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Sulfonation of 10-Carboxymethylene-9-acridanone Under Thermal and Microwave Conditions. Comparison of Kinetic Parameters

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Abstract—Sulfonation of 10-carboxymethylene-9-acridanone under thermal and microwave conditions was studied. The rate constants of the accumulation of the desired product in the reaction conditions were measured.

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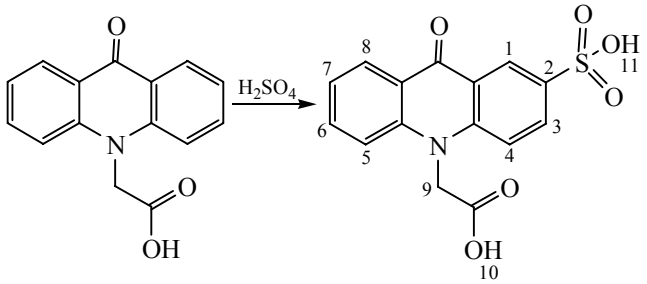
Among the inducers of endogenous interferon, which are a new class of antiviral, anticancer, and immunomodulatory drugs, 10-carboxymethylene-9-acridanone (acridoneacetic acid) is one of the most effective compounds [1]. Therefore, the study of its derivatives is of practical interest.

Presently, a synthesis under the microwave radiation is one of the promising methods for the synthesis of various organic compounds.

We performed the sulfonation of 10-carboxymethylene-9-acridanone during thermal heating and under microwave radiation (400 W, 2450 MHz) using a MARS instrument (Microwave Acceleration Reaction System, CEM Corporation).

The sulfonation of 10-carboxymethylene-9-acridanone in a concentrated sulfuric acid medium would likely proceed by analogy with the acridone sulfonation [2, 3].



As we have previously shown, 10-carboxymethylene-9-acridanone is unstable when heated under the acidic conditions and suffered degradation. Therefore, at first acridoneacetic acid was sulfonated with 20% oleum at a ratio of 2 ml of oleum per 1 g of 10-carboxymethylene-9-acridanone. The starting material was added to oleum by small portions with stirring, preventing the heating of the reaction mixture above 30°C.

After treating, only one reaction product was isolated in 67% yield. The structure of the compound was confirmed by the IR and ^{1}H NMR spectroscopy.

The IR spectrum contains an absorption band at 3430 cm^{-1}, which corresponds to the stretching vibrations of the OH-groups of the sulfo- and carboxy fragments. There are also absorption bands in the region of 2900–2850 (C–H), 1738 (C=O), 1621 (C=O, acridone ring), 1607–1540 cm^{-1} (C–C, Ar). The absorption bands at 1470–1000 cm^{-1} correspond to the stretching vibrations of the S=O bond and bending vibrations of the C–C and C–H bonds.

Analysis of the ^{1}H NMR spectrum of the obtained compound shows that the sulfonation occurs at the position 2 of the acridone ring.

The resulting compound is a bright yellow finely crystalline substance, which is readily soluble in water. Its aqueous solutions have an expressed blue fluorescence.

We also examined the sulfonation of 10-carboxymethylene-9-acridanone with the concentrated (93.4± 0.5%) sulfuric acid. The reaction was carried out at different temperatures. A molar ratio of the reactants,

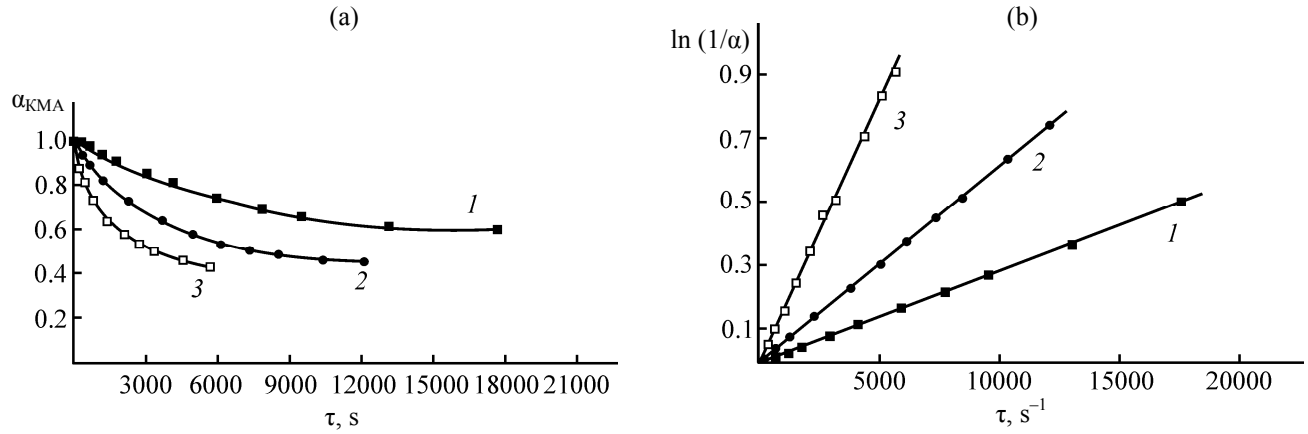


Fig. 1. Kinetic curves of 10-carboxymethylene-9-acridanone consumption in the reaction with concentrated sulfuric acid (a) under heating and (b) their presentation in log (1/α)–τ coordinates at: (*1*) 140, (*2*) 150, and (*3*) 160°C.

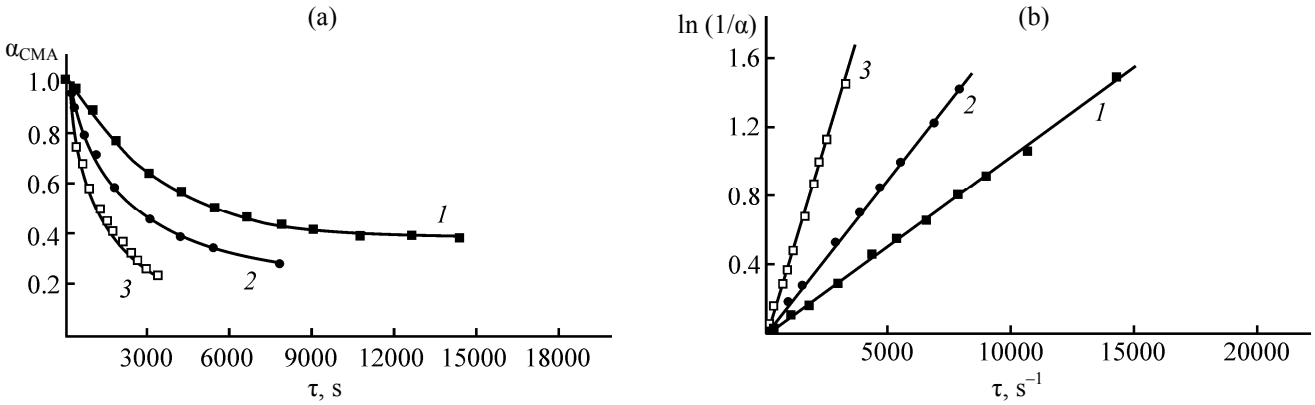


Fig. 2. Kinetic curves of 10-carboxymethylene-9-acridanone consumption in the reaction with concentrated sulfuric acid (a) under microwave radiation and (b) their presentation in log (1/α)–τ coordinates at: (*1*) 140, (*2*) 150, and (*3*) 160°C.

10-carboxymethylene-9-acridanone and concentrated sulfuric acid, is equal to 1:10.

Compared with the use of oleum, the sulfonation with sulfuric acid requires more rigid reaction conditions. The reaction proceeds only at 140°C for 7 h. According to the IR spectroscopy and TLC data, the reaction product is identical to the product obtained in oleum.

Raising the temperature of the reaction mixture to 150 and then to 160°C resulted in the reduction in the reaction time up to 4 and 2 h, respectively. However, with increasing temperature of the reaction mixture the resulting products became more colored. The product yield was 58–62%.

Further increase in the reaction temperature is accompanied by destruction of the starting material: in addition to the sulfonation product, *N*-methylacridone was detected in the reaction mixture due to the decarboxylation of 10-carboxymethylene-9-acridanone. The reaction product acquired a distinct brown color due to its contamination by tar.

Kinetic parameters of the sulfonation under thermal conditions and microwave irradiation

Conditions	Heating			Microwave irradiation		
t, °C	140	150	160	140	150	160
k, $s^{-1}\times10^{-5}$	3.26±0.16	7.3±0.36	16.47±0.82	9.14±0.46	20.25±1.10	44.98±2.25
Reaction time	420	240	120	240	130	55
Yield, %	58	59	62	60	76	80

Under the microwave irradiation, the sulfonation with concentrated sulfuric acid was carried out under the same temperature conditions. The reaction time was reduced to 240 min at 140°C, 130 min at 150°C, and 55 min at 160°C. The IR and ^{1}H NMR spectra of the isolated product were identical with the spectra of the product obtained in oleum and sulfuric acid in the thermal conditions.

To evaluate the effect of microwave irradiation on the rate of sulfonation of 10-carboxymethylene-9-acridanone we estimated the kinetic parameters of the reaction. The kinetic studies were carried out by thin layer chromatography with densitometry. Chromatograms obtained were treated on a Sorbfil videodensitometer at a wavelength of 254 nm using the Sorbfil 1.8 software [4].

A consumption degree of the starting 10-carboxymethylene-9-aridanone (CMA) and an accumulation degree of the sulfonation product were calculated from the experimental data obtained ($\alpha_{CMA} = c_{CMA}/c^0_{CMA}$).

It was found that under the studied conditions the reaction progress corresponds to the kinetics of the first order reaction. The consumption curves of 10-carboxymethylene-9-aridanone and the straight lines in the log $(1/\alpha)-\tau$ coordinates are presented in Figs. 1, 2.

The rate constants at different temperatures were determined by the quantitative thin-layer chromatography with densitometry according to [4] (Fig. 1, 2).

Based on the data obtained, we calculated the activation energies, which reached 121 kJ mol^{-1} in the thermal conditions and 118 kJ mol^{-1} in the microwave radiation conditions (see table).

As can be seen from the above data, in the studied reactions there is a microwave effect, which results in a faster sulfonation of 10-carboxymethylene-9-acridanone.

The microbiological studies of 0.5–2.0% solutions of the sulfonated product showed a moderate antibacterial activity against the test strains of some microorganisms.

EXPERIMENTAL

The purity of the starting materials and the reaction products was tested by thin layer chromatography (TLC). Chromatogram processing and kinetic studies were carried out on a highly efficient Sorbfil and PTLC-AF-B-UV plates using a Sorbfil densitometer [4]. A benzene–acetone–ethanol–acetic acid (5:8:10:0.2) mixture was used as an eluent.

The IR spectra were recorded on a Nicolet IR-200 FTIR spectrometer from KBr pellets. The ^{1}H NMR spectra were taken on a Bruker AV600SF spectrometer from DMSO-d_6 solutions.

Sulfonation of 10-carboxymethylene-9-acridanone under the thermal conditions. A mixture of 10 g (0.039 mol) of 10-carboxymethylene-9-acridanone and 20 ml (0.38 mol) of concentrated sulfuric acid was heated at the desired temperature with stirring for a specified period of time. The mixture was poured into 50 ml of glacial acetic acid and allowed to stand for 8–10 h, then the precipitate was filtered off, washed with 40–50 ml of glacial acetic acid and then with acetone. Yield 60–65%, mp 282–284°C (decomp., acetic acid). IR spectrum, ν, cm^{-1}: 3400.00–2362.67 (OH, CH), 1738 (C=O$_{carboxy}$), 1620 (>C=O$_{acr}$), 1586–1500 (C=C), 1217.52–1031 (S=O). ^{1}H NMR spectrum, δ, ppm: 13.12 s (2H, OH), 8.59 s (1H, C^{1}H), 8.36 d (1H, C$_3$H, *J* 7.0 Hz), 7.66 d (1H, C^{4}H, *J* 8,8 Hz), 7.67 d (1H, C^{5}H, *J* 8,8 Hz), 7.37 t (1H, C^{6}H, *J* 7.2 Hz), 7.82 t (1H, C^{7}H, *J* 7.0 Hz), 7.97 d (1H, C^{8}H, *J* 7.92 Hz), 5.34 s (2H, C^{9}H).

Sulfonation of 10-carboxymethylene-9-acridanone under the microwave irradiation. A mixture of 10 g (0.039 mol) of 10-carboxymethylene-9-acridanone and 20 ml (0.38 mol) of concentrated sulfuric acid was heated to the desired temperature with stirring for a specified period of time in a MARS microwave system at 400 W. The mixture was poured into 50 ml of glacial acetic acid and allowed to stand for 8–10 h, then the precipitate was filtered off, washed with 40–50 ml of glacial acetic acid and then with 25 ml of acetone. Yield 60–80%.

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