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# SYNTHESIS AND REACTIONS OF 5-HYDROXY-4-OXO-3-ARYLPYRROLIDINO[1,2-b]PYRAZOLES

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Successive treatment of epoxypropionylpyrazolines with N-bromosuccinimide in chloroform and triethylamine in acetone affords 5-hydroxy-4-oxo-3-arylpyrrolidino[1,2-b]-pyrazoles, which are oxygenated derivatives of the alkaloid withasomnine. The reaction proceeds via the cyclization of the intermediate pyrazole bromohydrins. Some reactions of the pyrrolidino[1,2-b]pyrazoles obtained have been examined.

In a study of the heterocyclization of compounds containing two reactive heterocycles, one of which is oxirane, we have developed a convenient synthesis of 5-hydroxy-4-oxo-3-arylpyrrolidino[1,2-b]pyrazoles, by cyclization of epoxypropionylpyrazolines. 5-Hydroxy-4-oxo-3-arylpyrrolidino[1,2-b]pyrazoles are functional derivatives of the alkaloid withasomnine, isolated from the roots of Withania somnifera Dunal [1-6].

We have shown that successive treatment of the readily accessible epoxypropionylpyrazolines (Ia-d) [7] with N-bromosuccinimide in chloroform and triethylamine in acetone gives 5-hydroxy-4-oxo-3-arylpyrrolidino[1,2-b]pyrazoles (Ia-d) in 70-86% yield. Reaction of the epoxypropionylpyrazoline (Ic) with N-bromosuccinimide gave the intermediate epoxypropionylpyrazole (IIIc) and the pyrazole bromohydrin (IVc), the pyrazole bromohydrins (IVa, c) cyclizing to the pyrrolidino[1,2-b]pyrazoles (IIa, c) on boiling in toluene, or treatment with triethylamine in acetone. It follows from these observations that the reaction of epoxypropionylpyrazolines with N-bromosuccinimide and triethylamine involves the intermediate formation of the pyrazole bromohydrins formed by cleavage of the epoxide ring during the aromatization of the pyrazoline ring in the presence of N-bromosuccinimide. The function of the triethylamine is solely to bind the acidic proton of the pyrazole ring in the intermediate pyrazole halohydrin, which facilitates intramolecular cyclization.

The cyclization of pyrazole bromohydrins to pyrrolidino[1, 2-b]pyrazoles has been found to be a general reaction. For example, reaction of the epoxypropionylpyrazole (IIIe) with hydrobromic acid gave the bicyclic ketone (IIe). The structures of products (IIa-e) were confirmed spectrally (Table 1) and by their chemical properties.

The IR spectra of (IIa-e) showed absorption at 3620 (OH) and 1730 $cm^{-1}$ (C=O).

Treatment of (IIa) and (IIe) with acetic anhydride converted them into the acetates (Va, e). Reduction of the carbonyl group in the bicyclic ketones (IIa, e) with sodium borohydride gave a mixture of stereoisomeric diols (VIa, e) and (VIIa, e) with trans- and cis-orientation

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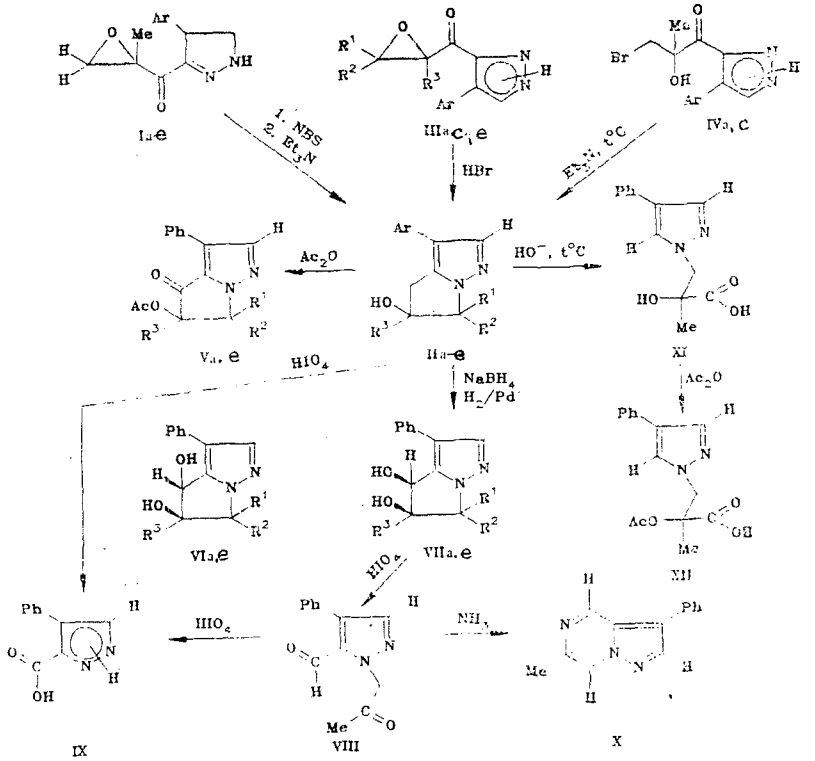
of the hydroxyl groups, in ratios of 4.7:1 and 4:1, respectively. Reversal of the stereochemistry of the reduction was seen when the ketone (IIa) was hydrogenated over palladium, when the cis-diol (VIIa) was formed preferentially. The configurations of the diastereoisomeric diols (VIa, e) and (VIIa, e) was confirmed by IR and PMR spectroscopy, and by oxidation with periodic acid. Specifically, in the IR spectra of the trans-diols (VIa, e) the hydroxyl group absorption at 3610 $cm^{-1}$ indicated the absence of intramolecular hydrogen bonding, which is possible when the hydroxyl groups are transoid-oriented. On the other hand, the IR spectrum of the cis-diol (VIIa) showed three bands for hydroxyl group absorption, at 3530, 3560, and 3610 $cm^{-1}$.



I—VII a—d $R^1=R^2=H$, $R^3=CH_3$, a $Ar=C_6H_5$, b $Ar=4\text{-}CH_3OC_6H_4$, c $Ar=4\text{-}BrC_6H_4$, d $Ar=3\text{-}NO_2C_6H_4$; e $R^1=R^2=CH_3$, $R^3=H$, $Ar=C_6H_5$

Cleavage of the cis-glycol (VIIa) with periodic acid to 1-acetonyl-4-phenyl-5-formylpyrazole (VIII) takes place quantitatively within one hour, whereas the trans-diol (VIa) is stable to this oxidant. The IR spectrum of the formylpyrazole (VIII) shows no absorption for the hydroxyl group, but bands are seen at 1680 and 1742 $cm^{-1}$ for the formyl and acetonyl carbonyl groups. On treatment with an excess of periodic acid, the aldehyde (VIII) is oxidized to 4-phenyl-5(3)-pyrazolecarboxylic acid (IX), which was also obtained by cleavage of the bicyclic ketone (IIa) with periodic acid.

The formylpyrazole (VIII) reacts with ammonia in methanol on heating to give 2-methyl-7-phenylpyrrolo[2,3-a]pyrazine (X). The IR spectrum of the latter shows no absorption at 1650-1750 $cm^{-1}$, but strong absorption is present at 1550 (C=N) and 1610 $cm^{-1}$ (C=C). The structure of (X) was confirmed by its PMR spectrum (Table 1).

Heating (IIa) to 130-150°C with concentrated aqueous-alcoholic alkali resulted in cleavage of the α-carbon bond of the bicyclic ketone to form 1-(2-hydroxy-2-carboxypropyl)-4-phenylpyrazole (XI), the structure of which was confirmed by its spectral properties and conversion to the acetate (XII).

Epoxypropionylpyrazolines and pyrazoles are therefore convenient compounds for conversion into oxygenated derivatives of the alkaloid withasomnine.

## EXPERIMENTAL

The IR spectra of the compounds in $CCl_4$ at a concentration of $10^{-3}$ mole/liter (layer thickness 1 cm) were obtained on a Specord-75 IR spectrophotometer. PMR spectra were recorded

TABLE 1. Properties of Compounds (IIa-e) and (IV-XII)

| Compound | Empirical formula | mp, °C | PMR spectrum, δ, ppm* | Yield, % |
|---|---|---|---|---|
| IIa | $C_{13}H_{12}N_2O_2$ | 182...183 | 1,54 (3H, s, $CH_3$); 4,38, 4,55 (2H, AB-system $J_{AB}$=12,0, $CH_2$); 5,36 (1H, s, OH); 7,30, 7,94 (5H, m, arom.); 8,20 (1H, s, 2-H) | 86 |
| IIb | $C_{14}H_{14}N_2O_3$ | 126...127 | 1,50 (3H, s, $CH_3$); 3,70 (3H, s, $OCH_3$); 4,26, 4,46 (2H, AB-system $J_{AB}$=12,0, $CH_2$); 6,82, 7,82 (4H, AB-system $J_{AB}$=9,0, arom); 8,07 (1H, s, 2-H) | 81 |
| IIc | $C_{13}H_{11}BrN_2O_2$ | 172...173 | 1,56 (3H, s, $CH_3$); 4,40, 4,52 (2H, AB-system, $J_{AB}$=12,0, $CH_2$); 6,30 (1H, s, OH); 7,55, 7,90 (4H, AB-system $J_{AB}$=9,0, arom); 8,30 (1H, s, 2-H) | 79 |
| IId | $C_{13}H_{11}N_3O_4$ | 154...155 | 1,52 (3H, s, $CH_3$); 3,10 (1H, s, OH); 4,36, 4,54 (2H, AB-system $J_{AB}$=12,0, $CH_2$); 7,64...8,66 (4H, m, arom.; 8,30 (1H, s, 2-H) | 70 |
| IIe | $C_{14}H_{14}N_2O_2$ | 134...135 | 1,35 (3H, s, $CH_3$); 1,67 (3H, s, $CH_3$); 4,58 (1H, s 5-H); 5,13 (1H, s, OH); 7,24, 7,90 (5H, m, arom.); 8,12 (1H, s, 2-H) | 90 |
| IVa | $C_{13}H_{13}BrN_2O_2$ | 108...109 | 1,57 (3H, s, $CH_3$); 3,70, 4,20 (2H, AB-system $J_{AB}$=10,5, $CH_2$); 4,40 (1H, s, OH); 7,25 (6H, m, NH, arom.); 7,90 (1H, s, 3(5)-H) | 73 |
| IVc | $C_{13}H_{12}Br_2N_2O_2$ | 134...135 | 1,58 (3H, s, $CH_3$); 3,66, 4,20 (2H, AB-system, $J_{AB}$=10,5, $CH_2$); 4,28 (1H, s, OH); 7,38 (5H, s, NH, arom.); 7,90 (1H, s, 3(5)-H) | 78 |
| Va | $C_{15}H_{14}N_2O_3$ | 116...117 | 1,60 (3H, s, $CH_3$); 2,02 (3H, s, $CH_3$); 4,57, 4,64 (2H, AB-system. $J_{AB}$=12,0, $CH_2$); 7,33, 8,00 (5H, m, arom.); 8,20 (1H, s, 2-H) | 91 |
| Ve | $C_{16}H_{16}N_2O_3$ | 53...54 | 1,35 (3H, s, $CH_3$); 1,70 (3H, s, $CH_3$); 2,12 (3H, s $CH_3$); 5,70 (1H, s 5-H); 7,23, 7,90 (5H, m, arom); 8,15 (1H, s, 2-H) | 93 |
| VIa | $C_{13}H_{14}N_2O_2$ | 157...158 | 1,50 (3H, s, $CH_3$); 3,90, 4,10 (2H, AB-system, $J_{AB}$=14,0, $CH_2$); 4,73 (3H, br.s, OH, 4-H); 7,20, 7,60 (5H, m, arom); 7,68 (1H, s, 2-H) | 70 |
| VIe | $C_{14}H_{16}N_2O_2$ | 170...172 | 1,22 (3H, s, $CH_3$); 1,47 (3H, s, $CH_3$); 4,26 (1H, d.d, $J$=5,0, $J$=3,5, 4-H); 5,10 (3H, m, 2-OH, 5-H); 7,20, 7,56 (m, arom.); 7,68 (1H, s, 2-H) | 71 |
| VIIa | $C_{13}H_{14}N_2O_2$ | 168...170 | 1,37 (3H, s, $CH_3$); 3,95, 4,05 (2H, AB-system, $J_{AB}$=14,0, $CH_2$); 4,73 (3H, br.s, OH, 4-H); 7,20, 7,60 (5H, m, arom.) 7,68 (1H, s, 2-H) | 15 |
| VIIe | $C_{14}H_{16}N_2O_2$ | 132...135 | 1,34 (3H, s, $CH_3$); 1,42 (3H, s, $CH_3$); 4,25 (1H, d.d, $J$=7,0, $J$=4,0, 4-H); 4,66 (1H, s, OH); 4,82 (1H, d, $J$=4,0, OH); 5,10 (1H, d, $J$=7,0, 5-H); 7,20, 7,56 (5H, m, arom.); 7,65 (1H, s, 2-H) | 18 |
| VIII | $C_{13}H_{12}N_2O_3$ | 103...104 | 2,18 (3H, s, $CH_3$); 5,26, 7,38 (5H, m, arom.) 7,60 (1H, s, 5-H); 9,75 (1H, s, CHO) | 84 |
| IX | $C_{10}H_8N_2O_2$ | 251...253 | 6,13 (2H m, NH, COOH); 7,28, 7,58 (5H, m, arom.); 7,70 (1H, s, 5-H) | 67 |
| X | $C_{13}H_{11}N_3$ | 134...135 | 2,43 (3H, s, $CH_3$); 7,44 (5H, m, arom); 8,07 (1H, s, 6-H); 8,16 (1H, s, 3-H); 9,75 (1H, s, 8-H) | 92 |
| XI | $C_{13}H_{14}N_2O_3$ | 180...181 | 1,30 (3H, s, $CH_3$); 3,45 (1H, s, OH); 4,16, 4,28 (2H, AB-system, $J_{AB}$=12,0, $CH_2$); 7,30 (5H, m, arom.); 7,74 (1H, s 5-H); 7,96 (1H, s, 3-H) | 86 |
| XII | $C_{15}H_{16}N_2O_4$ | 219...221 | 1,40 (3H, s, $CH_3$); 1,96 (3H, s, $CH_3$); 4,52, 4,80 (2H, AB-system, $J_{AB}$=12,0, $CH_2$); 7,30 (5H, m, arom.); 7,80 (1H, s, 3-H) | 81 |

*The spectra of (IIa, c), (IX), (XI), and (XII) were recorded in a mixture of DMSO-$D_6$ and acetone-$D_6$ (1:1), and the remainder in acetone-$D_6$.

on a Tesla BS-467A spectrometer in acetone-$D_6$ and a mixture of DMSO-$D_6$ and acetone-$D_6$, internal standard HMDS. The synthesis of (Ia-e) and (IIIa, c, e) has been reported [7]. The elemental analyses of (IIa-e) and (IVa,c-XII) for C, H, and N were in agreement with the calculated values.

3-Aryl-5-hydroxy-5-methyl-4-oxopyrrolidino[1,2-b]pyrazoles (IIa-d). A. To a solution of 25 mmole of the pyrazoline (Ia-d) in 50 ml of chloroform was added 4.5 g (25 mmole) of N-bromosuccinimide portionwise at a temperature not exceeding 50°C. After 0.5-1 h, the chloroform was removed in a rotary evaporator, the residue treated with 5 ml of triethylamine in 50 ml of acetone, and the mixture kept for 12 h at 20°C. The acetone was removed to a volume of 10 ml, and the solid filtered off, washed with water, and crystallized from acetone–methanol to give the pyrrolidino[1,2-b]pyrazoles (IIa-d).

B. A solution of 10 mmole of the bromohydrin (IVa) or (IVc) in 50 ml of toluene was boiled for 4 h. The solid which separated on cooling the mixture was filtered off and crystallized from methanol to give (IIa, c).

C. A solution of 5 mmole of the bromohydrin (Ia, c) and 1 ml of triethylamine in 30 ml of acetone was kept for 12 h at 20°C. The acetone was evaporated off, and the residue washed with water (25 ml) and crystallized from methanol to give the pyrrolidino[1,2-b]pyrazole (IIa, c) in 92-95% yield.

5-Acetoxy-4-oxo-3-phenylpyrrolidino[1,2-b]pyrazole (IIe). To a solution of 4.64 g (20 mmole) of (IIIe) in 10 ml of acetic acid was added 7 ml of 47% hydrobromic acid (60 mmole). after 1 h, the mixture was diluted tenfold with water, extracted with ether (5 × 30 ml), and dried over potassium carbonate. The solvent was removed to a volume of 10 ml, giving the bicyclic ketone (IIe), which was crystallized from ether. Yield 90%.

4-Aryl-5(3)-(3-bromo-2-hydroxy-2-methylpropionyl)pyrazoles (IVa, c). To 10 mmole of the pyrazole (IIIa) or (IIIc) in 10 ml of acetic acid was added 5 ml of 47% hydrobromic acid, and the mixture kept for 30 min at 25°C. It was then poured into 100 ml of water, extracted with ether (5 × 30 ml), the extract washed with sodium carbonate solution to pH 7-8, and dried over sodium sulfate. Removal of the ether to 20 ml and twofold dilution with hexane gave the bromohydrin (IVa, c).

5-Acetoxy-4-oxo-3-phenylpyrrolidino[1,2-b]pyrazoles (Va, e). A solution of 10 mmole of (IIa, e) in 20 ml of acetic anhydride was boiled for 10 h, cooled, diluted with 150 ml of water, neutralized with sodium carbonate solution to pH 7-8, and extracted with methylene chloride. The solvent was removed, and the residual (Va, e) crystallized from ether–hexane (1:3).

4,5-Dihydroxy-3-phenylpyrrolidino[1,2-b]pyrazoles (VIa, e; VIIa, e). A. To a solution of 25 mmole of the pyrazole (IIa, e) in 200 ml of methanol was added portionwise 1.0 g (26 mmole) of sodium borohydride, maintaining the pH of the solution near 7 with acetic acid. The mixture was kept for 1 h at 18-20°C, the solvent removed, and the residue diluted with 50 ml of water and extracted with methylene chloride (3 × 50 ml). Evaporation gave (VIa, e) and (VIIa, e), which were crystallized from ether. The diastereoisomers (VIa, e) and (VIIa, e) were separated by crystallization from ethanol–ether (1:4).

B. A solution of 1.0 g (4.4 mmole) of (IIa) in 100 ml of methanol with the addition of 0.1 g of palladium chloride was stirred vigorously in a hydrogen atmosphere until 4.4 mmole of the latter had been taken up (4-5 h). The catalyst was filtered off, the methanol removed, and the residue fractionally crystallized from ether–methanol to give the pure isomers (VIa) and (VIIa).

1-Acetonyl-4-phenyl-5-formylpyrazole (VIII). To a solution of 2.2 g (10 mmole) of the cis-diol (VIIa) in 50 ml of methanol was added at 10-15°C a solution of 2.28 g (10 mmole) of periodic acid in 10 ml of water. The mixture was kept for one hour at 18-20°C, concentrated to a volume of 20 ml in a rotary evaporator, diluted with 100 ml of water, and extracted with ether (5 × 20 ml). The ether extract was dried over magnesium sulfate, concentrated to 10 ml, and 20 ml of hexane added to give the formylpyrazole (VIII), which was crystallized from ether–hexane (1:2).

4-Phenyl-5(3)-pyrazolecarboxylic Acid (IX). A. To a solution of 1.10 g (5 mmole) of (VIII) was added 2.28 g (10 mmole) of periodic acid in 10 ml of water, and the mixture kept for seven days at 18-20°C. The methanol was evaporated, the residue diluted with 20 ml of water, and the pyrazolecarboxylic acid (IX) filtered off and crystallized from water acidified with hydrochloric acid. The constants for (IX) were in agreement with the reported values [8].

B. To a solution of 1.10 g (5 mmole) of (IIa) in 50 ml of methanol was added 2.28 g (10 mmole) of periodic acid in 10 ml of water. After seven days, the acid (IX) was isolated as described above.

2-Methyl-7-phenylpyrazolo[2,3-a]pyrazine (X). The formylpyrazole (VIII) (2.2 g, 10 mmole) was dissolved in 50 ml of methanol, an equimolar amount of 25% aqueous ammonia added, and the mixture heated to 50-60°C. The crystalline (X) which separated on cooling was filtered off and recrystallized from methanol.

1-(2-Hydroxy-2-carboxypropyl)-4-phenylpyrazole (XI). To 2.2 g (10 mmole) of (IIa) in 10 ml of diethylene glycol was added 1 ml of water and 2 g of potassium hydroxide. The mixture was heated for 2 h at 130-150°C, diluted with 90 ml of water, neutralized with hydrochloric acid to pH 7, and extracted with ether (5 × 25 ml). The ether solution was dried over sodium sulfate, and the residue recrystallized from benzene to give the acid (X).

1-(2-Acetoxy-2-carboxypropyl)-4-phenylpyrazole (XII). A mixture of 2.88 g (10 mmole) of the hydroxyacid (XI) and 10 ml of acetic anhydride was boiled for 1 h. The mixture was cooled, diluted with ten times its volume of water, neutralized with sodium carbonate to pH 6, and extracted with ether (4 × 30 ml). After drying over sodium sulfate, the solution was evaporated, and the product (XII) recrystallized from acetone.

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# 2-SUBSTITUTED IMIDAZOLES.

## 1. REACTIONS OF 1-METHYL-2-(2-FURYL)IMIDAZOLE WITH ELECTROPHILES


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1-Methyl-2-(2-furyl)imidazole has been synthesized. Electrophilic attack (bromination, nitration, formylation, acylation, and hydroxymethylation) occurs in most cases at the free α-position of the furan ring.


The mutual effects of the heterocyclic nuclei in bihetaryls are of interest, but have received little attention. Least of all is known about the reactivity of compounds in which azole and π-excessive rings are linked. The reactivity of such compounds is sometimes totally unexpected. For example, it has recently been reported that 2-(2-furyl)- and 2-(2-thienyl)-oxazoles are formylated in the oxazole ring [1], although the π-excess is greater in the furan and thiophen rings. The purpose of the present study was to examine the reactivity towards electrophilic substitution of 1-methyl-2-(2-furyl)imidazole (I). The imidazole ring is well known to be inert to electrophiles under acid conditions, but to readily undergo electrophilic substitution in neutral media [2]. For this reason, although it is not difficult to predict that electrophilic substitution will be directed towards the furan ring under acid conditions, this is not so under neutral conditions. Electrophilic substitution in 1-methyl-2-(2-furyl)-benzimidazole (II) has been examined [3, 4]. In this case, however, all the carbon atoms of the imidazole ring are blocked, so that the reactions take place exclusively at the free α-position of the furan substituent.


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