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SYNTHESIS OF 3-ARYL-5-METHYLPYRROLIDINO[1,2-b]PYRAZOLES

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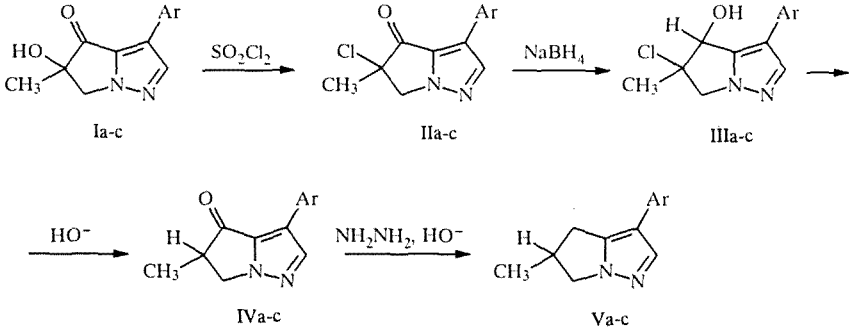
The sequential conversion of 5-hydroxy-5-methyl-4-oxo-3-arylpyrrolidino[1,2-b]pyrazoles to 5-methyl-5-chloro-4-oxo-, 4-hydroxy-5-methyl-5-chloro-, and 5-methyl-4-oxo-3-arylpyrrolidino[1,2-b]pyrazoles and the Huang-Minlon reduction of the last afforded 3-aryl-5-methylpyrrolidino[1,2-b]pyrazoles.

The heterocyclization of epoxypropionylpyrazolines and pyrazoles is a convenient preparative method for the synthesis of 5-hydroxy-4-oxo-3-arylpyrrolidino[1,2-b]pyrazoles [1, 2] – oxygenated analogs of the alkaloid vitasomnine [3, 4]. In the continuation of the study of the synthetic application of ketols of pyrrolidino[1,2-b]pyrazoles and for the purpose of synthesizing ketones of this series as well as alkyl-substituted analogs of vitasomnine, the present work presents results of the reduction of 5-hydroxy-5-methyl-4-oxo-3-arylpyrrolidino[1,2-b]pyrazoles (Ia-c).

The choice of the scheme of conversions presented below is determined by the fact that the direct reduction of 3-phenylpyrrolidino[1,2-b]pyrazole (Ia) according to Wolff–Kishner, as well as the utilization of the Huang-Minon modification, leads to a mixture of substances which yielded, besides 5-hydroxy-5-methyl-3-phenylpyrrodlino[1,2-b]pyrazole, the product of the dehydration of the hydazone of the bicyclic ketone (Ia) – 4-NH-diazenyl-5-methyl-3-phenylpyrrolidino[1,2-b]-1H-pyrazoline and 2-hydroxy-2-methyl-3-(4-phenylpyrazolyl)propanoic acid, formed by the cleavage of the pyrrolidine ring of the ketone (Ia). When the proposed four-stage scheme of reduction is utilized, the boiling of the compounds (Ia-c) with thionyl chloride in chloroform leads to the nucleophilic substitution of the tertiary alcohol group and the formation of the chloroketones (IIa-c). The IR spectra of the compounds (IIa-c) lack absorption in the region of 3400-3600 cm^{-1}, and the band of the stretching vibrations of the C=O group is observed at 1720 cm^{-1}. When subjected to the action of sodium borohydride in methanol, the chloroketones (IIa-c) are reduced stereospecifically to the 4-hydroxy-5-methyl-5-chloro-3-arylpyrrolidino[1,2-b]pyrazoles (IIIa-c) with the *cis* disposition of the chlorine and the hydroxyl group; this is confirmed by the case of their dehydrochlorination in the reaction with alcoholic alkali giving the 5-methyl-4-oxo-3-arylpyrrolidino[1,2-b]pyrazoles (IVa-c).



Ia-c IIa-c IIIa-c

IVa-c Va-c

I—V a Ar = C_6H_5; b Ar = 4-BrC_6H_4; c Ar = 4-$CH_3OC_6H_4$

The attack of the hydride ion from one diastereotopic side of the C=O group of the chloroketones (IIa-c) is probably caused by stearic and electronic interactions with the approach of the reagent. The IR spectra of the compounds (IIIa-c) lack the absorption of the carbonyl group; the absorption band of the OH group is situated in the region of 3540-3560 cm^{-1}, and the stretching vibrations of the C=O group of the compounds (IVa-c) are observed at 1700 cm^{-1}. The Huang-Minlon reduction

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TABLE 1. Characteristics of the Synthesized Compounds (IIa-c)-(Va-c)

Compound	Empirical formula	M.P., °C	PMR spectrum,* Chemical shifts, δ, ppm; SSCC (J, Hz)	Yield, %
IIa	$C_{13}H_{11}ClN_2O$	108...109	1,87 (3H, s, CH_3); 4,80 (2H, s, CH_2); 7,30and 7,90 (3Hand2H, and m, Ph); 8,20 (1H, s, 2-H)	77
IIb	$C_{13}H_{10}BrClN_2O$	140...141	1,85 (3H, s, CH_3); 4,76 (2H, s, CH_2); 7,38and 7,76 (4H, AB- syst., J = 9,0, Ar); 8,10 (1H, s, 2-H)	81
IIc	$C_{14}H_{13}ClN_2O_2$	98...99	1,54 (3H, s, CH_3); 3,70 (3H, s, OCH_3); 4,76 (2H, s, CH_2); 6,85and7,83 (4H, AB- syst., J =9,0, Ar); 8,08 (1H, s, 2-H)	73
IIIa	$C_{13}H_{13}ClN_2O_2$	187...188	1,73 (3H, s, CH3); 4,26, 4,44 (2H, AB- syst., J = 12,0, CH_2); 5,10 (1H, d, J =8,0, 4-H); 5,50 (1H, d, J = 8,0, OH); 7,20 and7,68 (3Hand2H, and m, Ar); 7,80 (1H, s, 2-H)	94
IIIb	$C_{13}H_{12}BrClN_2O$	233...234	1,70 (3H, s, CH_3); 4,30, 4,36 (2H, AB- syst., J = 12,0, CH_2); 5,00 (1H, d, J =8,0, 4-H); 6,24 (1H, d, J = 8,0,OH); 7,34 d 7,54 (4H, AB- syst., J = 9,0, Ar); 7,70 (1H, s, 2-H)	97
IIIc	$C_{14}H_{15}ClN_2O_2$	203...204	1,68 (3H, s, CH3); 3,72 (1H, s, OCH_3); 4,20, 4,40 (2H, AB- syst., J = 12,0, CH_2); 5,00 (1H, d, J = 8,0, 4-H); 6,00 (1H, d, J = 8,0, OH); 6,82 d 7,55 (4H, AB-,syst., J = 9,0, Ar); 7,66 (1H, s, 2-H)	91
IVa	$C_{13}H_{10}N_2O$	85...86	1,30 (3H, d, J = 7,3, CH_3); 3,26 (1H, d.d., J =7,3 and 4,1, 5-H); 4,00 (1H, q, J = 12,0, 4,1, 6-H); 4,66 (1H, q, J = 12,0, 7,3, 6-H); 7,20 and7,84 (3Hand2H, syst.m, Ar); 8,07 (1H, s, 2-H)	90
IVb	$C_{13}H_{11}BrN_2O$	152...153	1,35 (3H, d, J = 7,3, CH_3); 3,20 (1H, d. d, J = =7,3and4,1, 5-H); 3,92 (1H, q, J = 11,8, 4,1, 6-H)	93
IVc	$C_{14}H_{14}N_2O_2$	123...124	4,60 (1H, q, J = 11,8and7,3, 6-H); 7,34and7,64 (4H, AB- syst. J = 9,0, Ar); 7,86 (1H, s, 2-H); 1,46 (3H, d, J = 7,3, CH_3); 3,34 (1H, d.d, J = 7,3 and 4,1, 5-H); 3,82 (1H, s, OCH_3); 4,08 (1H, q, J = 11,8, 4,1, 6-H); 4,70(1H.q, J = 11,8and7,3, 6-H); 6,93and7,88 (4H, AB- syst., J = 9,0, Ar); 7,98 (1H, s, 2-H)	86
Va	$C_{13}H_{14}N_2$	77...78	1,26 (3H, d, J = 6,6, CH_3); 2,60 (1H, q, 4-H); 3,10 (1H, sextet , 5-H); 3,21 (1H, q, 4-H); 3,68 (1H, q 6-H); 4,25 (1H, q , 6-H); 7,14, 7,30...7,39 (5H, 2 m, Ar); 7,75 (1H, s 2-H)[2*]	71
Vb	$C_{13}H_{13}BrN_2$	104...105	1,31 (3H, q, J = 6,6, CH_3); 2,65 (1H, q, 4-H); 3,17 (1H, sextet , 5-H); 3,22 (1H, q, 4-H); 3,72 (1H, q, 6-H); 4,30 (1H, q); 7,28, 7,46 (4H, AB- syst., J = 9,0, Ar), 7,75 (1H, s, 2-H)[2]	60
Vc	$C_{14}H_{16}N_2O$	67...68	1,30 (3H, d, J = 6,6, CH_3); 2,60 (1H, q, 4-H); 3,10 (1H, sextet , 5-H); 3,20 (1H, q, 4-H); 3,60 (1H, q, 6-H); 3,68 (3H, s, OCH_3); 4,22 (1H, q, 6-H); 6,80, 7,54 (4H, AB-syst., J = 9,0, Ar); 7,70 (1H, s, 2-H)[2]	69

*For the compounds (IIa-c), (IIIa-c), and (IVa,b), the solvent is acetone-d_6. For (IVc) and (Va-c), the solvent is $CDCl_3$.

*2 $^2J_{44'} = 15.1$, $^3J_{45} = 5.8$, $^3J_{4'5} = 8.0$, $^3J_{CH35} = 6.6$, $^3J_{56} = 6.1$, $^2J_{66'} = 10.2$, and $^3J_{56} = 8.0$.

the ketones (IVa-c) leads to the 5-methyl-3-arylpyrrolidino[1,2-b]pyrazoles (Va-c). The structure of all the compounds synthesized is confirmed by the data of the PMR spectra, presented in Table 1. Therefore, the proposed scheme for the reduction of 5-hydroxy-5-methyl-4-oxo-3-arylpyrrolidino[1,2-b]pyrazoles allows the synthesis of 5-methyl-susbtituted analogs of a natural alkaloid; the ketones (IVa-c) with yields of 57-73%, and the pyrrolidinopyrazoles (Va-c) with yields of 39-46% calculated on the basis of (Ia-c).

EXPERIMENTAL

The PMR spectra of the compounds (IIa-c)-(Va-c) were taken on the Tesla BS-467A (60 MHz) and Bruker WM-360 (360 MHz) instruments; the internal standard was TMS. IR spectra were recorded on the Specord IR-75 spectrophotometer using solutions in $CHCl_3$ and CCl_4 (10^{-1} M). The initial substituted pyrrolidino[1,2-b]pyrazoles (Ia-c) were synthesized by the method described in the work [2]. The physicochemical and spectral characteristics of the compounds (IIa-c)-(Va-c) are presented in Table 1.

The data of the elemental analysis for C, H, and N correspond with the calculated data.

5-Methyl-4-oxo-5-chloro-3-arylpyrrolidino[1,2-b]pyrazoles (IIa-c). To 30 mmole of the compound (Ia-c) are added 10 ml of chloroform and 10 ml of thionyl chloride, and the mixture is boiled for 3 h using a reflux condenser. The solvent and the excess of the thionyl chloride are evaporated, and the residue is diluted with 100 ml of water. The product is extracted with ether (3 × 50 ml). After the concentration of the ether to 30-50 ml, the chloroketones (IIa-c) crystallize from the extract.

4-Hydroxy-5-methyl-5-chloro-3-arylpyrrolidino[1,2-b]pyrazoles (IIIa-c). The chloroketone (IIa-c) (25 mmole) is dissolved in 100-150 ml of methanol prior to the addition of 0.75 g of sodium borohydride. The crystallization of the product commences after 5-10 min. The deposited crystals are filtered off and washed with methanol. After the partial evaporation of the mother solution, an additional amount of the product (IIIa-c) is isolated.

5-Methyl-4-oxo-3-arylpyrrolidino[1,2-b]pyrazoles (IVa-c). To 20 mmole of the chlorohydrin (IIIa-c) in 40 ml of the 1:1 mixture of methanol–dioxane, or the 1:1 mixture of methanol–tetrahydrofuran, are added 2 ml of the 50% aqueous solution of potassium hydroxyde or 1.6 g of sodium methoxide in 10 ml of methanol. The mixture is maintained for 48 h at 20°C. The solvent is subsequently removed *in vacuo*, and the residue is dilute with 50 ml of water. The product is extracted with ether (4 × 40 ml), and the extract is dried over sodium sulfate. After the concentration of the extract to 20-50 ml and the addition of 10-25 ml of hexane, the ketone (IVa-c) is crystallized.

5-Methyl-3-arylpyrrolidino[1,2-b]pyrazoles (Va-c). The ketone (IVa-c) (15 mmole) and 3 ml of hydrazine hydrate are boiled for 1 h in 15-20 ml of diethylene glycol. Potassium hydroxide (2.4 g) is added further. The excess of the hydrazine is distilled off, and the mixture is maintained at 150-180°C until the cessation of the release of nitrogen (2 h). After the cooling, the reaction mixture is diluted with water to 100 ml, neutralized with dilute hydrochloric acid, and extracted with ether (5 × 40 ml). The extract is dried over sodium sulfate. After the evaporation of the ether, the product (Va-c) crystallizes from the 1:4-1:1 mixture of ether–hexane.

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