same dose, (II) increased the latent period of convulsions and the time of death to 77.0 min, and (X) changed these parameters by 15-25%, whereas pyracetam showed experimentally only weak anticonvulsive activity.

The test compounds displayed no ability to modify the pain threshold in mice, using the hot-plate method.

The LD_{50} values in white mice by the intraperitoneal route were 557 mg/kg for (XIV), and 1500-2000 mg/kg for the remaining compounds.

In electroencephalographic studies on cats and rabbits, (VI), (XII), and (XIV) (which had the greatest antihypoxemic effect) in intravenous doses of 100-200 mg/kg had no effect on spontaneous bioelectrical activity in various regions of the cerebral cortex. Reactions to the application of functional loading were also absent.

Like its derivatives, pyracetam had no effect on cerebral bioelectric activity. In experiments with the conditioned flight reflex in rats, (VI), (XII), and (XIV), like pyracetam, in an intraperitoneal dose of 500 mg/kg had no effect on the conditioned response.

Thus, six out of the 10 pyracetam derivatives tested increase the resistance of mice to acute hypoxic hypoxia. The greatest antihypoxic activity was shown by (VI). In this test, (VI) was approximately twice as active as pyracetam. Compound (VI) also displayed anticonvulsive activity in a model of convulsions induced the GABA antagonist thiosemicarbazide, suggesting the possible involvement of GABA-ergic structures in the mode of action of this compound. Antagonism to thiosemicarbazide, albeit less pronounced, was also shown by (II) and (X).

Like pyracetam itself, the test compounds had no analgesic activity.

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF DIACETYLENE ESTERS OF FATTY ACIDS

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UDC 615.281:547.29'26].012.1

Some symmetrical and unsymmetrical diacetylene have shown fairly high bactericidal properties [2-4].

In the course of directed synthesis with the aim of obtaining highly active bactericides, we have prepared some unsymmetrical diacetylenic esters of fatty acids, containing biologically active groupings. They were obtained by reacting the propargyl esters of lauric, margaric, and stearic acids with 1-bromophenylacetylene, 1-bromopropargyl alcohol, and the 1-bromopropargyl ether of m-nitrophenol in the presence of catalytic amounts of cuprous chloride and n-butylamine in an organic solvent, as follows:

$$RCOOCH_2C{\equiv}CH+BrC{\equiv}CR' \rightarrow RCOOCH_2C{\equiv}CC{\equiv}CR'+HBR;$$

I: $R = CH_3(CH_2)_{10}$, $R' = C_6H_5$; II: $R = CH_3(CH_2)_{15}$, $R' = C_6H_5$; III: $R = CH_3(CH_2)_{16}$, $R' = CH_2OC_6H_4NO_2$ = m; IV: $R = CH_3(CH_2)_{16}$, $R' = CH_2OH$; V: $R = CH_3(CH_2)_{15}$, $R' = CH_2OH$.

The diacetylene esters (I-V) (Table 1) are crystalline solids which are stable under normal conditions, and are readily soluble in alcohol, chloroform, ether, and acetone, but insoluble in water.

Tashkent Medical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 7, pp. 827-829, July, 1984. Original article submitted June 28, 1983.

0091-150X/84/1807-0482$08.50

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TABLE 1. Physicochemical Constants of Diacetylenic Esters of Fatty Acids, $RCOOH_2(C{\equiv}C)_2{-}R$

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
I	72	24—26	81,40 82,15	9,37 9,16	—	$C_{28}H_{30}O_2$	81,69	8,90	—
II	70	32—33	82,13 81,92	9,61 9,77	—	$C_{28}H_{40}O_2$	82,35	9,80	—
III	73	49—50	72,72 72,03	8,45 8,71	2,79 2,75	$C_{30}H_{43}NO_5$	72,43	8,65	2,81
IV	91	38—39	76,65 76,70	10,70 10,55	—	$C_{24}H_{40}O_3$	76,58	10,64	—
V	91	34—35	76,31 76,39	10,55 10,43	—	$C_{23}H_{38}O_3$	76,24	10,49	—

TABLE 2. Antimicrobial Activity of Compounds Prepared

Compound	Pyogenic organisms					Quasi-pathogenic organisms			Causative agents of intestinal infections					
	Staphylococcus aebus	Staphylococcus aureus	Staphylococcus citreus	Streptococcus faecalis	Streptococcus durans	Bacterium proteus vulgatis	Bacterium pyocyaneum	Cl. perfringens	Escherichia coli	Salmonellae typhi	Salmonellae paratyphi «B»	Salmonellae typhi murium	Salmonellae gallinarum	Shigella sonnei
I	25	22	25	30	25	30	35	—	40	35	30	25	30	25
II	—	—	—	—	—	40	30	—	—	—	—	—	—	—
III	20	23	20	25	—	40	35	—	—	—	—	—	—	—
IV	23	20	30	25	28	25	33	—	30	35	28	28	—	25
V	—	—	—	—	—	35	29	—	—	—	—	—	—	—
Streptomycin	20—22					20—22			20—22					
Levomycetin														

Note. Shown in the table are the diameters of the zones (in cm) in which no growth of the microorganisms was seen.

The structures of the compounds obtained were proved by, in addition to their elemental analyses, their IR and NMR spectra. The IR spectra of (I-V) contained absorption at 2180-2200 cm^{-1}, characteristic of the $-C{\equiv}C-C{\equiv}C-$ system, $\diagdown C{=}O$ stretching vibrations at 1740-1750 cm^{-1}, and absorption at 1500-1600 characteristic of the benzene ring, at 3450-3530 cm^{-1} charracteristic of OH stretching, and at low frequencies (2870-2945 cm^{-1}) absorption bands were present which were assigned to valence stretching of the $-CH_2-$ and CH_3- groups.

The NMR spectra of the diacetylenic esters contained a number of characteristic peaks, namely, signals for the methyl protons at 0.85-0.95 ppm, methylene protons at 1.25-1.30 ppm, and protons of the $-CH_2-CO$ and $-OCH_2-$ groups at 2.20-2.25 and 4.90-4.95 ppm. The singlets at 3.30-3.35 ppm indicate the presence of hydroxyl group protons, and signals are present at low field for the aromatic ring, in the form of a multiplet (7.20-7.60 ppm).

The effects of the compounds obtained on pyogenic and quasi-pathogenic microorganisms, and causative agents of intestinal infections were examined. For comparison, the sensitivities of the microorganisms were assessed in parallel to the antibiotics levomycetin and streptomycin [1].

The effects of the compounds on these microbial cultures were studied by serial dilution. The initial concentration of the compounds was 6.25 mg per 1 ml of broth.

A known volume of the original concentration of the drug was diluted twice, then twofold dilutions were prepared in 12 tubes, the 13th being the control (i.e., it contained the nutrient medium and the microbial culture, without the addition of the test compound).

The test compound was introduced into the medium containing different amounts of the test compounds, obtained in this way, and one small bacterial loop (0.01 ml) of a suspension

of a pure culture of the test microbial strain containing two billion microbial bodies per ml was introduced into each tube.

The inoculated mixture was placed in a thermostat at 37°C, and kept for from two to five days.

Studies were also carried out by the diffusion method in a two-layer agar gel, the amounts of compound used being 5, 10, 15, 20, 30, 35, 40, 45, and 50 mg.

When the microbial cultures had been incubated in the thermostat for the length of time indicated, the results were assessed by seeding from each test tube or from the zone of growth suppression on the agar gel onto a solid nutrient medium.

Repeated seedings were inoculated in a thermostat under the same conditions. Preliminary results were obtained after 18-24 h, and final results after 48 h in the thermostat at 37°C.

It was found (Table 2) that the most active compounds were 1-phenyl-1,3,5-pentadiyne laurate and 2,4-hexadiyne-6-yl stearate. They were 1.5-2 times as active as levomycetin and streptomycin against the microorganisms studied.

EXPERIMENTAL CHEMISTRY

IR spectra were obtained on a UR-20 apparatus (East Germany) in KBr disks, and NMR spectra on a Hitachi H-60 proton magnetic resonance spectrometer, frequency 60 MHz. The solvent used was carbon tetrachloride, and the internal standard hexamethyldisiloxane.

1-Phenyl-1,3-pentadiyn-5-yl Laurate (I). To a solution of 0.1 g of cuprous chloride in 15 ml of n-butylamine was added 0.5 g of hydroxylamine hydrochloride and 0.01 mole (2.66 g) of propargyl laurate in 20 ml of methanol. The reaction was carried out in an inert atmosphere (nitrogen), with vigorous stirring, 1-bromophenylacetylene (0.01 mole, 1.809 g) in 20 ml of methanol being added dropwise. The mixture was stirred for a further 30 min, treated with 200 ml of hydrochloric acid (1:20), and extracted with ether. Removal of the solvent followed by recrystallization from hexane gave the product. The constants of the diacetylenic esters (I-V) are shown in Table 1.

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