\frac{1}{200}$ 5 min. —; $\frac{1}{500}$ 5 min. +, 10 min. —

Bacillus Coli

Quinine, HCL..... 1% 5 min. —; $\frac{1}{200}$ 5 min. +, 10 min. —; $\frac{1}{500}$ 30 min. +

Chitenin, HCL..... 2% 5 min. +; 10 min. +, 30 min. —; $\frac{1}{200}$ 30 min. +

Bacillus Typhosus

H acid..... $\frac{1}{200}$ 30 min. $\begin{matrix}+\\+\end{matrix}$

Quinine, HCL..... $\frac{1}{200}$ 5 min. —; $\frac{1}{500}$ 5 min. +

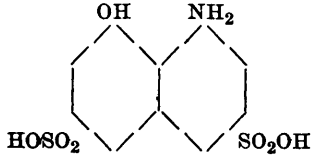
Chitenin, HCL..... 2% 10 min. +, 30 min. —; 1% 30 min. +

H acid..... $\frac{1}{200}$ 10 min. +, 30 min. —; $\frac{1}{500}$ 30 min. +

In these studies it is evident that the Gran staining cocci are more sensitive to the acid chitenin than are the negatively staining bacilli, coli and typhosus. This fact is in striking contrast to the results which Churchman[4] has obtained with the basic and the acid anilin dyes in which the Gram staining organisms are

more sensitive to the basic dyes than to the acid dyes, but the Gram negative bacili are more sensitive to the acid dyes.

In order to study this questions further we have tested the antiseptic action of H acid (aminonaphthol disulphonic acid),



an acid which is present in both trypan blue and the new trypanosome remedy (Baeyer 205[5])* The results are shown in the table above.

It is evident that the Gram positive cocci tested here are more sensitive to H acid than are the Gram negative bacilli, and therefore that Churchman's findings cannot be regarded as evidence of an entirely general rule.

197 (2157)

The synthesis and excretion of hippuric acid: The glycine factor.

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The rate of synthesis and excretion of hippuric acid in normal individuals and those with various renal disorder has already been studied by Kingsbury and Swanson[1] and this study made the basis of renal function test. In this work 2.4 grams of sodium benzoate was the dosage regardless of the size or weight of the individual. In the present paper the original work has

[4] Churchman, J., *Jour. Exper. Med.*, 1913, xvii, 373; PROC. SOC. EXPER. BIOL. AND MED., 1922, xix, 288-31.

* A sample of pure H acid was kindly prepared for us by Drs. Derick and Strachan, of the laboratories of the National Aniline Company, and the bacterial cultures were furnished by Dr. J. F. Noble, to whom we extend our sincere thanks.

[5] Bayer 205, *Science*, 1922, lvi, 514.

[1] Kingsbury, F. B., and Swanson, W. W., *J. Biol. Chem.*, 1921, xlv, 4; *Arch. Int. Med.*, 1921, xxviii, 220.