SYNTHESIS AND ANTIFUNGAL ACTIVITY OF 3-ARYL-6,7-DIHYDRO-5H-PYRROLO[1,2-a]IMIDAZOLES

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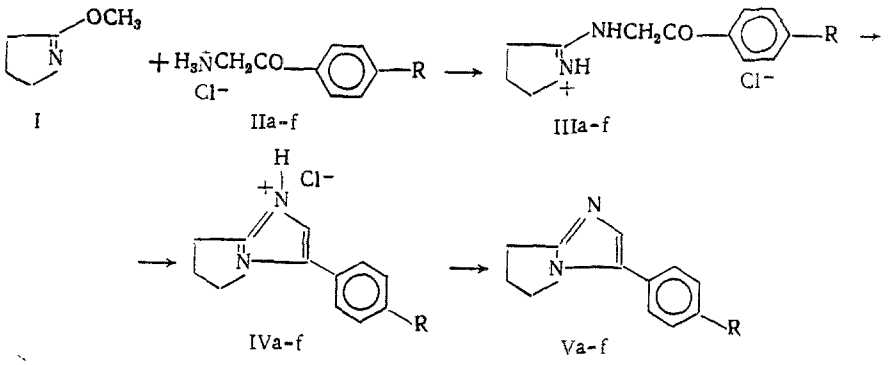
It is generally known that imidazole derivatives, such as Clotrimazole [2], Myconazole [3], and Ketoconazole [6], are effective antifungal preparations. We therefore undertook a search for compounds with antifungal activity among condensed heterocyclic compounds with an imidazole nucleus, particulary among the series of the 6,7-dihydro-5H-pyrrolo [1,2-a]-imidazoles.

It has been established earlier [4] that the 2-(R-amino-)-Δ^1-pyrrolines are formed as a result of nucleophilic displacement by appropriate primary amines in 2-alkoxy-Δ^1-pyrrolines. We have shown that when α-aminoacetophenone hydrochlorides are used as the primary amines in a condensation reaction with 2-methoxy-Δ^1-pyrroline the resultant products are salts of N-(4,5-dihydro-3H-pyrrole-2-yl)-α-aminoacetophenones (IIIa-f).

The structure of the synthesized salts IIIa-f was confirmed by PMR and IR spectral data. Thus, the PMR spectra of the synthesized compounds exhibjt pyrrolidine ring proton signals in the form of two triplets and a multiplet (groups 4-CH_2) as well as a diproton doublet of the methylene group in the residue of the corresponding phenacylamine.

Our study of the properties of the IIIa-f salts showed that when they are boiled in 0.1 N HCl they are cyclized to hydrochlorides of 3-aryl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (IVa-f). When the latter are treated with aqueous solutions of alkali the corresponding bases (Va-f) are obtained at a high yield.



R = H(IIa — Va), OCH_3(IIb — Vb), Cl (IIc — Vc), Br (IId — Vd), Ph (IIe — Ve), NO_2 (IIf — Vf)

The structure of the IVa-f salts and the Va-f bases was confirmed by spectral analysis of the cyclization production and the IR and PMR spectra of the starting quaternary IIIa-f salts. The IR spectra of compounds IVa-f and Va-f were lacking in absorption bands in the regions 3290-3000, 1735-1695, and 1685-1665 cm^{-1} which is characteristic for the starting salts IIIa-f and are related to ν_{NH}, $\nu_{C=O}$, and $\nu_{C=N}$ respectively. The PMR spectra of the cyclic products are lacking in methylene group NH-CH_2-CO signals in the region 5.05-4.20 ppm that were observed in the case of compounds IIIa-f, but those spectra did exhibit imidazole ring proton signals at 7.06-7.65 ppm.

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TABLE 1. Properties of Compounds IIIa-f, IVa-f, and Va-f

Compound	Yield, %	mp, °C	Found, %		Empirical formula	Calculated, %	
			Cl	N		Cl	N
IIIa	78	192—193	15,0	11,4	$C_{12}H_{15}ClN_2O$	14,9	11,7
IIIb	69	196—197	13,5	10,2	$C_{13}H_{17}ClN_2O_2$	13,2	10,4
IIIc	83	194—195	26,0	10,4	$C_{12}H_{14}Cl_2N_2O$	26,0	10,3
IIId	72	204—206	—	8,76	$C_{12}H_{14}BrClN_2O$	—	8,82
IIIe	65	224—226	11,5	8,75	$C_{18}H_{19}ClN_2O$	11,3	8,90
IIIf	62	195—197	12,2	15,1	$C_{12}H_{14}ClN_3O_3$	12,5	14,8
IVa	83	216—218	16,0	12,4	$C_{12}H_{13}ClN_2$	16,1	12,7
IVb	80	218—220	13,9	11,0	$C_{13}H_{15}ClN_2O$	14,2	11,2
IVc	75	222—224	27,8	10,8	$C_{12}H_{12}Cl_2N_2$	27,8	11,0
IVd	79	222—223	—	9,29	$C_{12}H_{12}BrClN_2$	—	9,35
IVe	57	236—238	11,7	9,11	$C_{18}H_{17}ClN_2$	11,9	9,44
IVf	68	236—237	13,2	15,5	$C_{12}H_{12}ClN_3O_2$	13,3	15,8
Va	91	113—115	—	15,5	$C_{12}H_{12}N_2$	—	15,2
Vb	85	145—146	—	13,4	$C_{13}H_{14}N_2O$	—	13,1
Vc	88	144—146	16,5	12,6	$C_{12}H_{11}ClN_2$	16,2	12,8
Vd	82	156—157	—	10,5	$C_{12}H_{11}BrN_2$	—	10,7
Ve	72	202—203	—	11,0	$C_{18}H_{16}N_2$	—	10,8
Vf	79	190—191	—	18,1	$C_{12}H_{11}N_3O_2$	—	18,3

Note. Compounds IIIa-d, IVa, and IVb were recrystallized from 2-propanol; compounds IIIe, f, IVc, d from ethanol; VIe, f from methanol; Vb-d from heptane; Ve, f from benzene. Va was purified by vacuum sublimation.

TABLE 2. Antifungal Activity of IIIa-f, IVa-f

Compound	M. canis		T. mentagrophytes var. gyps.		T. rubrum		C. albicans	
	III	IV	III	IV	III	IV	III	IV
a	500	500	500	500	500	500	500	250
b	500	250	500	250	500	250	500	250
c	500	500	500	500	500	500	500	125
d	500	500	500	125	500	250	500	62,5
e	62,5	500	62,5	125	250	500	500	500
f	62,5	500	62,5	500	500	500	500	500

Note. Listed values are minimal inhibiting concentrations (in μg/ml).

EXPERIMENTAL (CHEMICAL)

IR spectra of the synthesized compounds were recorded on a Specord IR-71 instrument (GDR) in KBr pellets. PMR spectra were recorded on a tKR-60 (60 MHz) instrument. The solvents were CF_3COOH and $CDCl_3$. Chemical shifts are given in a δ scale with reference to TMS.

The starting reagent 2-methoxy-Δ^1-pyrroline I was obtained by method [4], and the hydrochlorides of α-aminoacetophenones IIa-f were prepared by the standard methods [1-5].

N-(4,5-Dihydro-3H-pyrrole-2-yl)α-amino(p-R-acetone) Hydrochlorides (IIIa-f). A mixture composed of 9.9 g (0.1 mole) of I and 0.1 mole of the corresponding hydrochloride of α-aminoacetophenone IIa-f in 150 ml of absolute ethanol was stirred for 24 h at 20°C. The precipitate was then filtered off, washed with ether, and recrystallized from the polar solvent. Data on compounds IIIa-f are given in Table 1.

3-Aryl-6,7-Dihydro-5H-pyrrolo[1,2-a]imidazole Hydrochlorides (IVa-f). A solution of 0.05 mole of the appropriate salt of IIIa-f in 50 ml of 0.1 N HCl was boiled for 5 h. The reaction mixture was then cooled to 0°C and the precipitate was filtered off, washed with water, and dried. Data on compounds IVa-f are given in Table 1.

3-Aryl-6,7-Dihydro-5H-pyrrolo[1,2-a]imidazoles (Va-f). A 20 ml portion of a 10% NaOH solution was added to a solution of 0.01 mole of the appropriate IVa-f compound in 100 ml of water. The resultant precipitate was filtered off, washed with water, and dried. Data on compounds Va-f are given in Table 1.

EXPERIMENTAL (PHARMACOLOGICAL)

Antifungal activity against pathogenic fungi (*M. canis*, *T. mentagrophytes* var. *gypseum* *T. rubrum*, and *C. albicans*) was tested by the double series dilution method in a liquid Sabouraud medium (pH 6.8) at an incoculum denisty of $1 \cdot 10^6$ fungal bodies per 1 ml.

The pharmacological tests showed that compounds IIIa-f and IVa-f exhibit moderate antifungal activity. A comparison of the antifungal activity of compounds IIIa-d to that of their IVa-d cyclization products allows us to conclude that the cyclization of N-(4,5-dihydro-3H-pyrrole-2-yl)-α-amino (p-R-acetophenones) to derivatives of 3-aryl-6,7-dihydro-5H-pyrrolo-[1,2-a]imidazole results in greater antifungal activity. An opposite relationship was observed for compounds IIIe-f in which case their activity against the pathogenic fungi *M. canis* and *T. mentagrophytes* var. *gypseum* was almost ten times that of compounds IVe-f (Table 2).

Thus, the fact that the synthesized compounds exhibit antifungal activity holds promise for the further study of both the 3-aryl-6,7-dihydro-5H-pyrrolo[1,2-a]-imidazole derivatives and the salts of N-(4,5-dihydro-3H-pyrrole-2-yl)-α-amino(p-R-acetophenones) as potential antifungal agents.

LITERATURE CITED

1. H. E. Baumgarten and J. M. Petersen, J. Am. Chem. Soc., 82, No. 2, 459-463 (1960).
2. K. H. Buchel, W. Draber, E. Reger, and M. Plempel, Arzneim.-Forsch., 22, No. 8, 1260-1272 (1972).
3. A. L. Costa, A. Valenti, L. E. Loteta, and S. Midili, Mykosen, 20, No. 11, 431-440 (1977).
4. A. Etienne and Y. Correia, Bull. Soc. Chim. France, No. 10, 3704-3712 (1969).
5. C. Mannich and F. L. Hahn, Berichte, 1542-1552 (1911).
6. J. Van Vutsen, Am. J. Med., 74, No. 1B, 9-15 (1983).