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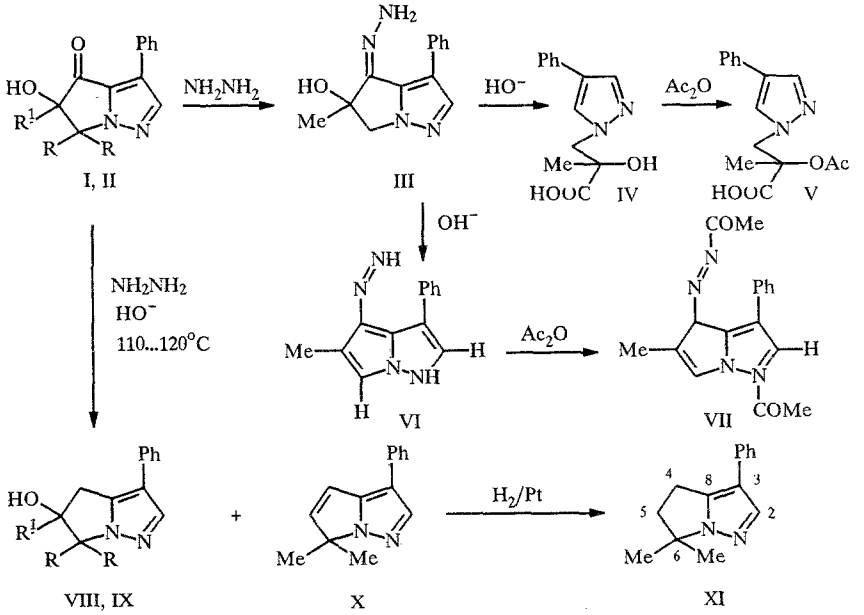
WOLFF–KISHNER REDUCTION OF 5-METHYL- AND 6,6-DIMETHYL-5-HYDROXY-4-OXO-3-PHENYLPYRROLIDINO-[1,2-b]PYRAZOLES

N. M. Kuz'menok and A. M. Zvonok

The reduction of 5-hydroxy-5-methyl-4-oxo-3-phenylpyrrolidino[1,2-b]pyrazole by heating with hydrazine hydrate in alkaline solution is accompanied by fission of the bicyclic skeleton or by dehydration depending on the solvent and reaction temperature. A two-stage synthesis of 6,6-dimethyl-3-phenyl-pyrrolidino[1,2-b]pyrazole from 5-hydroxy-6,6-dimethyl-4-oxo-3-phenylpyrrolidino[1,2-b]pyrazole is proposed.

We previously suggested a convenient method of synthesizing 5-hydroxy-4-oxo-3-arylpyrrolidino[1,2-b]pyrazoles by the heterocyclization of epoxypropionylpyrazolines and epoxypropionylpyrazoles [1-3]. The 5-hydroxy-4-oxo-3-arylpyrrolidino[1,2-b]pyrazoles are functional derivatives of the alkaloid withasomnine, isolated from the root of *Withania somnifera* Dun [4, 5]. This was the reason for developing a route for reduction with the aim of synthesizing analogs of the natural 3-phenylpyrrolidino[1,2-b]pyrazole. The results obtained on reducing 5-methyl- and 6,6-dimethyl-5-hydroxy-4-oxo-3-phenyl-pyrrolidino[1,2-b]pyrazoles (I) and (II) by heating their hydrazides in alkaline medium are presented in this study.



I, VIII R = H, R^1 = Me; II, IX R = Me, R^1 = H

It was established that the reaction of the substituted pyrrolidino[1,2-b]pyrazole (I) with hydrazine hydrate in hydroxyl-containing solvents (methanol, butanol, diethylene glycol) leads to the hydrazone (III). Heating the latter with alkali, after

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TABLE 1. Characteristics of Compounds (III)-(XI)

Compound	Empirical formula	Mp, °C	PMR spectrum		Yield, %
			solvent	chemical shifts, δ, ppm, coupling constants J, Hz	
III	$C_{13}H_{14}N_4O$	164...165	Acetone-D_6, DMSO-D_6	1,50 (3H, s); 4,18 (2H, s); 5,60 (1H, s); 5,82 (2H, s); 7,35 (5H, s); 7,64 (1H, s)	62
IV	$C_{13}H_{14}N_2O_3$	180...181	Acetone-D_6, DMSO-D_6	1,30 (3H, s); 3,45 (1H, s); 4,16, 4,28 (2H, ABsyst. J_{AB} = 12,0); 7,30 (5H, m); 7,74 (1H, s); 7,96 (1H, s)	45
V	$C_{15}H_{16}N_2O_4$	219...221	CCl_4, acetone-D_6	1,40 (3H, s); 1,96 (3H, s); 4,52, 4,80 (2H, ABsyst. J_{AB} = 12,0); 7,30 (5H, m); 7,80 (1H, s); 7,94 (1H, s); 8,98 (1H, s)	81
VI	$C_{13}H_{12}N_4$	113...115	Acetone-D_6, DMSO-D_6	1,65 (3H, s); 7,20 (5H, m); 7,30 (1H, s); 7,76 (1H, s)	59
VII	$C_{17}H_{16}N_4O_2$	166...167	$CDCl_3$	2,00 (3H, s); 2,45 (3H, s); 2,70 (3H, s); 7,30 (5H, m); 8,00 (1H, s); 8,30 (1H, s)	73
VIII	$C_{13}H_{14}N_2O$	139...140	Acetone-D_6	1,36 (3H, s); 3,00 (2H, s); 3,90 (2H, s); 4,60 (1H, s); 7,24 (5H, m); 7,60 (1H, s)	51
IX	$C_{14}H_{16}N_2O$	147...148	Acetone-D_6	1,20 (3H, s); 1,32 (3H, s); 2,82 (2H, d, J = 6,0); 3,14 (2H, d, J = 6,0); 3,14 (2H, d, J = 6,0); 4,40 (1H, t, J = 6,0); 4,70 (1H, s); 7,14 (5H, m); 7,56 (1H, s)	70
X	$C_{14}H_{14}N_2$	51...52	Acetone-D_6	1,36 (6H, s); 6,60, 6,82 (2H, AB syst. J = 6,0); 7,30 (5H m); 7,70 (1H, s)	68
XI	$C_{14}H_{16}N_2$	91...92	$CDCl_3$	1,52 (6H, s); 2,49 (2H, t, J = 7,2); 3,02 (2H, t, J = 7,2); 7,46 (5H, m); 7,99 (1H, s)	93

distilling off the excess of hydrazine hydrate, to 180-200°C is accompanied by fission of the bicyclic hydrazone skeleton with the formation of 2-hydroxy-2-methyl-3-(4-phenylpyrazolyl)propionic acid (IV). Bands were present in the IR spectrum of the acid (IV) for the stretching vibrations of the carboxyl C=O group and the OH group at 1700 and 3470 cm^{-1}. The structure of the α-hydroxy-β-pyrazolylpropionic acid (IV) was also confirmed by converting it into the α-acetoxy derivative (V) by heating with acetic anhydride. The formation of acid (IV) probably occurs by a retrodecomposition of the hydrazone (III) to the initial ketol (I) with subsequent fission of the pyrrolidine ring by nucleophilic attack by hydroxide ion at the carbonyl group. The mechanism proposed was confirmed by isolating compound (IV) on heating the bicyclic ketol (I) in diethylene glycol in the presence of alkali [2].

On boiling the hydrazone (III), obtained by the reaction of the bicyclic ketol (I) with hydrazine hydrate without isolation, with a fourfold excess of potassium hydroxide in methyl cellosolve, dehydration occurs leading to the formation of 4-NH-diazenyl-5-methyl-3-phenyl-pyrrolidino[1,2-b]-1H-pyrazoline (VI). This was converted into the corresponding N,N-diacetyl derivative (VII) by the action of acetic anhydride.

Reduction of the carbonyl group to methylene was successfully affected by decomposing the initially formed hydrazone (III) with a fourfold excess of alkali in diethylene glycol at 110-120°C. The formation of compound (VI) (17% yield), in addition to 5-hydroxy-5-methyl-3-phenylpyrrolidino[1,2-b]pyrazole (VIII), was shown by TLC.

The composition and structure of compounds (I)-(VIII) were confirmed by results of elemental analysis and PMR spectra (see Table 1). Unlike ketol (I) the 6,6-dimethyl substituted analog was reduced under the same conditions at 140-180°C with the formation of a mixture of alcohol (IX) and olefin (X) in a 1:2.3 ratio. On lowering the reaction temperature to 120-140°C the decomposition of the compound (II) hydrazone formed initially leads to the exclusive formation of the alcohol (IX). Catalytic hydrogenation of the 2H,5H-pyrrolo[1,2-b]pyrazole (X) over platinum affords 6,6-dimethyl-3-phenylpyrrolidino[1,2-b]pyrazole (XI), a methylated analog of withasomnine.

A solitary signal was present in the PMR spectrum of compound (XI) for the protons of the two methylene groups at 1.52 ppm and the signals of the methylene protons were two triplets with J = 7.2 Hz. This indicates that the pyrrolidino[1,2-b]pyrazole (XI) in solution undergoes a rapidly occurring inversion of the electron pair of the pyrrolidine ring nitrogen. This

was also confirmed by the coincidence of the signals of the methylene group carbon atoms at 26.96 ppm in the ^{13}C NMR spectrum.

6,6-Dimethyl-5-hydroxy-4-oxo-3-phenylpyrrolidino[1,2-b]pyrazole, unlike the 5-methyl derivative, may be reduced to a methyl substituted analog of the alkaloid withasomnine by a two-stage scheme, including Huang–Minlon reduction and catalytic hydrogenation, in 68% yield calculated on the bicyclic ketol (II).

EXPERIMENTAL

The IR spectra of compounds were taken on a Specord IR 75 spectrophotometer for 10^{-1} M solutions in CCl_4. The NMR spectra were measured on a Bruker WM 360 spectrometer, internal standard was HMDS. The synthesis of compounds (I) and (II) is described in [2].

Data of elemental analysis for C, H, and N for compounds (III)-(XI) corresponded to calculated values.

2-Acetoxy-2-methyl-3-(4-phenylpyrazolyl)propionic acid (V) was described in [2].

4-Hydrazono-5-hydroxy-5-methyl-3-phenylpyrrolidino[1,2-b]pyrazole (III). A. Hydrazine hydrate (3.3 ml: 50 mmoles) was added to a solution of the ketone (I) (4.6 g: 20 mmoles) in diethylene glycol (30 ml). The solution was boiled for 1 h, the excess of hydrazine was distilled off, the residue diluted with water (200 ml), and extracted with chloroform (3 × 15 ml). After removing the chloroform the hydrazone (III) was recrystallized from methanol.

B. Hydrazine hydrate (1.1 ml: 21 mmoles) was added to ketol (I) (4.6 g) in methanol or butanol (35 ml) and the mixture boiled for 2 h. Hydrazone (III) crystallized after condensing the mixture to 15-20 ml.

2-Hydroxy-2-methyl-3-(4-phenylpyrazolyl)propionic Acid (IV). A. The hydrazone (III) (2.4 g: 10 mmoles) was dissolved in diethylene glycol (10 ml). Potassium hydroxide (2.24 g) was added and the reaction mixture kept at 180-200°C for 2 h. After diluting the reaction mixture with water (100 ml), compound (IV) was extracted with ether (3 × 50 ml), and the extract dried over sodium sulfate. After distilling off the ether the acid (IV) was crystallized from toluene.

B. Hydrazine hydrate (10 ml) and potassium hydroxide (4.5 g) were added to a solution of the bicyclic ketol (I) in diethylene glycol (20 ml) and the mixture boiled for 2 h. The excess of hydrazine and water were distilled off, and the residue kept at 180-200°C for 2 h. Compound (IV) was isolated as described in experiment A.

4-NH-Diazenyl-5-methyl-3-phenylpyrrolo[1,2-b]-1H-pyrazoline (VI). The bicyclic ketol (I) (6.9 g: 30 mmoles) was dissolved in methyl cellosolve (50 ml), hydrazine hydrate (12 ml) added, and the mixture boiled for 2 h. Potassium hydroxide (5 g) was then added, the reaction mixture boiled for 10 min, cooled, water (200 ml) was poured in, and the whole extracted with ether (3 × 80 ml). The ether extract was dried over sodium sulfate. After evaporation of the ether the congealed oil was crystallized from a hexane–ether (1:1) mixture.

4-N-Acetyldiazenyl-1-acetyl-5-methyl-3-phenylpyrrolo[1,2-b]pyrazoline (VII). Acetic anhydride (10 ml) was added to compound (VI) (1.2 g: 5 mmoles), the mixture kept for 15 min, the precipitated crystals were filtered off, washed with water, and dried in a Fisher apparatus at 80°C.

5-Hydroxy-5-methyl-3-phenylpyrrolidino[1,2-b]pyrazole (VIII). The hydrazone (III) (2.4 g: 10 mmoles) was dissolved in triethylene glycol (50 ml). A burette for collecting gas was connected to the reaction flask, potassium hydroxide (2.4 g: 40 mmoles) was added, and the mixture maintained at 100-120°C until 250-260 ml nitrogen was evolved. The reaction mixture was then cooled, diluted with water (500 ml), and extracted with ether (3 × 100 ml). The extract was dried with sodium sulfate, and filtered through a layer of silica gel (2 cm), washing the latter with ether. Compound (VIII) crystallized after partial removal of the ether and was recrystallized from benzene.

5-Hydroxy-6,6-dimethyl-3-phenylpyrrolidino[1,2-b]pyrazole (IX). The bicyclic ketol (II) (2.44 g: 10 mmoles) was dissolved in ethylene glycol (15 ml), hydrazine hydrate (4.5 ml) was added, and the mixture kept at 140-150°C for 1 h. After cooling, potassium hydroxide (2 g) was added to the reaction mixture, which was then kept at 120-140°C until cessation of gas evolution. The reaction mixture was then diluted with two volumes of water, neutralized with dilute hydrochloric acid, and extracted with ether (3 × 100 ml). After drying the extract with sodium sulfate and partially removing the ether, compound (IX) (1.6 g) crystallized and was recrystallized from a mixture of ether–hexane (3:1).

6,6-Dimethyl-3-phenyl-2H,5H-pyrrolo[1,2-b]pyrazole (X). A mixture of the bicyclic ketol (II) (2.42 g: 10 mmoles) and hydrazine hydrate (10 ml) in triethylene glycol (10 ml) was boiled for 1 h. After evaporating the excess of hydrazine hydrate, potassium hydroxide (2 g) was added to the residue and the mixture kept at 140-180°C for 2 h until evolution of gas bubbles had ceased. The reaction mixture was diluted with a tenfold volume of water, extracted with ether (3 × 100 ml), and

the extract dried over sodium sulfate. After evaporating the ether, the residue was crystallized from ether, and compounds (IX) and (X) isolated in a ratio of 1:2.3.

6,6-Dimethyl-3-phenylpyrrolidino[1,2-b]pyrazole (XI). Compound (X) (1.06 g: 5 mmoles) was dissolved in methanol (30 ml), platinum dioxide (0.04 g) was added, and the reaction mixture saturated with hydrogen. After absorption of an equimolar quantity of hydrogen the catalyst was filtered off, the methanol evaporated, and the residue crystallized from a hexane–ether (4:1) mixture to isolate the product (XI). ^{13}C NMR spectrum ($CDCl_3$): 21.90 (t, $C_{(5)}$); 26.85 (q, $C_{(5)}-CH_3$); 41.55 (t, $C_{(4)}$); 61.15 (s, $C_{(6)}$); 114.91 (s, $C_{(8)}$); 124.90, 125.20, 128.50 (d, o-, p-, and m-C_{Ph}); 133.30 (s, i-C_{Ph}); 140.20 (d, $C_{(2)}$); 140.20 (s, $C_{(3)}$).

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