XXIX. BACTERICIDAL ACTION OF THE TELLURIUM DERIVATIVES OF ALIPHATIC β -DIKETONES. PART II.

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ALTHOUGH the β -diketones are feeble germicides [Morgan and Cooper, 1921], their tellurium derivatives recently discovered by Morgan, Drew and their co-workers [1920, 1922] contain this metalloid in the unsaturated bivalent condition and are accordingly likely to exhibit stronger germicidal action in view of the circumstance that the more saturated telluric acid is known to possess antiseptic properties. Preliminary experiments on four of the tellurium derivatives by the Chick-Martin test revealed high phenol coefficients, but it was found that further growths occurred on subculturing the broth tubes into fresh broth. It was accordingly suggested that these compounds were not true germicides, but rather growth inhibitors, and it was calculated that tellurium propionylacetone would exert a definite inhibitory effect in a concentration of 1 in 5,000,000.

In a subsequent paper [Morgan, Cooper and Burtt, 1923] the inhibitory method showed that these compounds were inhibitors to micro-organisms in remarkably low concentrations, for instance, tellurium dipropionylmethane in 1 in 10,000,000 to 1 in 40,000,000. An examination of several compounds of this type indicated that the bactericidal power increased considerably as the homologous series was ascended, until with a second substitution of methyl the maximum efficacy was attained, and beyond this limit there was a diminution in germicidal power. Moreover, it was noticed that the chemical structure of the parent β -diketone influenced bactericidal power, and that position isomerism was also an important controlling factor.

Many other compounds of this type have since been prepared and examined especially with the view of ascertaining whether they are suitable for purposes of inner disinfection.

EXPERIMENTAL METHOD.

Preliminary experiments showed that the Chick-Martin test was unsuited to the examination of these compounds and in the present work the inhibitory test was used exclusively. The method has been described and discussed in a previous paper [1923], the inhibitory action of the tellurium compounds being such that growths frequently became apparent on the second day only and the tubes were generally incubated for three days or more. Tubes free

from visible growth at the end of an experiment have been subcultured into fresh broth, but in no instance has further growth occurred. It is evident, therefore, that while these compounds belong to the "inhibitor" class they are nevertheless true germicides, differing from those of the phenol type only in that they act very slowly and in exceedingly low concentration. Since some of the compounds examined were of doubtful stability, freshly made solutions were always employed and the substances dissolved in water without undue heating. Lemco-peptone broth (acidity +7E) was used as a standard medium, but for special experiments urine and blood serum were also employed.

Tables II and III and particularly IV show wide variations in resistance of the various organisms to the tellurium diketones. The concentration of phenol necessary to destroy a given organism generally varied but little; often the range was within $\pm 5\%$ of the mean bactericidal concentration. The resistance of the organisms to the tellurium compounds, on the contrary, showed wide variations, an extreme case of this being that of *B. typhosus* ii (Table II) with which the bactericidal concentration of tellurium dipropionylmethane varied from 1 in 5,000,000 to 1 in 40,000,000. In investigating the bactericidal action of these compounds many tests must therefore be made and the substances examined as far as possible at the same time and under the same conditions. Accordingly the tabulated data are the mean results which have been obtained from several experiments.

BACTERICIDAL ACTION ON *B. COLI COMMUNIS* IN BROTH.

For the purposes of ascertaining the most efficient germicides, and for elucidating general principles of structure, two strains (i and ii) of *B. coli communis* were employed as the test organism. Whenever a strict comparison between the bactericidal powers of two or more substances was required, the tests were carried out on the same day, with the same broth culture of the organism. Such comparisons were found to hold consistently whenever both substances acted on the same culture, even though the actual values obtained varied widely from one experiment to another. In all some sixteen compounds were tested with *B. coli communis* in broth and the results are given in Table I.

Table I. *Bactericidal action on B. coli communis in broth.*

	Tellurium β -diketone	Mean bactericidal concentration	Equimolecular phenol coefficient
1.	Tellurium acetylacetone	1 in 500,000	2,300
2.	" 3-methylacetylacetone	1 in 900,000	4,300
3.	" 3-ethylacetylacetone	1 in 2,500,000	12,700
4.	" 3- <i>n</i> -butylacetylacetone	1 in 2,800,000	14,500
5.	" 3-methylpropionylacetone	1 in 5,000,000	25,400
6.	" 3-ethylpropionylacetone	1 in 2,000,000	10,700
7.	" dipropionylethylmethane	1 in 2,800,000	14,500
8.	" propionylacetone	1 in 3,000,000	14,400
9.	" <i>n</i> -butyrylacetone	1 in 3,000,000	15,200
10.	" <i>n</i> -valerylacetone	1 in 1,200,000	6,400
11.	" <i>n</i> -hexoylacetone	1 in 700,000	3,900
12.	" <i>n</i> -heptoylacetone	1 in 500,000	2,900
13.	" dipropionylmethane	1 in 9,000,000	45,800
14.	" propionyl- <i>n</i> -butyrylmethane	1 in 3,000,000	16,000
15.	" di- <i>n</i> -butyrylmethane	1 in 5,000,000	27,000
16.	" 3 : 3-diethylacetylacetone	1 in 900,000	5,100

From an examination of Table I a certain amount of data as to the effect of chemical structure on the bactericidal action of tellurium compounds on *B. coli communis* may be derived.

Homologous series. (a) Tellurium compounds derived from the diketones $R \cdot CH_2 \cdot CO \cdot CH_2 \cdot CO \cdot CH_3$ furnish the best example of homologous series, rising from tellurium acetylacetone to tellurium *n*-heptoylacetone (Nos. 1, 8, 9, 10, 11, 12). These substances have the general formula I, where $R = H$

in the parent compound and $R = C_5H_{11}$ in tellurium *n*-heptoylacetone. The equimolecular germicidal power rises rapidly from initial member (1) to the next (8), there is a slight increase in power on the part of (9), and then the germicidal power of the next three homologues diminishes steadily, (12) having nearly the same activity as (1). In this series the bactericidal power reaches a limit when $R = C_2H_5$, in tellurium *n*-butyrylacetone.

(b) Tellurium compounds derived from the diketones

have the general formula II:

(1) When $R = R'$, the initial member (1) has a weak bactericidal power, but an enormous increase in power follows the substitution of two methyl groups to give tellurium dipropionylmethane (13). This substance has easily the highest germicidal power of the tellurium compounds yet studied. The conversion of R and R' into ethyl radicles in (15) results in a considerable diminution in efficacy.

(2) When R is greater than R' by one methylene group, as exemplified by (8) and (14), the higher homologue is slightly more powerful than the lower.

(c) Tellurium compounds derived from the diketones

have the general formula III and are represented by compounds (1), (2), (3) and (4), in which R rises from H to C_4H_9 . There is a steady rise in germicidal

power as the series is ascended up to tellurium 3-ethylacetylacetone but the 3-*n*-butyl compound has only bactericidal value of the same order as the former substance.

(d) Tellurium compounds derived from diketones

having the formula IV, show a decrease in germicidal power as the homologous series rises from (5) to (6)—R = CH₃ and C₂H₅ respectively—which is a marked contrast to series (c) and evidently the result of the change from acetylacetone to propionylacetone as the starting-point.

Function of Alkyl Groups.

A consideration of the diverse effects on bactericidal power obtained by using members of various homologous series leads to the following conclusion. The conversion of tellurium acetylacetone into tellurium propionylacetone, resulting in the formation of an ethyl group, corresponds with a considerable rise in bactericidal power. The subsequent introduction of one methyl group in any of three possible positions causes a further rise in germicidal efficacy. Any further substitution of alkyl then causes a diminution in bactericidal power.

This generalisation is shown clearly by the following comparisons:

		Equimolecular phenol coefficient
1.	Tellurium propionylacetone	14,400
	„ 3-methylpropionylacetone	25,400
	„ 3-ethylpropionylacetone	10,700
2.	„ propionylacetone	14,400
	„ <i>n</i> -butyrylacetone	15,200
	„ <i>n</i> -valerylacetone	6,400
3.	„ propionylacetone	14,400
	„ dipropionylmethane	45,800
	„ propionyl- <i>n</i> -butyrylmethane	16,000

The accumulation of alkyl groups thus causes a rise in bactericidal activity, followed by a diminution, the maximum effect being caused by the formation of the ethyl group enhanced by the further addition of one methyl group. The effect of accumulation of alkyl groups upon physiological action is of interest in this connection. Generally speaking, the intensity of action increases steadily as the homologous series is ascended, but examples are to be found in which a limit is reached, in much the same way as with the bactericidal action of the tellurium diketones. Similar constitutive effects have been observed in the veronal group of drugs where the maximum effect is reached at the propyl derivative (proponal).

Isomerism.

The change in bactericidal power of a tellurium compound induced by introducing an alkyl group varies considerably according to the orientation of this substituent. These tellurium derivatives fall into three main groups, those in which substitution in the parent acetylacetone is

- symmetric, as in formula R·CH₂·CO·CH₂·CO·CH₂R;
- dissymmetric, as in formula R·CH₂·CO·CH₂·CO·CH₂R';
- central, as in formula R·CH₂·CO·CHR''·CO·CH₂·R'.

The following are representative cases of isomerism, the figures in brackets being the equimolecular phenol coefficients of the substances.

	Symmetric	Dissymmetric	Central
1.	—	Tellurium propionylacetone (14,400)	Tellurium 3-methylacetylacetone (4,300)
2.	Tellurium dipropionylmethane (45,800)	Tellurium <i>n</i> -butyrylacetone (15,200)	Tellurium 3-ethylacetylacetone (12,700) Tellurium 3-methylpropionylacetone (25,400)
3.	—	Tellurium <i>n</i> -valerylacetone (6,400) Tellurium propionyl- <i>n</i> -butyrylmethane (16,000)	Tellurium 3-ethylpropionylacetone (10,700) —
4.	Tellurium di- <i>n</i> -butyrylmethane (27,000)	Tellurium <i>n</i> -hexoylacetone (3,900)	Tellurium dipropionylethylmethane (14,500) Tellurium 3- <i>n</i> -butylacetylacetone (14,500)

In each case it is evident that symmetric substitution is more effective than any other type and that in general those tellurium compounds of which the parent diketones show the nearest approach to terminal symmetry are the most potent germicides. For instance, tellurium propionyl-*n*-butyrylmethane is more powerful than tellurium *n*-valerylacetone. The introduction of a single alkyl group into the terminal position is generally associated with greater germicidal power than the introduction of the same group into the central 3 position, except in the case of more dissymmetric derivatives.

Substitution by two separate methyl groups is more valuable than substitution by one ethyl group, since this leads to a nearer approach to symmetric terminal substitution (see example 2).

Consideration of the effects of homologous series and isomerism on the germicidal power of tellurium diketone derivatives shows that there are two main conditions necessary for high germicidal power. These are (1) the formation of an ethyl group followed by the further introduction of a methyl group in the para-position; (2) symmetric terminal substitution of the parent diketone. Tellurium dipropionylmethane (formula V), which is derived from the diketone $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}_3$, alone fulfils both these conditions and this is probably the explanation of its outstanding bactericidal power.

BACTERICIDAL ACTION WITH ORGANISMS OTHER THAN *B. COLI COMMUNIS*.

Broth inhibitory tests were carried out on various tellurium compounds with *B. typhosus* and with *Staphylococcus pyogenes aureus*. Two strains of *B. typhosus* were employed, strain (i) being a somewhat old culture, and (ii) a more recently isolated strain. The germicidal values obtained are given in Table II.

Table II. *Bactericidal action of tellurium β -diketones on B. typhosus i.*

Tellurium β -diketone	Mean bactericidal concentration	Equimolecular phenol coefficient
Tellurium acetylacetone	1 in 900,000	3,300*
" 3-methylacetylacetone	1 in 1,500,000	5,900
" 3-ethylacetylacetone	1 in 2,200,000	9,100
" 3-methylpropionylacetone	1 in 5,000,000	21,000
" propionylacetone	1 in 2,300,000	9,000
" <i>n</i> -butyrylacetone	1 in 2,400,000	10,000
" dipropionylmethane	1 in 7,500,000	31,000
" propionyl- <i>n</i> -butyrylmethane	1 in 3,000,000	13,000
" di- <i>n</i> -butyrylmethane	1 in 3,000,000	13,800
" 3 : 3-diethylacetylacetone	>1 in 500,000	< 2,200

Bactericidal action of tellurium β -diketones on B. typhosus ii.

Tellurium 3-methylpropionylacetone	1 in 8,000,000	33,000*
" 3-ethylpropionylacetone	1 in 2,500,000	11,000
" dipropionylmethane	1 in 20,000,000	83,000

* Mean bactericidal concentration for phenol = 1 in 650.

It will be seen from Table II that *B. typhosus* i was less sensitive to change in chemical structure than *B. coli communis*, the smaller difference in activity between tellurium acetylacetone and tellurium dipropionylmethane being clearly noticeable. Nevertheless, the general rules with regard to substitution and structure hold in this case as with *B. coli communis*.

Both strains were equally resistant to phenol, but *B. typhosus* ii was much more susceptible to the tellurium compounds than the former strain, although the same chemical relationships apply as before.

The experiments with *Staphylococcus pyogenes aureus* (Table III) show that the two strains, i and ii, have entirely different resistances to the action of the tellurium compounds; notwithstanding this, however, the comparative relationships already observed between the germicidal powers of these compounds are still maintained.

Table III. *Bactericidal action of tellurium β -diketones on Staphylococcus pyogenes aureus i.*

Tellurium β -diketone	Mean bactericidal concentration	Equimolecular phenol coefficient
Tellurium acetylacetone	1 in 18,500	98*
" 3-methylacetylacetone	1 in 42,000	240
" 3-ethylacetylacetone	1 in 112,000	680
" propionylacetone	1 in 400,000	2,300
" <i>n</i> -butyrylacetone	1 in 450,000	2,700
" dipropionylmethane	1 in 900,000	5,400
" propionyl- <i>n</i> -butyrylmethane	1 in 620,000	3,900

* Mean bactericidal concentration for phenol = 1 in 450.

Bactericidal action of tellurium β -diketones on Staphylococcus pyogenes aureus ii.

Tellurium <i>n</i> -butyrylacetone	1 in 4,000,000	20,000*
" dipropionylmethane	1 in 6,000,000	30,000
" dipropionylethylmethane	1 in 5,000,000	25,000

* Mean bactericidal concentration for phenol = 1 in 535.

The explanation of the above remarkable divergence depends on the fact that the resistances of *Staphylococcus* and *Streptococcus* vary considerably at different periods of their life-history. In Table IV the results with *Staphylococcus pyogenes aureus* (i a) and *Streptococcus haemolyticus* were obtained when the organisms had been freshly cultivated on artificial media from the animal body. Under these conditions the cocci are so highly resistant that the tellurium compounds are seen to act selectively on organisms of the coliform group, thus resembling quinones as previously mentioned [Morgan, Cooper and Burtt, 1923]. On further cultivation in artificial media, however, the resistance of these organisms to tellurium derivatives diminished five to ten times, but in their resistance to phenol there was practically no change. Organisms of the coliform group did not exhibit this remarkable change in susceptibility. It is interesting also to note that the final resistance to tellurium dipropionylmethane of the *Staphylococcus* (i b) after cultivation in artificial media was of the same order as that of the other strains (ii) and (iii), which had also been grown for some time in laboratory media.

BACTERICIDAL ACTION OF TELLURIUM DIPROPIONYLMETHANE ON A VARIETY OF ORGANISMS.

Tellurium dipropionylmethane, having by far the greatest germicidal power, was tested by the inhibitory method in broth with a considerable number of species of bacteria including bacilli (coliform and otherwise), cocci and the acid-fast group. The results are arranged in Table IV.

B. phlei was taken to represent the acid-fast group including tubercle and leprosy. This type of organism caused a difficulty in technique, since the culture grows in lumps or flakes, and not as a homogeneous suspension.

To this tellurium compound *B. pyocyaneus* showed a very marked resistance which may be associated with the extremely rapid growth of the organism.

Table IV. *Bactericidal action of tellurium dipropionylmethane in broth.*

Organism	Mean bactericidal concentration	Equimolecular phenol coefficient
<i>B. coli communis</i> i	1 in 9,000,000	46,000
" ii	1 in 10,000,000	51,000
<i>B. typhosus</i> i	1 in 7,500,000	31,000
" ii	1 in 20,000,000	83,000
<i>B. paratyphosus</i> A	1 in 17,000,000	57,000
" B	1 in 4,000,000	22,000
<i>B. pyocyaneus</i>	1 in 250,000	800
<i>B. phlei</i>	1 in 750,000	4,500
<i>Staphylococcus pyogenes aureus</i> i a	1 in 900,000	5,400
" " i b	1 in 10,000,000	46,000
" " ii	1 in 8,000,000	46,000
" " iii	1 in 6,000,000	30,000
<i>Streptococcus haemolyticus</i> a	1 in 540,000	2,900
" " b	1 in 2,800,000	13,500

The remarkable bactericidal power of tellurium dipropionylmethane indicated in Table IV is also well exhibited by a comparison with that of other

well known disinfectants, as shown by the inhibitory test, using *B. coli communis*, the numbers indicating germicidal concentration: phenol 1 in 530, mercuric chloride 1 in 2,000,000, benzoquinone 1 in 20,000, tellurium dipropionylmethane 1 in 8,000,000.

BACTERICIDAL ACTION OF THE TELLURIUM β -DIKETONES
IN MEDIA OTHER THAN BROTH.

In order to test the applicability of the substances to internal disinfection, inhibitory tests, for the most part with tellurium dipropionylmethane, were carried out in blood serum and in urine.

Test in blood serum. The serum employed was ox blood serum, heated at 56° to destroy the complement and to produce sterility. The inhibitory test was carried out in the usual way and the serum tubes subcultured into broth after two days' incubation. The test organism was grown in serum from nutrient agar for 24 hours. It was found that the compounds lost their efficacy in serum to a remarkable degree. Thus tellurium dipropionylmethane failed to kill either strain of *B. typhosus* in a concentration of 1 in 50,000.

It was hoped that tellurium 3 : 3-diethylacetylacetone would give better results, since it cannot function as a weak acid, thus differing from the other derivatives. Nevertheless, this substance failed to kill *B. typhosus* in a concentration of 1 in 50,000. Tellurium 3-methylpropionylacetone also failed to show bactericidal action in a similar concentration.

This collapse of germicidal power in serum employed as medium could be the result of either or all of three factors: (i) change in cultural characteristics of organism, due to growth in serum; (ii) change in hydrogen ion concentration, serum being on the alkaline side, whereas the broth used was acidic; (iii) complex reaction or decomposition of the tellurium compound with serum proteins.

(i) On growing the two strains of *B. typhosus* in serum, and using this culture for a broth inhibitory test, it was found that the resistance of the organisms was not noticeably different from the normal.

(ii) The use of broth of p_H equal to that of serum in the inhibitory test caused no very definite change in bactericidal power.

(iii) A broth inhibitory test was carried out, using a broth culture of *B. typhosus*. In one case tellurium dipropionylmethane solutions were made up in water as usual, and in another case in serum (1 cc. of 0.01 % aqueous solution was added to 9 cc. of serum to make a 0.001 % solution in serum), the serum solution being left for one hour before use. The control experiment gave a normal result (sterilisation in 1 in 10,000,000), while that in which a serum solution of the tellurium derivative was added to the broth showed that the substance had lost its bactericidal action in concentrations down as far as 1 in 500,000. A control experiment, in which the tellurium dipropionylmethane was dissolved in broth instead of in water, showed no divergence from that in which water was used.

It is thus seen that in some way the serum had succeeded in rendering the tellurium dipropionylmethane non-bactericidal, and it is evidently factor (iii), the protein content of the serum, which is responsible for the diminution in activity of these compounds in serum.

We have nevertheless shown that tellurium dipropionylmethane in serum is capable of inhibiting growth to a considerable degree, even in concentrations much less than those in which it fails to be germicidal. The rate of increase in numbers of *B. typhosus* in ordinary serum and in serum containing one part of tellurium dipropionylmethane per million was compared. The two tubes were each inoculated with one drop of a serum culture of *B. typhosus* and incubated. The numbers of organisms present in each tube were counted by plating on agar at the beginning and after three and nine hours. The results were as follows:

Pure serum	Serum + Tellurium dipropionylmethane
Beginning of experiment: 30,000,000 organisms per cc.	26,000,000 organisms per cc.
After three hours at 37°: 70,000,000 organisms per cc.	25,000,000 "
After nine hours at 37°: 90,000,000 organisms per cc.	31,000,000 "

The experiment shows that in the presence of one part of tellurium dipropionylmethane per million growth of the organism is very slow.

Tests in urine. The urine was sterilised before use by steaming and the test organisms used were grown in urine for 24 hours instead of broth. Tellurium dipropionylmethane was examined with various organisms and the following results were obtained:

Organism	Mean bactericidal concentration	Organism	Mean bactericidal concentration
<i>B. coli communis</i> ii	1 in 5,500,000	<i>B. paratyphosus</i> A	1 in 9,000,000
<i>B. typhosus</i> i	1 in 3,300,000	" B	1 in 6,000,000
" ii	1 in 4,000,000	<i>S. pyogenes aureus</i> ii	1 in 2,900,000

The results show that whilst there is a perceptible diminution of activity in urine as compared with broth, on the whole the results are quite of the same order (see Table IV), and tellurium dipropionylmethane has a very pronounced action in urine.

PHYSIOLOGICAL ACTION OF TELLURIUM β -DIKETONES.

Experiments to determine the toxicity to animals of certain of these substances were next carried out with a view of ascertaining whether there was any likelihood of them being suitable for administration to man as internal disinfectants.

Method. The animals used were mice (weight approximately 20 g.). The tellurium compounds in aqueous solution were injected subcutaneously into the back leg, with the usual precautions against sepsis. The solutions were of such strength that the required dose was contained in 0.2 to 0.25 cc. The following doses were found to be fatal:

Tellurium β -diketone	Actual dose (g.)	Dose per kilogram body weight (g.)
Tellurium dipropionylmethane	0.00010	0.005
„ 3-methylpropionylacetone	0.0003	0.014
„ 3-ethylacetylacetone	0.000375	0.013

These substances are therefore extremely poisonous and it is evident that tellurium dipropionylmethane is the most toxic of the three isomerides, while central substitution of the diketone gives less toxic compounds. Bactericidal power and toxicity are thus similarly influenced by chemical structure.

The general symptoms and behaviour of mice suffering from poisoning by these substances were similar in each experiment. With the dose well below the toxic value no symptoms were observable. As the dose was increased the mouse usually showed signs of slight *malaise*, and a small quantity of blood would be passed in the urine a few hours after the injection. Normal recovery took place in about two days. When a lethal dose had been injected the mouse speedily showed signs of *malaise*, hematuria followed, and the animal soon died.

The post-mortem examination of mice which had succumbed showed similar conditions in every case. The lungs and heart did not have an unusual appearance. The liver was sometimes enlarged slightly; the kidneys were also slightly swollen and abnormally dark in colour and the spleen was almost invariably enlarged.

In the case of one experiment, the animal was dissected within 30 minutes after death, its organs were preserved in formalin and submitted to a medical colleague for histological examination. Microscopic examination of the tissue showed that the animal had died from some generalised toxic condition which affected in particular the spleen, liver and kidney. Quite the most characteristic symptom of poisoning by a tellurium diketonic derivative is hematuria, which in extreme cases is probably the primary cause of death.

Further experiments showed that these substances are cumulative in large doses but not in small doses. Thus, a dose of 0.10 mg. of tellurium 3-methylpropionylacetone caused decided but not fatal symptoms, while in another experiment the same quantity, divided into three doses, given at two days' intervals, caused no apparent symptoms. The same compound, however, caused slight symptoms following a dose of 0.125 mg., and a second injection of the same quantity two days later resulted in marked symptoms of severe poisoning.

POSSIBILITY OF THE THERAPEUTIC APPLICATION OF TELLURIUM DERIVATIVES.

The foregoing experiments with tellurium diketones in serum show that these substances would be of little value in the blood stream unless their action as growth inhibitors only was desired.

On the other hand, the tellurium compounds retain their efficacy in urine and it would appear possible that they might be of use in treatment of infections of the urinary organs, and clinical tests are in progress. In the case

of mice, the lethal dose of tellurium dipropionylmethane is 0.005 g. per kilogram body weight, that is, a concentration of 1 in 200,000 if we suppose the substance to be distributed evenly throughout the body. Experiments have shown that a concentration of 1 in 2,000,000 in urine is more than sufficient to kill any of the organisms examined.

Thus the ratio between lethal concentration and bactericidal concentration is over ten in the case of tellurium dipropionylmethane. Lethal dose and bactericidal concentration of tellurium 3-methylpropionylacetone (the substance of the next greatest bactericidal power) are both rather higher than those of the former substance, but the ratio between lethal and bactericidal concentrations seems to be about the same.

The two compounds which appear to be most suitable for therapeutic application are tellurium dipropionylmethane and tellurium 3-methylpropionylacetone; the necessary concentration of the former would be less, but the latter, a more easily prepared compound, is more readily soluble in water.

BACTERICIDAL ACTION OF TELLURIC ACID.

For purposes of comparison with the researches on tellurium diketones, the bactericidal power of telluric acid by the inhibitory test in broth and blood serum has been determined, with the following results:

Broth	Bactericidal concentrations	Blood serum	Bactericidal concentrations
<i>B. coli communis</i>	1 in 3,000	<i>B. coli communis</i>	1 in 900
<i>B. typhosus</i>	1 in 5,000	<i>B. typhosus</i>	1 in 900
<i>S. pyogenes aureus</i>	{ 1 in 30,000 1 in 50,000		

The results show that telluric acid is much less active than the diketone compound but has a remarkable selective germicidal action on *S. pyogenes aureus* which is quite without parallel in the study of the above substances. The bactericidal action of telluric acid is decidedly less in serum than in broth, but the germicidal power in serum does not show the complete collapse characteristic of the diketone derivatives. Joachimoglu [1922] found telluric acid to be germicidal to coliform organisms in concentrations of 1 in 40,000, but in our experiments we have found it to be less active.

SUMMARY.

1. The tellurium derivatives of the aliphatic β -diketones are extremely powerful germicides to many different types of bacteria.
2. Two conditions of chemical structure are mainly contributory to high bactericidal power, namely (a) symmetry of the parent β -diketone, (b) presence of methyl and ethyl groups in para-positions within the heterocyclic ring. These conditions are simultaneously fulfilled only in the case of tellurium dipropionylmethane, which is therefore the most active of the series, being sometimes bactericidal in the case of *B. typhosus* in as low a concentration as 1 in 40,000,000.

3. The bactericidal power of these compounds increases considerably as the homologous series is ascended, until with the formation of an ethyl group and subsequent substitution of one methyl group, a limit is reached, and with further substitution of alkyl groups there is a diminution in efficacy.

4. Position isomerism plays an important part in determining germicidal power, the relative positions of the alkyl groups in the molecule considerably affecting the activity of these compounds.

5. With such powerful germicides as those under consideration, small cultural changes in an organism or small differences between various strains of the same organism may profoundly affect the results.

6. The tellurium compounds lose their strong bactericidal action in the presence of serum, but retain their inhibitory power.

Their *germicidal* action, however, is retained in urine.

7. The compounds are very toxic to mice, attacking the kidneys in particular, causing hematuria. Differences of toxicity appear to correspond with differences in bactericidal power.

8. It would appear possible that the tellurium diketones, and particularly tellurium dipropionylmethane and tellurium 3-methylpropionylacetone, may find application in medicine as urinary antiseptics.

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