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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF PHOSPHONIUM SALTS AND YLIDES CONTAINING THE N-TRICHLOROETHYLAMIDE FRAGMENT

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Several carbonyl-containing phosphonium salts and phosphonium ylides display antimicrobial activity [1], particularly toward staphylococci and pathogenic fungi [2, 3].

We have carried out the directed syntheses to search for highly active and relatively nontoxic phosphorus-containing antimicrobial preparations [4, 5] and have now proceeded to the synthesis of phosphonium ylides and salts containing the physiologically active N-trichloroethylamide fragment. We synthesized the (1-alkoxy-2,2,2-trichloroethylaminocarbonyl)-aroylmethylene- and (1,2,2,2-tetrachloroethylaminocarbonyl)aroylmethylenetriphenylphosphoranes XI-XIII (Table 1) by reaction of aroylmethylenetriphenylphosphoranes [6] with 1,2,2,2,2-tetrachloro- and 1-alkoxy-2,2,2-trichloroethyl isocyanates

$$Ar{-}CO{-}CH{=}PPh_3 + O{=}C{=}N{-}CH(R){-}CCl_3 \longrightarrow$$
$$\longrightarrow Ph_3P{=}C(COAr){-}CO{-}NH{-}CH(R){-}CCl_3$$
I — XIII
R=Cl, OMe, OBu

Ylides I-XIII (Table 1) are crystalline substances that are stable under normal conditions, highly soluble in polar organic solvents (alcohol, chloroform, nitromethane, DMF, etc.), but are almost insoluble in water.

We prepared phosphonium chlorides XIV-XIX by saturating chloroform solutions of the ylides with dry hydrogen chloride [6] and synthesized phosphonium bromides XX-XXIV by mixing chloroform solutions of the ylides with an equimolar quantity of bromine

$$Ph_3P{=}C(COAr){-}CO{-}NH{-}CH(R){-}CCl_3 \longrightarrow$$
$$\xrightarrow{+HCl} Cl^{-}Ph_3P^{+}{-}CH(COAr){-}CONHCH(R)CCl_3$$
$$\xrightarrow{+Br_2} Br^{-}Ph_3P^{+}{-}CBr(COAr){-}CONHCH(R)CCl_3$$
XIV — XIX
XX — XXIV

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TABLE 1. Physical Constants and Antimicrobial Activity of (1-Alkoxy-2,2,2-trichloroethylaminocarbonyl)aroylmethylenetriphenylphosphoranes, $Ph_3P{=}C(COAr){-}CONHCH(R){-}CCl_3$

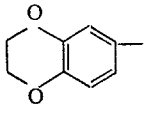
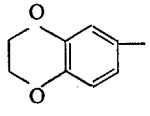
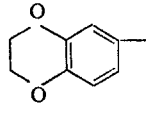
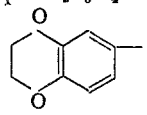
Compound	Ar	R	Yield, %	Melting point, °C	Found %			Formula	Calculated, %			Minimum bacteriostatic concentration, μg/ml						
					N	P	Hal		N	P	Hal	Staph. aureus 209	E. coli 365	Candida albicans 688	Bac. anthracoides 297	S. typhi 495	Proteus vulgaris 409	Ps. aeruginosa 125
I	C_6H_5	Cl	92	108 — 10	2,24	5,30	23,96	$C_{29}H_{22}Cl_4NO_2P$	2,38	5,26	24,06	15,62	31,25	31,25	15,62	31,25	62,5	62,5
II	p-Br—C_6H_4	Cl	82	144 — 6	2,05	4,60	33,08	$C_{29}H_{21}BrCl_4NO_2P$	2,09	4,64	33,18	7,81	31,25	31,25	31,25	31,25	62,5	31,25
III	p-$CH_3OC_6H_4$	Cl	90	199 — 201	2,27	5,05	22,87	$C_{30}H_{24}Cl_4NO_3P$	2,26	5,00	22,90	15,62	62,5	62,5	31,25	62,5	62,5	62,5
IV	p-$NO_2C_6H_4$	Cl	87	135 — 7	4,31	4,85	22,29	$C_{29}H_{21}Cl_4NO_4P$	4,42	4,88	22,36	250	250	250	125	250	250	250
V		Cl	90	164 — 6	2,24	4,80	21,80	$C_{31}H_{24}Cl_4NO_4P$	2,16	4,78	21,90	31,25	31,25	31,25	62,5	31,25	62,5	62,5
VI	C_6H_5	OCH_3	94	89 — 92	2,45	5,27	18,22	$C_{30}H_{25}Cl_3NO_3P$	2,39	5,29	18,18	62,5	125	31,25	31,25	62,5	125	125
VII	p-$CH_3C_6H_4$	OCH_3	85	146 — 8	2,30	5,12	17,69	$C_{31}H_{27}Cl_3NO_3P$	2,34	5,17	17,76	7,81	31,24	31,25	15,62	31,25	62,5	62,5
VIII	p-$CH_3OC_6H_4$	OCH_3	94	86 — 8	2,25	5,09	17,15	$C_{31}H_{27}Cl_3NO_4P$	2,28	5,04	17,29	7,81	31,25	7,81	15,62	31,25	31,25	62,5
IX		OCH_3	77	162 — 4	2,15	4,78	16,47	$C_{32}H_{27}Cl_3NO_5P$	2,18	4,82	16,54	3,96	31,25	31,25	31,25	62,5	62,5	62,5
X	p-$CH_3C_6H_4$	OC_4H_9	65	107 — 9	2,12	4,86	16,57	$C_{34}H_{33}Cl_3NO_3P$	2,19	4,83	16,59	125	250	250	125	250	250	250
XI	p-$CH_3OC_6H_4$	OC_4H_9	60	96 — 8	2,01	4,64	16,20	$C_{34}H_{33}Cl_3NO_4P$	2,13	4,71	16,19	250	500	250	62,5	62,5	125	250
XII	p-$NO_2C_6H_4$	OC_4H_9	84	146 — 8	4,20	4,58	15,80	$C_{33}H_{30}Cl_3N_2O_5P$	4,17	4,61	15,83	31,25	62,5	62,5	31,25	31,25	62,5	62,5
XIII		OC_4H_9	65	145 — 7	2,01	4,45	15,51	$C_{35}H_{33}Cl_3NO_5P$	2,04	4,52	15,53	62,5	125	62,5	62,5	125	125	125

TABLE 2. Physical Constants and Antimicrobial Activity of (1-Alkoxy-2,2,2-trichloroethylaminocarbonyl)aroylmethylenetriphenylphosphonium Halides, Pr_3P^+—CR(COAr)—CONHCH(R')—CCl_3X^-

Compound	Ar	R'	R	X	Yield, %	Melting point, °C	Found, %			Formula	Calculated, %			Minimum bacteriostatic concentration μg/ml						
							N	P	Hal^-		N	P	Hal^-	Staph. aureus 209	E. coli 365	Candida albicans 688	Bac. anthracoides 297	S. typhi 495	Proteus vulgaris 409	Ps. aeruginosa 128
XIV	p-BrC_6H_4	H	Cl	Cl	92	129—31	1,87	4,37	4,97	$C_{29}H_{22}BrCl_5NO_3P$	1,99	4,40	5,03	31,25	31,25	31,25	7,81	31,25	62,5	62,5
XV	p-$NO_2C_6H_4$	H	Cl	Cl	90	106—8	4,13	4,61	5,15	$C_{29}H_{22}Cl_2N_2O_4P$	4,18	4,62	5,29	31,25	31,25	31,25	7,81	31,25	62,5	62,5
XVI		H	Cl	Cl	87	156—8	2,01	4,47	5,06	$C_{31}H_{25}Cl_5NO_4P$	2,05	4,53	5,18	31,25	31,25	15,62	7,81	31,25	62,5	62,5
XVII	p-$CH_3OC_6H_4$	H	Cl	Cl	85	135—7	2,12	4,69	5,38	$C_{30}H_{25}Cl_5NO_3P$	2,14	4,72	5,40	15,62	31,25	15,62	15,62	62,5	125	31,25
XVIII	p-$CH_3OC_6H_4$	H	OCH_3	Cl	95	164—6	2,02	4,67	5,37	$C_{31}H_{28}Cl_4NO_4P$	2,15	4,75	5,44	31,25	31,25	15,62	31,25	31,25	62,5	31,25
XIX	p-$CH_3OC_6H_4$	H	OC_4H_9	Cl	84	138—40	1,98	4,29	5,04	$C_{34}H_{34}Cl_4NO_4P$	2,02	4,47	5,11	125	250	125	62,5	62,5	62,5	125
XX	p-$CH_3OC_6H_4$	Br	OCH_3	Br	88	84—6	1,90	3,97	10,21	$C_{31}H_{27}Br_2Cl_3NO_4P$	1,81	4,00	10,31	7,81	15,62	15,62	7,81	15,62	31,25	31,25
XXI	p-$CH_3OC_6H_4$	Br	OC_4H_9	Br	77	82—3	1,68	3,77	9,77	$C_{34}H_{33}Br_2Cl_3NO_4P$	1,72	3,79	9,78	7,81	15,82	15,62	7,81	31,25	62,5	31,25
XXII	p-BrC_6H_4	Br	Cl	Br	94	87—9	1,61	3,71	9,55	$C_{29}H_{21}Br_3Cl_4NO_3P$	1,69	3,74	9,65	31,25	62,5	31,25	31,25	62,5	62,5	125
XXIII	p-$NO_2C_6H_4$	Br	Cl	Br	89	100—103	3,47	3,92	9,97	$C_{29}H_{21}Br_2Cl_4N_2O_4P$	3,53	3,90	10,06	7,81	15,62	31,25	15,62	31,25	62,5	62,5
XXIV	p-$CH_3OC_6H_4$	Br	Cl	Br	90	125—8	1,63	3,94	10,21	$C_{30}H_{24}Br_2Cl_4NO_3P$	1,78	3,98	10,26	7,81	15,62	31,25	15,62	31,25	62,5	62,5

The synthetic phosphonium salts XIV-XXIV (Table 2) are much more soluble in organic solvents than are the starting ylides, and some are also moderately water soluble. The solubility in polar solvents varies in the order ylides < phosphonium bromides < phosphonium chlorides.

We recorded the IR and UV spectra of the synthetic ylides and phosphonium salts. The IR spectra of compounds I-XX have intense aroyl $\nu_{C=O}$ bands in the 1690-1730 cm^{-1} region and amide $\nu_{C=O}$ bands in the 1640-1610 cm^{-1} region. The presence in the spectra of the ylides of an intense band in the 1360-1380 cm^{-1} region is due to the phosphorus—carbon ylide linkage. The UV spectra of compounds I-XX have two principal maxima, the first in the 230-235 nm region (log ε 4.02-4.46) and the second in the 262-272 nm region (log ε 4.23-4.67).

We used serial dilution in nutrient broth [7] to evaluate the activity of the synthetic preparations against several species of bacteria and fungi. Tables 1 and 2 show that the minimum bacteriostatic concentrations of the test compounds toward *Staphylococcus aureus* (strain 209) and *Bacillus anthracoides* (strain 297) are in the range 3.96-125 μg/ml, while, toward *Escherichia coli* (strain 365), *Salmonella typhi* (strain 495), *Proteus vulgaris* (strain 409), and *Pseudomonas aeruginosa* (strain 128) they are 31.25-250 μg/ml.

The fungistatic effect of ylides I-XIII (Table 1) toward the yeastlike *Candida albicans* (strain 688) is apparent in concentrations of 7.81-250 μg/ml, while that of the phosphonium salts appears at 15.62-31.25 μg/ml.

The antimicrobial activity of the synthetic preparations correlates with their chemical structure. Thus increase in the length of the radical R in the alkyl part considerably reduces the potency (compounds X, XI, and XIII-XIX), with the exception of XII, which shows no great loss of biological activity (compare for example compounds IV and XII, XII and IX, X). The phosphonium compounds XIV-XXIV have roughly the same activity toward the gram-negative and gram-positive microorganisms (Table 2).

The antimicrobial activity of ylides and phosphonium halides is known to depend to a considerable extent on the nature and size of the α-carbon substituent [4, 5]. However, the introduction of the —CONHCH(R)—CCl_3 fragment into the α position of the ylides and the phosphonium salts doubles or trebles the antimicrobial potency relative to the compounds synthesized earlier [4, 5].

EXPERIMENTAL CHEMICAL SECTION

Spectra were recorded on: IR, a UR-20 in Vaseline oil; and UV, an SF-4A spectrophotometer in 1×10^{-5} M solutions in ethanol.

(1,2,2,2-Tetrachloroethylaminocarbonyl)aroylmethylenetriphenylphosphoranes I-V. To a solution of the aroylmethylenetriphenylphosphorane (5 mmole) in anhydrous carbon tetrachloride (80 ml) warmed to 30°C was added dropwise with stirring a solution of 1,2,2,2-tetrachloroethyl isocyanate (5 mmole) in carbon tetrachloride (20 ml) over a period of 10-15 min. A white amorphous precipitate appeared instantly and increased in quantity as more isocyanate was added. The mixture was refluxed for another 1 h. The precipitate was then filtered off, washed with ether and with hexane, and recrystallized from alcohol. The physical constants of synthetic ylides I-VII are summarized in Table 1.

(1-Alkoxy-2,2,2-trichloroethylaminocarbonyl)aroylmethylenetriphenylphosphoranes IV-XIII. By the same method as in the previous synthesis the aroylmethylenetriphenylphosphorane (5 mmole) in anhydrous carbon tetrachloride (80 ml) and 1-alkoxy-2,2,2-trichloroethyl isocyanate (5 mmole) in carbon tetrachloride (20 ml) gave VI-XIII. The physical constants of synthetic ylides I-XIII are summarized in Table 1.

(1-Chloro- and 1-Alkoxy-2,2,2-trichloroethylaminocarbonyl)aroylmethylenetriphenylphosphonium Halides XIV-XXIV were prepared by the published procedure [6] by saturating a solution of the ylide (5 mmole) in chloroform (40 ml) with dry hydrogen chloride or by adding bromine (0.2 ml) dissolved in chloroform (15 ml).

The yields and physical constants of synthetic phosphonium salts XIV-XXIV are summarized in Table 2.

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IMIDAZOLE DERIVATIVES.

XV. SYNTHESIS AND BIOLOGICAL ACTIVITY OF BENZOLINE DERIVATIVES

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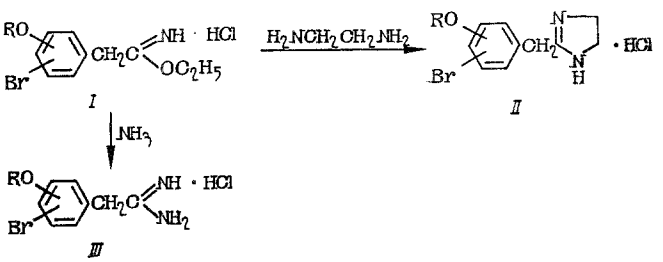
UDC 615.31:547.781.1

In the preceding publications we described the synthesis of substituted benzimidazolines, hydrazinoimidazoline hydrazones, and certain mercapto derivatives of 2-imidazoline [1-4].

In a continuation of these investigations, we prepared 2-benzyl-2-imidazolines containing bromine or an alkoxy group in positions 3,4 or 5,2 of the benzyl radical. We studied the possibility of synthesizing N-substituted imidazolines, and prepared 1-benzyl- and 1-(β-dialkylaminoethyl)-2-(4-chlorobenzyl)-2-imidazolines. Several α-(β-dialkylaminoethyl)-α-(phenyl)acetamidine hydrochlorides have been synthesized.

Benzylimidazolines (II) were prepared by cyclization of α-(alkoxy-bromophenyl)acetimidate ester hydrochlorides (I) with ethylenediamine; compounds I were also used in the synthesis of substituted α-(phenyl)-acetamidines (III).



It is known that N-substituted imidazolines can be obtained by intramolecular cyclization of amidines [5], cyclization of derivatives of carboxylic acids with N-substituted ethylenediamine [1, 6, 7], and alkylation of imidazolines with alkyl halides in the presence of sodium ethoxide [8, 9].

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