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SEARCH FOR ANTIMICROBIAL DRUGS IN BENZOHYDRO[THIA]CHROMYLIUM SALTS AND THEIR DERIVATIVES

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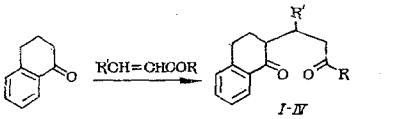
UDC 615.281:547.818.6

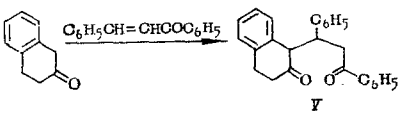
We have previously shown [1] that benzohydro(thia)chromylium and dibenzohydro(thia)-xanthylium salts possess high antistaphylococcal and antifungal activity. The present investigation was undertaken in order to synthesize and examine the antimicrobial activity of new benzohydrothiachromylium salts, and their isologs and derivatives.

The initial 1,5-diketones (I-V) (Table 1) were prepared for the first time by the Michael reaction, from the α- or β-tetralones and the appropriate chalcones.



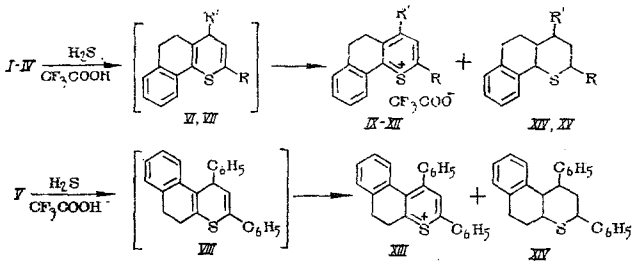
I-IV

I: R = C_6H_5, R' = $C_6H_4OCH_3$-p; III: R = $C_6H_4OCH_3$-p, R' = C_6H_5
II: R = C_6H_5, R' = $C_6H_3(OCH_3)_2$ m,p; IV: R = R' = $C_6H_4OCH_3$-p



V

Reaction of the ketopropyl-α-tetralones (I-IV) and the ketopropyl-β-tetralone (V) with hydrogen sulfide in trifluoroacetic acid gave the dihydrothiachromylium trifluoroacetates (IX-XIII) and the corresponding hexahydrothiochromenes (XIV-XVI), the topology of the π-system of which differs in the type of annelation of the rings.



N. G. Chernyshevskii Saratov University. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 5, pp. 545-548, May, 1982. Original article submitted July 30, 1981.

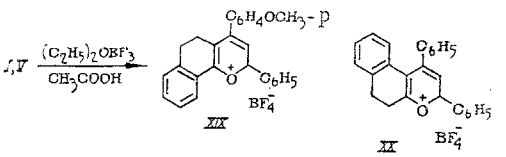
0091-150X/82/1605-0348$07.50

Intermediates formed in the reaction are the 4H-thiochromenes (VI-VIII), which disproportionate to the benzohydrothiachromylium salts (IX-XIII) and the saturated sulfides (XIV-XVI). The latter were obtained in quantitative yields by direct synthesis, via ionic hydrogenation of the benzohydrothiochromenes (VI-VIII), obtained from the corresponding dioxocompounds by treatment with hydrogen sulfide and hydrogen chloride in methanol.

Anion exchange reactions converted the trifluoroacetates (IX and XIII) into 2-phenyl-4-p-methoxyphenyl-7,8-benzo-5,6-dihydro- (XVII) and 2,4-diphenyl-5,6-benzo-7,8-dihydrothiachromylium tetrachloroferrate (XVIII).

The oxygen analogs of the benzohydrothiachromylium salts (2-phenyl-4-p-methoxyphenyl-7,8-benzo-5,6-dihydrochromylium fluoroborate (XIX) and 2,4-diphenyl-5,6-benzo-7,8-dihydrochromylium fluoroborate (XX)) were isolated from the products of the reaction of the 1,5-diketones (I) and (V) with boron trifluoride etherate in acetic acid.

The structures of the new compounds were confirmed by their elemental analyses (Tables 1 and 2), and by IR, UV, and PMR spectroscopy.



In the ketopropyl-α-tetralones (I-IV), both the carbonyl groups are conjugated with the aromatic rings, as shown by the presence in their IR spectra of strong absorption at 1680-1690 cm^{-1} (ν C=O). The diketone (V) showed absorption at 1715 and 1695 cm^{-1} (unconjugated and conjugated C=O groups).

The IR spectra of all the benzohydrothiachromylium salts (IX-XIII, XVII, XVIII) contained bands for stretching vibrations at 1560-1575 cm^{-1}, characteristic of the thiapyrilium structure, and the presence of the CF_3COO^- anion was shown by the bands at 1130-1205 and 1690-1758 cm^{-1} (ν CF and ν COO^- respectively).

The pyrilium structure of (XIX) and (XX) was shown by the absorption of the cation at 1540 cm^{-1}, and of the anion at 1040-1070 cm^{-1} (ν BF_4^-).

The PMR spectra of the benzohydro(thia)chromylium salts showed characteristic signals for the aromatic protons at δ 7.19-7.75 ppm, and for the methylene protons at high field (δ 2.53-2.87 ppm). The signal for the 3H proton, occuring as a doublet in the spectra of the benzohydrochromylium salts, occurs at higher field (δ 8.13-8.22 ppm) than in those of the benzohydrothiachromylium salts (δ 8.44-8.51 ppm).

The vibrational frequencies of the double bonds in the heterocycles 2R, 4R'-7,8-benzo-5,6-dihydro- (VI, VII) and 2,4-diphenyl-5,6-benzo-7,8-dihydrothiochromenes (VIII) occur at 1600 and 1640 cm^{-1}. These are absent in the saturated sulfides (XIV-XVI). The electronic spectra of the benzodihydrothiochromenes (VI-VIII) show strong absorption typical of the γ-thiopyran ring system at 242-245 nm, and an inflexion at 276-286 nm.

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity of the compounds was determined by double serial dilution in meat-peptone broth (pH 7.2-7.4) against *St. aureus* 209 P, *E. coli* 675, *Pr. vulgaris* 38, *Ps. pyocyaneum* 168, and *Candida albicans* 45.

Antiphage activity was measured by the Grazia agar slope method against DNA-containing (T_6) and RNA-containing phases (MS-2) on *E. coli* B and H FrC respectively. The compounds were dissolved in DMF, followed by dilution with sterile distilled water. The trifluoroacetate (X) was examined in aqueous solution. The results of the tests for antimicrobial activity are given in Table 3.

It will be seen from Table 3 that the compounds displayed antimicrobial activity against all the test microbes, but differed in their selectivity against the staphylococci and fungi of the *Candida* species.

TABLE 1. 1,5-Diketones (I-V)

Diketone	Yield, %	mp, °C	Found, %		Molecular formula	Calculated, %	
			C	H		C	H
I	78	123—125	81,20	6,33	$C_{26}H_{24}O_3$	81,25	6,25
II	53	102—102,5	78,38	6,56	$C_{27}H_{26}O_4$	78,26	6,28
III	47	99—100	81,20	6,20	$C_{26}H_{24}O_3$	81,25	6,25
IV	57	94—95	78,33	6,28	$C_{27}H_{26}O_4$	78,26	6,28
V	93	153—155	84,31	6,50	$C_{25}H_{22}O_2$	84,20	6,42

TABLE 2. Benzohydro(thia)chromylium Salts, Benzohydro- and Hexahydrothiochromenes

Compound	Yield, %	mp, °C	Found, %			Molecular formula	Calculated, %		
			C	H	S		C	H	S
VI	99	145—146	81,32	5,54	8,40	$C_{26}H_{27}OS$	81,67	5,75	8,39
VII	80,2	118—119	78,59	5,96	7,93	$C_{27}H_{24}O_2S$	78,59	5,87	7,77
VIII	62	96—98	84,95	5,60	9,25	$C_{25}H_{20}S$	85,30	5,73	9,11
IX	57,6	199—200	67,95	4,30	5,93	$C_{28}H_{21}O_3F_3S$	68,01	4,25	6,47
X	54,7	188—190	64,96	4,21	6,02	$C_{29}H_{23}O_4F_3S$	65,16	4,30	5,99
XI	40	115—118	—	—	5,64	$C_{28}H_{21}O_2F_3S$	—	—	5,72
XII	52	164—165	—	—	5,98	$C_{29}H_{23}O_4F_3S$	—	—	6,10
XIV	26	151—152	79,99	6,90	8,32	$C_{25}H_{26}OS$	80,2	6,9	8,5
XV	17	169—170	77,81	6,67	7,78	$C_{27}H_{28}O_2S$	77,86	6,78	7,70
XVI	27	132—134	83,98	6,75	8,93	$C_{25}H_{24}S$	84,34	6,80	9,01
XVII*	60	144—146	—	—	5,71	$C_{26}H_{21}OFeCl_4S$	—	—	5,53
XVIII†	58	99—101	—	—	5,29	$C_{25}H_{19}FeCl_4S$	—	—	5,83
XIX	73	245—247	68,97	4,07	—	$C_{26}H_{21}BF_4O_2$	69,00	3,97	—
XX	61	110—112	71,24	4,63	—	$C_{25}H_{19}BF_4O$	71,09	4,5	—

*Calculated, %: Cl 6.12. Found, %: Cl 6.60.
†Calculated, %: Cl 25.83. Found, %: Cl 25.41.
Note: Sulfides (XIV-XVI) were isolated from the products of the reaction of diketones (I, II, and V) with hydrogen sulfide in trifluoroacetic acid.

It is noteworthy that the highest activity is displayed by 2R, 4R'-7,8-benzo-5,6-dihydrothiachromylium trifluoroacetates (IX-XII) and 2-phenyl-4-p-methoxyphenyl-7,8-benzo-5,6-dihydrothiachromylium tetrachloroferrate (XVII).

A change in the type of annelation of the rings (transposition of the condensed benzene ring from the 7,8- to the 5,6-position of the alicycle) resulted in a decrease in the bacteriostatic activity of (XIII) and (XVIII). This is probably due to a change in the electronic structure of the molecule resulting from the reduction in the charge on the thiapyrilium cation.

A similar effect was observed in the pyrilium salts (XIX, XX), which are isoelectronic analogs of the thiapyrilium salts. The activity of (VI-VIII) also decreased on passing from the thiapyrilium to the thiopyran structure.

In addition to their antimicrobial activity, all the compounds exhibited antiphage activity. On adding to the phage—bacteria system in concentrations of 100 μg/ml, they suppressed the multiplication of both the DNA-containing (T_6), and to a greater extent the RNA-containing MS-2 phages.

The compounds are of low toxicity. The LD_{50} values following a single dose to white mice averaged 265-400 mg/kg.

Thus, the high antimicrobial and antiphage activity of the compounds, together with their low toxicity, suggest that the search for chemotherapeutic drugs of high activity in the 7,8-benzohydro(thia)chromylium salts series holds high promise.

TABLE 3. Antimicrobial Activity of Benzohydro(thia)chromylium Salts, and of Benzodihydro- and Benzohexahydro-thiochromenes

Compound	Test microbes				
	St. aureus	E. coli	Pr. vulgaris	Ps. pyocyaneum	Candida albicans
VI	25	50	50	25	50
VII	50	50	25	12	50
VIII	50	50	50	50	50
IX	0,7	50	50	50	0,7
X	0,3	100	100	100	0,3
XI	0,78	50	50	50	0,78
XII	0,7	50	50	50	0,7
XIII	100	100	100	100	100
XVII	0,7	100	100	100	0,7
XVIII	100	50	100	50	50
XIX	6	50	100	50	6
XX	100	100	100	100	100
XIV	12	50	100	50	12

EXPERIMENTAL CHEMICAL PART

IR spectra were recorded on a UR-20 instrument (East Germany), in vaseline oil and hexachlorobutadiene. UV spectra were obtained on an SF-4A spectrophotometer with a thickness of the absorbing layer of 2.05×10^{-3} cm, optical density measurements every 2 nm, and at concentrations of 5×10^{-3} moles·liter^{-1}. The PMR spectra of the samples were obtained on and RYa-2306 spectrometer with a working frequency of 60 MHz at 22°C, internal standard hexamethyldisilane.

Diketones (I-V) were obtained by condensing α- and β-tetralones with the appropriate α,β-unsaturated ketones (1:1) in the presence of sodium hydroxide at 50-60°C in alcoholic solution (constants given in Table 1).

2R,4R"-7,8-Benzo-5,6 (IX-XI) and 2,4-Diphenyl-5,6-benzo-7,8-dihydrothiachromylium Trifluoroacetates (XVIII); 2R,4R'-7,8-Benzo- (XVI, XV) and 2,4-Diphenyl-5,6-benzohexahydrothiochromenes (XVI). Dry trifluoroacetic acid (30 ml) was saturated for 1 h with hydrogen sulfide, 0.01 mole of the diketone (I-V) added, and saturation with hydrogen sulfide continued for 5 h. The reaction was followed by TLC (eluant hexane–ether–chloroform, 4:1:1). The crystals of the sulfides (XIV-XVI) which separated were isolated, washed with ethanol, and dried in a vacuum desiccator. The yields and melting points of the compounds are given in Table 2. Purification was effected by recrystallization from ethanol. The filtrate after removal of the sulfides was evaporated to a thick, oily residue which was triturated with ether. The crystals of the trifluoroacetates (IX-XII) which separated were isolated, dried in a vacuum desiccator, and purified by precipitation from chloroform with ether. The salt (XIII) was identified as its tetrachloroferrate (XVIII). The physicochemical constants of the salts (IX-XII) are given in Table 2.

2-Phenyl-4-p-methoxyphenyl-7,8-benzo-5,6- (XVII) and 2,4-Diphenyl-5,6-benzo-7,8-dihydrothiachromylium Tetrachloroferrates (XVIII). To a solution of 0.003 mole of the trifluoroacetate (IX) or (XIII) in 20 ml of glacial acetic acid was added 0.008 mole of ferric chloride in 10 ml of glacial acetic acid. The reaction mixture was kept for 10 h, and the yellow crystals which separated were isolated, washed with ether, and dried in a vacuum desiccator (Table 2).

2R,4R'-7,8-Benzo-5,6- (VI, VII) and 2,4-Diphenyl-5,6-benzo-7,8-dihydrochromenes (VIII). A solution of the diketone (I, II, or V) in 30 ml of glacial acetic acid was saturated with hydrogen sulfide for 1 h, and then simultaneously with hydrogen sulfide and hydrogen chloride. The reaction was followed by TLC (eluant, hexane–ether–acetone, 4:1:1). The bright yellow crystals of the dihydrosulfides (VI-VIII) were isolated, washed with acetic acid and ethanol, and dried in the vacuum desiccator. Purification was effected by recrystallization from alcohol–acetone (2:1) (Table 2).

2R,4R'-7,8-Benzo- (XIV, XV) and 2,4-Diphenyl-5,6-benzohexahydrothiochromenes (XVI). To a solution of 0.02 mole of the benzodihydrothiochromene (VI-VIII) in 0.04 mole of triethylsilane was added 0.06 mole of dry trifluoroacetic acid. The reaction mixture was warmed to 60-80°C, and after 3-5 min the starting material had been completely converted into the corresponding sulfide (XIV-XVI), which separated as colorless crystals. These were isolated, washed with alcohol, and dried to give 95-98% of the sulfide (XIV-XVI), the melting points of which corresponded with those of the sulfides obtained by reacting the diketone (I, II, or V) with H_2S in trifluoroacetic acid. 2-Phenyl-4-p-methoxyphenyl-7,8-benzo-5,6-dihydro- (XIX) and 2,4-diphenyl-5,6-benzo-7,8-dihydrochromylium fluoroborates were synthesized as described in [1], purification being effected by reprecipitation from chloroform with ether (Table 2).

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PYRROLO[3,2-d]PYRIMIDINES.

III. 7-AMINOMETHYL-SUBSTITUTED PYRROLO[3,2-d]PYRIMIDINES

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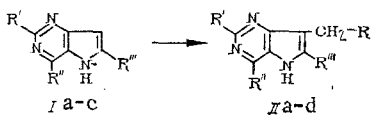
UDC 615.281:547.853.3

Some previously-synthesized amino-derivatives of pyrrolo[3,2-d]pyrimidines have been found to possess bacteriostatic activity [1].

Continuing investigations in this series of compounds, we have synthesized some aminomethyl derivatives of pyrrolo[3,2-d]pyrimidines. The standard Mannich reaction was used to synthesize the 7-aminomethyl-substituted compounds (IIa-d), isolated as their hydrochlorides (IIa, b), base (IIc), and picrate (IId).



I a-c II a-d

a) $R' = R''' = H$, $R'' = OH$;
b) $R' = R''' = CH_3$, $R'' = OH$;
c) $R' = R''' = CH_3$, $R'' = OCH_3$;

a) $R' = R''' = H$, $R'' = OH$, $R = N(C_2H_5)_2$;
b) $R' = R''' = CH_3$, $R'' = OH$, $R = N(C_2H_5)_2$;
c) $R' = R''' = CH_3$, $R'' = OCH_3$, $R = N(CH_2)_5$;
d) $R' = R''' = CH_3$, $R'' = OCH_3$, $R = N(CH_3)_2$;

The aminomethyl derivatives (Va-e) were synthesized from pyrrolo[3,2-d]pyrimidines containing an aldehyde group in the 7-position [2]. Reaction of the aldehydes (IIIa-c) with amines first gave the Schiff's bases (IVa-e), which were subsequently reduced with alcoholic sodium borohydride to the amines (Va-e). The IR spectra of the Schiff's bases showed characteristic absorption for the >C=N group at 1630 cm^{-1}, which disappeared on reduction to (Va-e). Reaction of 4-chloro-2-phenylpyrrolo[3,2-d]pyrimidine-7-aldehyde (IIIb) with an excess of cyclohexenylethylamine in aqueous solution resulted in replacement of the chlorine atom in addition to reaction at the aldehyde group, giving (IVe), which was reduced to the corresponding diamine (Ve).

*Deceased.

All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 5, pp. 548-552, May, 1982. Original article submitted October 29, 1981.

 0091-150X/82/1605-0352$07.50