SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 5-ARYL-4-ACYL-1-(N,N-DIMETHYLAMINOETHYL)-3-HYDROXY-3-PYRROLIN-2-ONES

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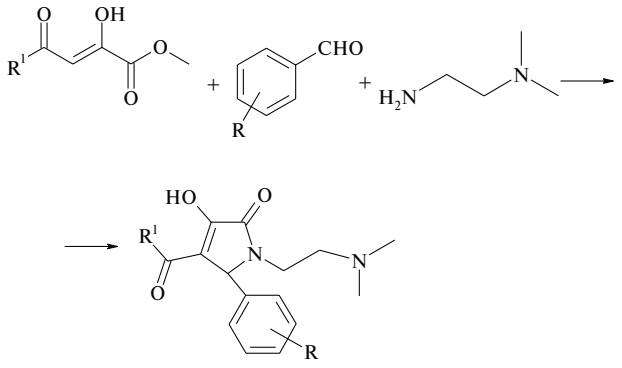
Previously we demonstrated that substituted 3-hydroxy-3-pyrrolin-2-ones possess pharmacological activity of various types including antimicrobial [1, 2], antiinflammatory [3], and nootropic [1]. Taking into account that some of the antimicrobial agents used in medicine contain dialkylaminoalkyl groups [4], it was interesting to synthesize a series of 5-aryl-4-acyl-1-(N,N-dimethylaminoethyl)-3-hydroxy-3-pyrrolin-2-ones and study their antimicrobial properties.

With a view to this synthesis, we have studied the reactions of acylpyruvic acids with a mixture of N,N-dimethylethylenediamine and an aromatic aldehyde. The results of our investigation showed that mixing equimolecular amounts of the initial reagents in warm ethyl alcohol or dioxane leads with a good yield to the formation of compounds I – XXVIII (Table 1).



I – XXVIII

R^1 = CH_3 (I – XI), C_6H_5 (XII – XXII), C_6H_5Cl-*p* (XXIII – XXV), $C_6H_5OCH_3$-*p* (XXVI – XXVIII);
R = H (I, XII, XXIII, XXVI); 2-F (II, XIII); 4-F (III, XIV); 2-Cl (IV, XV); 4-Cl (V, XVI, XXIV, XXVII); 4-Br (VI, XVII, XXV, XXVIII);
2-OCH_3 (VII, XVIII); 4-OCH_3 (VIII, XIX); 3,4-$(OCH_3)_2$ (IX, XX); 3-OCH_3, 4-OH (X, XXI); 4-OH (XI, XXII).

Compounds I – XXVIII appear as colorless crystalline substances poorly soluble in alcohols and water, but soluble in water – alcohol mixtures. All these compounds develop a

TABLE 1. Physicochemical Properties and Yields of Compounds I – XXVIII

Compound	Yield, %	M.p., °C (solvent)	Empirical formula
I	78.0	242 – 243 (ethanol)	$C_{16}H_{20}N_2O_3$
II	96.4	216 – 218 (ethanol)	$C_{16}H_{19}FN_2O_3$
III	63.7	240 – 242 (ethanol)	$C_{16}H_{19}FN_2O_3$
IV	98.3	225 – 227 (isopropanol)	$C_{16}H_{19}ClN_2O_3$
V	90.2	246 – 248 (toluene)	$C_{16}H_{19}ClN_2O_3$
VI	49.1	242 – 244 (toluene)	$C_{16}H_{19}BrN_2O_3$
VII	85.3	178 – 180 (isopropanol)	$C_{17}H_{22}N_2O_4$
VIII	87.4	223 – 224 (toluene)	$C_{17}H_{22}N_2O_4$
IX	44.0	224 – 226 (toluene)	$C_{18}H_{24}N_2O_5$
X	82.3	212 – 214 (toluene)	$C_{17}H_{22}N_2O_5$
XI	85.5	205 – 207 (toluene)	$C_{16}H_{20}N_2O_4$
XII	82.8	239 – 241 (toluene)	$C_{21}H_{22}N_2O_3$
XIII	92.4	220 – 222 (isopropanol)	$C_{21}H_{21}FN_2O_3$
XIV	87.3	218 – 220 (isopropanol)	$C_{21}H_{21}FN_2O_3$
XV	70.3	198 – 200 (toluene)	$C_{21}H_{21}ClN_2O_3$
XVI	75.5	245 – 247 (toluene)	$C_{21}H_{21}ClN_2O_3$
XVII	56.7	205 – 207 (toluene)	$C_{21}H_{21}BrN_2O_3$
XVIII	45.3	138 – 140 (toluene)	$C_{22}H_{24}N_2O_4$
XIX	68.4	222 – 224 (toluene)	$C_{22}H_{24}N_2O_4$
XX	82.9	180 – 182 (isopropanol)	$C_{23}H_{26}N_2O_5$
XXI	68.2	242 – 244 (toluene)	$C_{22}H_{24}N_2O_5$
XXII	93.9	228 – 230 (toluene)	$C_{21}H_{22}N_2O_4$
XXIII	62.5	194 – 196 (toluene)	$C_{21}H_{21}ClN_2O_3$
XXIV	81.4	221 – 223 (toluene)	$C_{21}H_{20}ClN_2O_3$
XXV	63.7	183 – 185 (toluene)	$C_{21}H_{20}BrClN_2O_3$
XXVI	59.5	201 – 203 (toluene)	$C_{22}H_{24}N_2O_4$
XXVII	42.3	221 – 223 (toluene)	$C_{22}H_{23}ClN_2O_4$
XXVIII	55.5	219 – 221 (toluene)	$C_{22}H_{23}BrN_2O_4$

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TABLE 2. Spectroscopic Characteristics of Compounds I – XXVIII

Compound	R^1	R	IR spectrum: ν, cm^{-1}			^1H NMR spectrum: δ, ppm							
			C=C (lactam)	C=O (ketone)	OH	H_{arom}		$C_{(5)}H$	$(CH_3)_2N$	$C_{(2)}H_2$	$C_{(1)}H_2$		Other protons
						R^1CO	Ar				H_A	H_B	
I	CH_3	H	1686	1611	–	–	7.29 (m)	5.38	2.82	3.12	4.00	3.39	2.31 (s, 3H, CH_3CO), 9.31 (s, 1H, OH)
II	"	2-F	1686	1626	3446	–	7.17 (m)	5.59	2.79	3.12	3.97	3.34	2.30 (s, 3H, CH_3CO), 9.36 (s, 1H, OH)
III	"	4-F	1689	1603	–	–	7.06 (t, 2H, $C_{(o)}H$), 7.27 (t, 2H, $C_{(m)}H$)	5.41	2.82	3.11	4.00	3.39	2.32 (s, 3H, CH_3CO), 9.41 (s, 1H, OH)
IV	"	2-Cl	1689	1626	3485	–	7.13 (m)	5.53	2.78	3.13	3.98	3.35	2.33 (s, 3H, CH_3CO), 9.35 (s, 1H, OH)
V	"	4-Cl	1690	1620	–	–	7.06 (d, 2H, $C_{(o)}H$), 7.15 (d, 2H, $C_{(m)}H$)	5.43	2.79	3.15	3.99	3.33	2.29 (s, 3H, CH_3CO), 9.51 (s, 1H, OH)
VI	"	4-Br	1692	1609	–	–	7.01 (d, 2H, $C_{(o)}H$), 7.17 (d, 2H, $C_{(m)}H$)	5.48	2.83	3.13	3.96	3.34	2.34 (s, 3H, CH_3CO), 9.56 (s, 1H, OH)
VII	"	2-OCH_3	1683	1620	3416	–	7.26 d, 7.03 t	5.69	2.84	3.17	3.47	3.32	2.33 (s, 3H, CH_3CO), 3.84 (s, 3H, OCH_3), 9.35 (s, 1H, OH)
VIII	"	4-OCH_3	1680	1609	3333	–	6.76 (d, 2H, $C_{(o)}H$), 7.13 (d, 2H, $C_{(m)}H$)	5.40	2.79	3.18	3.75	3.44	2.33 (s, 3H, CH_3CO), 3.74 (s, 3H, OCH_3), 9.47 (s, 1H, OH)
IX	"	3,4-$(OCH_3)_2$	1677	1604	–	–	7.10 (m)	5.55	2.90	3.20	3.65	3.55	2.38 (s, 3H, CH_3CO), 3.86 (s, 6H, OCH_3), 9.58 (s, 1H, OH)
X	"	3-OCH_3, 4-OH	1680	1617	–	–	6.70 (d, 1H, $C_{(o)}H$), 6.65 (d, 1H, $C_{(m)}H$), 6.80 (s, 1H, $C_{(o)}H$)	5.43	2.87	3.17	3.87	3.34	2.33 (s, 3H, CH_3CO), 3.68 (s, 3H, OCH_3), 9.75 (s, 1H, OH)
XI	"	4-OH	1674	1603	3405	–	6.65 (d, 2H, $C_{(o)}H$), 7.24 (d, 2H, $C_{(m)}H$)	5.53	2.84	3.21	3.89	3.37	2.38 (s, 3H, CH_3CO), 9.85 (s, 1H, OH)
XII	C_6H_5	H	1696	1616	–	7.49 (m)		5.45	2.37	2.64	3.78	2.75	–
XIII	"	2-F	1698	1606	3382	7.65 (m)		5.89	2.85	2.71	3.91	3.26	–
XIV	"	4-F	1697	1621	–	7.29 (t, 2H, $C_{(m)}H$), 7.72 (d, 2H, $C_{(o)}H$), 7.35 (t, 1H, $C_{(p)}H$)	7.06 (t, 2H, $C_{(o)}H$), 7.27 (t, 2H, $C_{(m)}H$)	5.81	2.81	3.01	3.69	2.94	–
XV	"	2-Cl	1692	1620	–	7.72 (d), 7.27 (m)		5.85	2.64	2.99	3.59	2.75	–
XVI	"	4-Cl	1683	1602	–	7.79 (m), 7.97 (m)		5.89	2.93	3.20	4.06	3.48	–
XVII	"	4-Br	1692	1629	–	7.29 (t, 2H, $C_{(m)}H$), 7.72 (d, 2H, $C_{(o)}H$), 7.35 (t, 1H, $C_{(p)}H$)	7.28 (d, 2H, $C_{(o)}H$), 7.43 (d, 2H, $C_{(m)}H$)	5.35	2.61	2.89, 3.06	3.82	2.75	–

TABLE 2. (Continued)

Compound	R^1	R	IR spectrum: ν, cm^{-1}			^1H NMR spectrum: δ, ppm							
			C=C (lactam)	C=O (ketone)	OH	H_{arom}		$C_{(5)}H$	$(CH_3)_2N$	$C_{(2)}H_2$	$C_{(1)}H_2$		Other protons
						R^1CO	Ar				H_A	H_B	
XVIII	"	2-OCH_3	1689	1601	–	7.97 (m), 7.75 (m)		6.10	2.93	3.15	3.87	3.30	3.96 (s, 3H, OCH_3), 9.75 (s, 1H, OH)
XIX	"	4-OCH_3	1686	1603	3396		6.86 (d, 2H, $C_{(o)}H$), 7.19 (d, 2H, $C_{(m)}H$)	5.59	2.63	3.11	3.75	3.25	3.86 (s, 3H, OCH_3), 9.75 (s, 1H, OH)
XX	"	3,4-$(OCH_3)_2$	1694	1617	3545	7.79 (m)	7.19 (s, 1H, $C_{(o)}H$), 8.14 (m, 1H, $C_{(o)}H$), 7.98 (m, 1H, $C_{(m)}H$)	5.79	2.93	3.17	3.67	3.31	3.82 (s, 3H, OCH_3), 9.52 (s, 1H, OH)
XXI	"	3-OCH_3, 4-OH	1674	1603	–	7.32 (t, 2H, $C_{(m)}H$), 7.39 (t, 1H, $C_{(o)}H$), 7.71 (d, 1H, $C_{(o)}H$)	6.73 (d, 1H, $C_{(o)}H$), 6.68 (d, 1H, $C_{(m)}H$), 6.82 (s, 1H, $C_{(o)}H$)	5.30	2.51	2.75	3.78	2.89	3.71 (s, 3H, OCH_3), 8.82 (s, 1H, OH-*p*)
XXII	"	4-OH	1668	1601	3359		6.76 (d, 2H, $C_{(o)}H$), 7.13 (d, 2H, $C_{(m)}H$)	5.39	2.53	3.00	3.86	3.04	9.87 (s, 1H, OH)
XXIII	4-ClC_6H_4	H	1689	1623	3483	7.31 (d, 2H, $C_{(o)}H$), 7.75 (d, 2H, $C_{(m)}H$)	7.25 (m)	5.34	2.62	2.55	3.79	2.99	–
XXIV	"	4-Cl	1692	1600	3454	7.21 (d, 2H), 7.31 (t, 4H), 7.77 (d, 2H)		5.37	2.61	2.92	3.79	2.84	–
XXV	"	4-Br	1694	1608	3425	7.28 (q, 6H), 7.75 (d, 2H)		5.30	2.67	2.89	3.79	3.10	–
XXVI	4-$OCH_3C_6H_4$	H	1688	1610	3364	6.87 (d, 2H, $C_{(o)}H$), 7.28 (d, 2H, $C_{(m)}H$)	7.25 m, 7.73 (d, 2H, $C_{(o)}H$)	5.47	2.32	2.55	3.77	2.74	3.81 (s, 3H, OCH_3)
XXVII	"	4-Cl	1697	1601	3508	6.87 (d, 2H, $C_{(o)}H$), 7.76 (d, 2H, $C_{(m)}H$)	7.25 (d, 2H, $C_{(o)}H$), 7.32 (d, 2H, $C_{(m)}H$)	5.45	2.40	2.70	3.79	2.80	3.82 (s, 3H, OCH_3)
XXVIII	"	4-Br	1679	1616	3434	6.87 (d, 2H, $C_{(o)}H$), 7.25 (d, 2H, $C_{(m)}H$)	7.40 (d, 2H, $C_{(o)}H$), 7.75 (d, 2H, $C_{(m)}H$)	5.43	2.40	2.69	3.76	2.78	3.82 (s, 3H, OCH_3)

characteristic intense cherry-red color on reacting with an alcohol solution of iron chloride.

The IR spectra of hydroxypyrrolinones I – XXVIII contain absorption bands related to the stretching vibrations of lactam carbonyl groups (1674 – 1694 cm^{-1}) and side-chain ketone carbonyl groups (1601 – 1629 cm^{-1}). The absorption band due to vibrations of the hydroxy groups is broadened so as to become unobservable in most cases. Only the IR spectra of compounds II, IV, VII, VIII, XIII, XIX, and XX display this absorption band at 3333 – 3545 cm^{-1}, and the spectra of compounds XXIII – XXVIII (R^1 = *p*-C_6H_4Cl and *p*-$C_6H_4OCH_3$), at 3364 – 3508 cm^{-1}.

The ^1H NMR spectra of compounds I – XXVIII display signals due to methine protons in position 5 of the heterocycle (at 5.30 – 6.10 ppm), a singlet due to six protons of a dimethylamino group (2.32 – 2.93 ppm), and signals of methylene protons of the substituents at nitrogen atoms (a single multiplet due to $C_{(2)}H_2$ at 2.55 – 3.20 ppm and two multiplets due to $C_{(1)}H_2$: at 3.47 – 4.0 ppm ($H_{(A)}$) and 2.74 – 3.55 ppm ($H_{(B)}$). In addition, there is a group of lines due to aromatic protons (in the region of 6.68 – 7.98 ppm), a signal of protons of the acetyl residue in compounds I – XI (2.30 – 2.36 ppm), a singlet due to protons of the methoxy group in compounds VII – X, XVIII – XXI, XXVI – XXVIII

(3.71 – 3.96 ppm), a broad signal from protons of the enol hydroxy groups (9.31 – 9.75 ppm), and a signal of protons in the phenol hydroxy group (8.82 – 8.84 ppm) in compounds XXI, XXII, X, XI (Table 2).

The data of ^{1}H NMR spectroscopy and the reaction with iron(III) chloride suggest that the synthesized compounds I – XXVIII occur predominantly in the enolic form.

EXPERIMENTAL CHEMICAL PART

The ^{1}H NMR spectra were measured on Bruker DRX 500 (working frequency, 500.13 MHz) and WM-250 (250.13 MHz) spectrometers (Germany) using DMSO-d_6 as the solvent and HMDS as the internal standard. The IR absorption spectra were recorded on the UR-20 and Specord M-80 spectrophotometers (Germany) using samples prepared as nujol mulls. The course of the reactions was followed and purity of the reaction products was checked by TLC on Silufol UV-254 plates eluted with a benzene – acetonitrile – ethyl acetate (2 : 1 : 1) mixture. The spots of 4-acetylpyrrolin-2-ones (I – XI) were revealed by exposure to iodine vapor, while the spots of compounds XII – XXVIII were detected under UV illumination. The data of elemental analyses agree with the results of calculations using the empirical formulas.

General procedure for the synthesis of 5-aryl-4-acyl-1-(N,N-dimethylaminoethyl)-3-hydroxy-3-pyrrolin-2-ones (I – XXVIII). To a warm solution of 0.01 mole of an aromatic aldehyde and 0.01 mole of a 2,4-dioxobutanoic acid methyl ether in 10 ml of 96% ethyl alcohol was added N,N-dimethylethylenediamine (0.01 mole) and the reaction mixture was allowed to stand for 24 h at room temperature. The precipitate was separated by filtration and recrystallized (see Table 1).

EXPERIMENTAL BIOLOGICAL PART

The synthesized compounds were tested for bacteriostatic activity using a conventional method of double serial dilutions in a beef-infusion broth. A daily culture grown in the broth was washed off with a sterile physiological solution of sodium chloride and used to prepare the stock solution with a bacterial load of 500×10^6 microbial cells per ml (as determined according to the bacterial standard). The stock solution was diluted to 1/100 with sterile broth to obtain a working solution, and 0.1 ml of this solution (with a microbial load of 5×10^6 per ml) was introduced into 2 ml of the broth. The bacterial load in the sample was 250,000 microbes per ml. The bacteriostatic effect was assessed by the presence or absence of the growth of test microbes upon incubation for 18 – 20 h at 36 – 37°C. The acting dose was estimated as the minimum concentration (MIC, μg/ml) inhibiting microbial growth.

It was established that all the synthesized compounds exhibited a weak antimicrobial activity with MIC ranging from 250 to 1000 μg/ml.

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