Compounds (XII-XV) inhibited the growth of Actinomycetes, their biological activity being nearly identical.

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF FURAN-CONTAINING ISOXAZOLES, TRIAZOLES, AND 1,4-DIKETONES

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In earlier works [1, 4, 5] on the furan-containing phosphonium salts we studied the oxidation of 1,3-dipolar cycloaddition products of 5-styryl-2-furoylmethylenetriphenylphosphonium ylides and the antimicrobial activity of the synthesized compounds.

It is already known that aroylmethylenetriphenylphosphonium ylides react with acid chlorides of α-oxohydroxamic acids to form the corresponding isoxazoles [6]. The authors of this work assumed that the formation of the isoxazole ring goes through the oxime phosphonium rearrangement. We used that method for the synthesis of furan-containing isoxazoles. Thus, the phosphonium ylides (Ia-c) were allowed to react with α-chloro-α-isonitrosoacetophenone (II) [7] in the presence of Et_3N in a modification of the method of [6] which was Et_3N was introduced not to the reagent mixture, but to the solution of II. The precipitate thus occurring was identified as $Et_3N \cdot HCl$. This confirmed our proposal that Et_2N does not "strip off" the ylide proton, and a significantly stronger acid, the oxime, thus forms $PhCOC{\equiv}N \rightarrow O$. When $Et_3N \cdot HCl$ is removed from the reaction mixture, the possibility of its participation in the reactions subsequently taking place is excluded, and then the ylide solution Ia-c was added to the filtrate. We propose that in the given case the formation of the isoxazole is realized by a 1,3-dipolar cycloaddition of the N-oxide of benzoylnitrile generated in situ to the double bond of the enolbetaine structure of the phosphonium ylide. We confirmed the existence of the N-oxide of benzoylnitrile with the help of IR spectra of the reaction mixture, in which the valence oscillation bands of the C≡N bond at 2260 cm^{-1} disappeared with time.

The structures of the isoxazoles IIIa-c were confirmed by IR spectral data, which contained bands for the C=O groups in the 1684-1652 cm^{-1} region, characteristic of aromatic ketones; bands at 1600, 1150, and 1020 cm^{-1} (isoxazole ring) [3]; valence oscillation bands for the C=C bond at 1620-1625 cm^{-1}, and also bands at 1570 and 1490 cm^{-1} characteristic of the furan ring, as well as bands at 955-960 cm^{-1} for deformation of the C-H bonds in the trans C=C.

The 1,3-dipolar cyclization of phosphonium ylides Ia-c also react with organic azides according to the pattern above. The first benzfuroyl azide (IV) showed the possibility for the synthesis of the furan-containing triazoles (Va-c).

The structure of the triazoles Va-c was verified with the help of IR spectra, in which were present absorptions at 1705-1700 cm^{-1} (C=O), 1610-1605 cm^{-1} (C=C), 1580 and 1500 cm^{-1} (furan ring), and at 1180, 1130, 1170, and 1010 cm^{-1}, characteristic of the 1,2,3-triazole ring [9].

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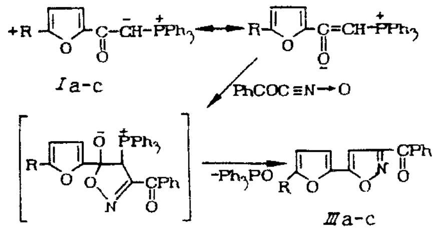
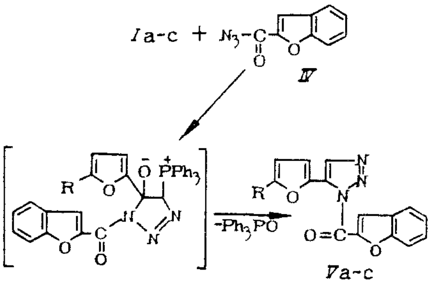
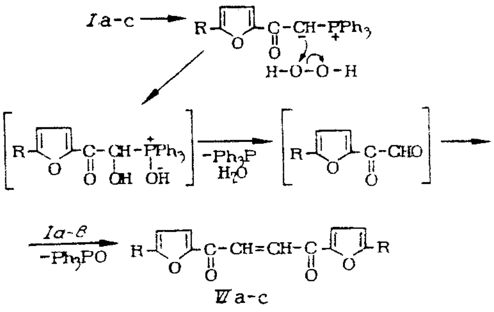
It is known that aroylmethylenetriphenylphosphonium ylides are capable of oxidation. Depending upon the oxidant and the conditions of the reaction, different results are obtained [8, 11]. With the aim of the synthesis of symmetrical difuroyl ethylenes containing styryl substituents in position 5 of the furan ring, we brought about the oxidation of the ylides Ia-c. If hydrogen peroxide was used as the oxidant, the reaction proceeded in the system CH_2Cl_2–30% H_2O_2. We considered that the mechanism in the present case was analogous to the mechanism for the oxidation of ylides with peracetic acid [8].

IR spectra of the unsaturated 1,4-diketones (VIa-c) contained absorptions of 3090 cm^{-1} (C–H), 1651 cm^{-1} (C=O), 1590 cm^{-1} (C=C), and 1540 and 1485 cm^{-1} (furan ring).







R=PhCH=CH(a); 4-BrC$_6$H$_4$CH=CH (b); 4-ClC$_6$H$_4$CH=CH (c).

EXPERIMENTAL (CHEMICAL)

IR spectra were recorded on an IKS-29 spectrometer in Vaseline oil paste, and the UV spectra were determined in ethanol (concentration = 5 × 10^{-5} mole/liter) on a Specord M-40 spectrophotometer. The characteristics of the synthesized compounds are recorded in Table 1. The values found for elemental analyses corresponded with those calculated.

3-Benzoyl-5-(5-R-2-furyl)isoxazoles (IIIa-c). To a solution of 0.37 g (0.002 mole) of benzoylhydroxamoyl chloride in 10 ml of tetrahydrofuran (THF) was added 0.2 g (0.002 mole) of Et_3N. After 15 minutes the resulting precipitate was filtered off and to the filtrate was added all at once a solution of 0.002 mole of phosphonium ylide Ia-c in 20 ml of THF. The mixture was stirred at room temperature for 3 h, the solvent was evaporated under aspirator vacuum, and the residue was crystallized from ethanol.

2-(2-Benzfuroyl)-5-(5-R-2-furyl)-1,2,3-triazoles (Va-c). To a solution of 0.002 mole of phosphonium ylide Ia-c in 20 ml of Ch_2Cl_2 was added 0.37 g (0.002 mole) of benzfuroyl azide and the mixture was stirred to complete disappearance of the phosphonium ylide)followed by TLC). The solvent was then evaporated under vacuum, the residue was treated with ethanol, the precipitate was filtered off and recrystallized from benzene.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Yield, %	Mp, °C	Empirical formula
IIIa	72	122	$C_{22}H_{15}NO_3$
IIIb	86	144—5	$C_{22}H_{14}BrNO_3$
IIIc	81	138—9	$C_{22}H_{14}ClNO_3$
Va	88	159—60	$C_{23}H_{15}N_3O_3$
Vb	64	167—8	$C_{23}H_{14}BrN_3O_3$
Vc	83	130—4	$C_{23}H_{14}ClN_3O_3$
VIa	57	210—2	$C_{28}H_{20}O_4$
VIb	66	268—70	$C_{28}H_{18}Br_2O_4$
VIc	70	254—6	$C_{28}H_{18}Cl_2O_4$

1,4-Di[3-(5-R-2-furyl)]-but-2-enediones (VIa-c). To a solution of 0.002 mole of phosphonium ylide Ia-c in 10 ml of CH_2Cl_2 was added 1.26 g (0.01 mole) of 30% H_2O_2. The mixture was stirred at 50°C with periodic agitation. After the initial exothermic reaction, the stirring was discontinued. After 2 h the resulting precipitate was filtered off and the organic layer was separated from the mother liquor, washed with H_2O, dried with $CaCl_2$, and concentrated under vacuum. The residue was treated with ethanol and an additional quantity of diketone VIa-c was filtered off. Recrystallization was from ethanol.

EXPERIMENTAL (BIOLOGICAL)

The antimicrobial activity of the subject compounds was studied by the generally-accepted method of 2-fold serial dilution in beef bouillon, pH 7.2-7.4 [2, 12]. The test organisms were 13 standard strains belonging to 11 families: Staphylococcus aureus 209, Staphylococcus aureus ATCC 25923, Escherichia coli K-12, Bacillus subtilis F-800, Pseudomonas aeruginosa 136, Serratia marcescens 1266, Proteus vulgaris 410, etc. The microbial loading was $1\text{-}5 \cdot 10^6$ microbial cells per ml of daily bouillon cultures [10]. The minimum suppressing concentration (MSC) and the minimum bactericidal concentration (MBS) were determined. Materials for testing were dissolved in dimethylsulfoxide and 0.87% NaCl to a final concentration of 1000 µg/ml.

The studied compounds showed antimicrobial activity with respect to Gram-positive and Gram-negative bacteria (MSC = 625-500 µg/ml). The most activity was shown by the furan-containing isoxazoles, and the least by the furan-containing 1,4-diketones. It should be noted that the substitution of H and Br in the para-position of the styrene by Cl leads to an increase in the antimicrobial activity primarily compared to the Gram-negative microorganisms. Introduction of Br into the para-position promotes a 2- to 8-fold increase in the activity of the studied compounds against the hay bacillus.

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