III. THE BACTERICIDAL ACTION OF TELLURIUM DERIVATIVES OF CERTAIN ALIPHATIC β -DIKETONES.

BY GILBERT THOMAS MORGAN, EVELYN ASHLEY COOPER
AND ARNOLD WIGHAM BURTT.

From the Chemical Department, University of Birmingham, Edgbaston.

(Received December 22nd, 1922.)

IN a previous paper [Morgan, Drew and Cooper, 1922] attention was drawn to the powerful inhibitory effect of the tellurium derivatives of aliphatic β -diketones upon the growth of *B. coli communis*. Attempts made to estimate the phenol coefficients of these substances in the ordinary way showed that on sub-culturing the broth tubes into fresh broth growths occurred, indicating that the bacilli had not been necessarily destroyed by the short exposures, e.g. 30 minutes, to solutions of the tellurium compounds. The phenol coefficients could not therefore be estimated accurately, but indirect evidence was obtained of a strong inhibitory action, and it was calculated that in the case of tellurium propionylacetone the inhibitory effect would be appreciable even in a concentration of 1 in 5,000,000.

These tellurium compounds would, therefore, be classified in the usual way as growth-inhibitors, rather than as disinfectants, but it is probably more correct to regard them as substances which possess the remarkable property of slowly exerting a marked germicidal action in extremely low concentration, and in this respect they differ fundamentally from phenols and other substances which are only active in much higher concentration.

Further experimental work has since been carried out with the following objects in view:

1. To ascertain the influence of chemical constitution on the germicidal power of these tellurium derivatives, with the object of obtaining substances of definite chemical structure fulfilling the requirements of high germicidal power, and minimum toxicity to higher animals.
2. To investigate the specific action of tellurium compounds on different micro-organisms.

For this work the usual method of determining phenol coefficients has been superseded by the following process, in which a comparative basis has been introduced as an essential condition of the inhibitory method.

Experimental method.

To constant volumes (8 cc.) of Lemco-peptone broth (acidity = + 7E) varying volumes of sterile distilled water were added, so that on the subsequent addition of requisite amounts of the tellurium β -diketone solutions, the total volume would in each case be 10 cc. Before the addition of the germicidal substance, however, one drop¹ of a 24 hours' culture of the test-organism was added to each tube. After thoroughly mixing, the disinfecting solutions were added, and after repeated mixing the tubes were incubated at 37° for 48 hours. In this way a definite number of organisms were subjected to the action of the various concentrations of germicide for a definite period in the presence of a sufficient food supply. For each experiment a series of phenol control-tubes was set up in a similar way and at the end of 48 hours the phenol coefficients could thus be calculated.

This method of experiment conforms more closely with actual conditions and is thus of more practical value than the ordinary phenol coefficient test in investigating the action of germicides of possible use for internal application, inasmuch as the disinfectant is allowed to act slowly over a considerable period at body temperature and in the presence of organic matter.

It should be pointed out that if the culture tubes were subcultured into fresh broth, no growths occurred on subsequent incubation. This result demonstrates that in these experiments the tellurium compounds were really exerting a bactericidal action, and were not only growth-inhibitors.

The phenol coefficients have previously been expressed in terms of concentrations of *grams per cc.* We consider it, however, more accurate to calculate the results in terms of molecular weights, and our results are therefore set forth as equimolecular phenol coefficients, *i.e.*

$$\text{phenol coefficients} \times \frac{\text{molecular weight of substance tested}}{\text{molecular weight of phenol}}.$$

In certain cases considerably different results are obtained.

The β -diketones employed in producing the tellurium compounds are acetylacetone and its homologues with the substituted alkyl group attached either to a terminal carbon atom or to the central one (position 3) as shown by the following formulae:

The general structures of the corresponding types of tellurium derivatives are to be represented as follows:

¹ We have employed smaller and also larger numbers of organisms in different experiments, but the results are not appreciably affected by variation in numbers.

For convenience of terminology these substances are referred to in the following table as derivatives of methane.

The organism employed in the experiments was *B. coli communis*, and it was found that while the resistance to phenol was remarkably constant, that of the same organism to the tellurium compounds varied considerably. For this reason the results in column II in the following table are expressed as ranges of concentration through which the substances were found to be bactericidal, while in column III a characteristic mean concentration is set forth. For convenience the concentrations are expressed in grams per cc. but in column IV the phenol coefficients are "equimolecular" coefficients and represent accurately the relative germicidal powers of the substances examined.

Table I.

	Substance	Range of minimum concentration bactericidal to <i>B. coli</i>	Mean bactericidal concentrations	"Equimolecular" phenol coefficients
1.	Tellurium diacetylmethane	1 in 270,000– 750,000 (4) ¹	1 in 500,000	2,800
2.	" 3-methyldiacetylmethane	1 in 550,000– 1,000,000 (4)	1 in 900,000	4,000
3.	" 3-ethyldiacetylmethane	1 in 1,250,000– 3,500,000 (6)	1 in 2,500,000	13,000
4.	" acetylpropionylmethane	1 in 1,000,000– 5,500,000 (5)	1 in 3,000,000	14,000
5.	" dipropionylmethane	1 in 7,000,000–10,000,000 (6)	1 in 9,000,000	45,000
6.	" acetylbutyrylmethane	1 in 1,000,000– 5,500,000 (10)	1 in 3,000,000	15,000
7.	" propionylbutyrylmethane	1 in 1,500,000– 4,500,000 (4)	1 in 2,800,000	14,000
8.	Phenol	1 in 510– 590	1 in 550	—

¹ The figures in brackets indicate the number of tests.

A consideration of the tabulated results shows that these tellurium compounds possess an extraordinarily high bactericidal power. The equimolecular phenol coefficients for the different members of the series range from 2,800 to 45,000 even in the presence of organic matter, the most active member being tellurium dipropionylmethane, which is bactericidal in a dilution of 1 in 9,000,000.

The bactericidal action increases considerably as the homologous series is ascended, until with a third substitution of the methyl group (as in tellurium propionylbutyrylmethane) a limit is reached and there is even a diminution in germicidal activity.

The efficacy of the compounds is furthermore influenced by the chemical structure of the β -diketone, position isomerism playing a very important part in determining bactericidal power. Thus, tellurium acetylpropionylmethane and tellurium 3-methyldiacetylmethane are isomeric, the methyl group in the former being attached to a terminal carbon atom, in the latter to the central atom, in position 3. Tellurium dipropionylmethane and tellurium 3-ethyldiacetylmethane form a similar pair of isomerides. In each case it is seen that a terminal substitution of methyl group enhances bactericidal power to a very much greater extent than when substitution is effected centrally.

Again, tellurium dipropionylmethane, tellurium acetylbutyrylmethane and

tellurium 3-ethyldiacetylmethane are all three isomeric, the chemical constitution of the three β -diketones from which they are derived being respectively

The results set forth in Table I show that the tellurium compound of the symmetrical β -diketone (1) is much more efficacious than that of the dissymmetrical isomeride (2), which in turn is somewhat more active than the third isomeride, where substitution has been effected entirely in the central position.

Results of much the same order have been obtained with a different strain of *B. coli*.

A few experiments with the following organisms have also been carried out: (1) *B. paratyphosus* A and B; *B. typhosus*; (2) *Streptococcus haemolyticus*, *Staphylococcus pyrogenes aureus*, and the results so far indicate that the foregoing tellurium compounds exert a selective action on coliform organisms, the cocci on the other hand being much more resistant. In this respect the substances resemble benzoquinone [Cooper, 1912; Morgan and Cooper, 1921] and telluric acid [Joachimoglu, 1922] which has been found by the latter to be selectively inhibitory to coliform organisms in a concentration of 1 in 40,000.

The authors are extending the investigations to other pathogenic organisms including the acid-fast group, and, with the object of ascertaining whether these tellurium compounds can be employed for the purpose of inner disinfection, experiments are shortly being carried out to determine their toxicity to higher animals.

The authors desire to express their thanks to the Advisory Council of the Department of Scientific and Industrial Research for grants which have helped to defray the expenses of this investigation.

REFERENCES.

- Cooper (1912). *Brit. Med. J.* June 1, 8, 15.
 Joachimoglu (1922). *Z. Urol.* 16, 97.
 Morgan and Cooper (1921). *Biochem. J.* 15, 587.
 Morgan, Drew and Cooper (1922). *J. Chem. Soc.* 121, 922.