with subsequent loss of nitrous acid, generating the unsaturated diketone.

Since the splitting of the furan ring with nitric acid takes place in a consistent stereochemical manner, it would appear to be safe to utilize the reaction as a means of determining configurations of new unsaturated 1,4-diketones, providing of course that both *cis* and *trans* isomers are known and both are stable under the conditions involved in this synthesis.

Experimental Part

Since all the compounds dealt with in this paper are known, a brief outline of the oxidation method only will be given: 1 g. of the furan to be oxidized was suspended or dissolved in 5 cc. of glacial acetic acid and a solution of 1 cc. of concd. nitric acid (sp. gr. 1.42) in 3 cc. of glacial acetic acid was added slowly, and the mixture allowed to stand for one hour. The temperature was maintained constant at 100° for the 2,5-diphenyl-dichloro and dibromofurans, and at 25° for 2,5-diphenylfuran itself. The solutions were then diluted with ice water and the precipitated organic material washed with water and recrystallized from ethanol. The products were obtained in about 80% yields and were identified by mixed melting points with authentic samples.

Summary

Various 2,5-diphenylfurans are oxidized consistently to *cis* unsaturated 1,4-diketones, probably through a 1,4 addition mechanism.

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[CONTRIBUTION FROM THE INSECTICIDE DIVISION, BUREAU OF CHEMISTRY AND SOILS, U. S. DEPARTMENT OF AGRICULTURE]

A Further Study of the Toxicity of Derivatives of Rotenone with the Goldfish as the Test Animal

BY W. A. GERSDORFF

The preparation[1] of various derivatives of rotenone in the Insecticide Division of the Bureau of Chemistry and Soils afforded an opportunity to investigate the effect of slight changes in chemical structure on toxicity. Previous toxicological studies on rotenone,[2] dihydrorotenone,[2] acetylrotenone,[3] and rotenolone[3] have shown that the dihydro derivative has higher toxicity whereas the acetyl and hydroxy derivatives have lower toxicity than rotenone. This paper presents the results of similar investigations made with acetyldihydrorotenone, acetylrotenolone, dihydrorotenolone and acetyldihydrorotenolone. The method used by the author, in which the goldfish is used as the test animal, has been described in a previous paper.[4] The size of the fish, however, was greater, averaging for one of the two lots used 2.4 g. and for the other, 2.9 g.

Acetyldihydrorotenone (m. p. 209–211°), an acetate of the enol type, was prepared[5,6] by treating dihydrorotenone with acetic anhydride and sodium acetate.

Acetylrotenolone (m. p. 184°) was obtained[7,8] as the main product of the reaction of iodine and an alkali acetate with an alcoholic solution of rotenone. It is the acetate of a hydroxyrotenone in which the hydroxyl group is attached to one of the adjacent asymmetric carbon atoms of the dihydro-γ-pyrone system.

Acetyldihydrorotenolone (m. p. 189°) was prepared[7,8] in a similar reaction with dihydrorotenone. It differs from acetylrotenolone only in that the double bond in the isopropylene group is saturated with hydrogen.

Dihydrorotenolone was prepared[7,8] by the saponification of the preceding compound. This substance failed to crystallize with the methods tried, but its purity was established by a methoxyl determination. Its formula is that of the hydroxy derivative corresponding to the preceding compound.

Although two lots of goldfish were used in the tests, they were apparently similar in their resistance to these toxic substances, comparative results falling well within the limit of error.

The survival time curves and the velocity of fatality curves, which were plotted from the toxicity data, are given in Figs. 1 and 2.

Comparative data obtained from the velocity of fatality curves are given in Table I. In each case the straight line which is an approximation of that portion of the curve corresponding to the

(1) LaForge, Haller and Smith, *Chem. Rev.*, **12**, 181–213 (1933).
(2) Gersdorff, THIS JOURNAL, **52**, 5051–5056 (1930).
(3) Gersdorff, *ibid.*, **55**, 1147–1152 (1933).
(4) Gersdorff, *ibid.*, **52**, 3440–3445 (1930).
(5) LaForge, Haller and Smith, *loc. cit.*, p. 191.
(6) Smith and LaForge, THIS JOURNAL, **54**, 2996–3000 (1932).
(7) LaForge, Haller and Smith, *loc. cit.*, p. 202.
(8) LaForge and Smith, THIS JOURNAL, **52**, 1091–1098 (1930).

greatest rate of increase in the velocity of fatality with increase in concentration is prolonged to cut the x-axis at a point designated c_0; the slope of this line is designated tan θ and its measurement is expressed in the dimensions of both coördinates. In this way values are obtained for the theoretical threshold of toxicity, that is, the concentration below which the substance does not cause death, and the maximum rate of increase of the velocity of fatality with increase in concentration. Beyond this portion of the curve in the direction of higher concentrations there is a region of constant velocity, that is, the curve has become practically horizontal. This is assumed to occur when the

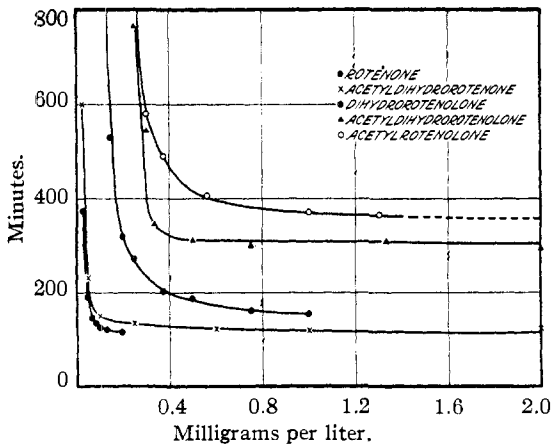

Fig. 1.—Survival time curves.

survival times corresponding to concentrations, one of which is double the other, do not differ by more than 5%. This region corresponds to a minimum survival time which is designated t_0. The values given for t_0 in the table are read directly from the survival time curve and are probably a little higher than those of the asymptotes, but they will serve for a practical comparison of the substances at this portion of the curves. The values given for rotenone and dihydrorotenolone are less accurate than the others because of the incompleteness of their curves.

TABLE I

COMPARATIVE TOXICITY OF CERTAIN ROTENONE DERIVATIVES TO GOLDFISH AT 27°

Substance	C_0, mg. per liter[a]	Tan θ, cc. per mg. per min.[b]	t_0, min.[c]
Rotenone	0.01	0.16	About 110
Acetyldihydrorotenone	.02	.13	120
Dihydrorotenolone	.05	.022	150
Acetyldihydrorotenolone	.08	.011	305
Acetylrotenolone	.09	.0078	360

[a] The theoretical threshold of toxicity, *i. e.*, the concentration necessary to just kill. [b] The maximum rate of increase of the velocity of fatality with increase in concentration. [c] The minimum survival time.

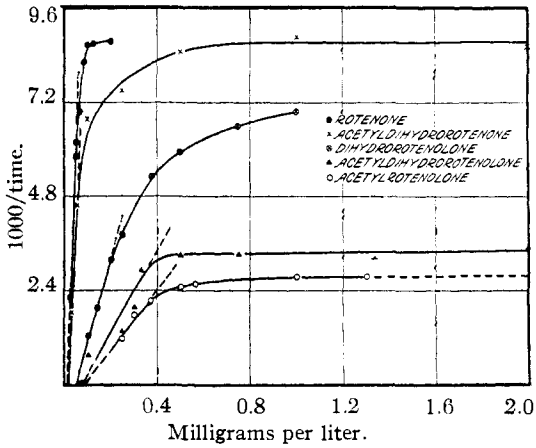

Fig. 2.—Velocity of fatality curves.

Conclusions

The compounds studied have, according to each of the three criteria, threshold of toxicity, maximum rate of increase of the velocity of fatality and minimum survival time, the following decreasing order of toxicity to goldfish: rotenone, acetyldihydrorotenone, dihydrorotenolone, acetyldihydrorotenolone and acetylrotenolone.

Comparison according to the second of these criteria, which is the more serviceable from the standpoint of practicality, inasmuch as it has reference to that portion of each curve in which the proportional change in the two variables, concentration and time, is not greatly different, shows the results to be consistent with those previously published in permitting the following generalizations to be drawn:

1. The dihydro compounds produced by saturation of the double bond in the side chain with hydrogen have appreciably higher toxicities than the corresponding unsaturated compounds.

2. The enol acetates and the acetyl derivatives of the hydroxy compounds have appreciably lower toxicities than the parent compounds.

3. The hydroxy compounds have much lower toxicities than the parent compounds.

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