Hetarylpyrazoles. IV (1). Synthesis and Reactions of 1,5'-Bipyrazoles

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A number of 1,5'-bipyrazoles were obtained from the condensation of pyrazol-5-ylhydrazine and 1,3-dicarbonyl compounds. Electrophilic substitution reactions of these 1,5'-bipyrazoles occur at the four position of the pryazole ring.

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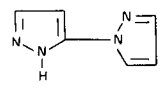
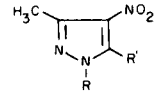
The derivatives of a pyrazole ring linked to an aromatic ring or a heteroaromatic ring have been found to contain antirheumatic and antipyretic properties. The compounds such as antipyrine (3), dipyron (4), phenylbutazone (5), and mepyrazole (6) are well known drugs. The *N*-substitution of a pyrazole ring by another heteroaromatic ring and especially by another pyrazole ring may lead to interesting ring systems. In this paper we shall report our results regarding the synthesis and some reactions of 1,5'-bipyrazole system (I) for which only two references were found in the literature (7,8). More recently synthesis of I by *cine* substitution was reported (9) which prompts us to publish our findings.

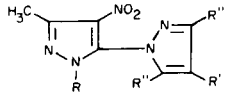
The key intermediate for the synthesis of I is pyrazole-5-ylhydrazine which could not be obtained directly from 5-aminopyrazole by diazotization and reduction of the resulting diazonium salt, or from 5-halopyrazoles by a nucleophilic displacement by hydrazine. However an electron-withdrawing group such as a nitro group in the four position activates the 5-halo group towards nucleophilic reactions (10) and a chloronitropyrazole in this was may be transformed into the corresponding pyrazole-5-ylhydrazine.



I



II R = Ph; R' = Cl
III R = Ph; R' = $NHNH_2$



IV, R = Ph, R' = H, R'' = R''' = H
V, R = Ph, R' = H, R'' = R''' = CH_3
VI, R = R'' = R''' = Ph, R' = H
VII, R = Ph, R' = $CO_2C_2H_5$, R'' = H, R''' = NH_2
VIII, R = Ph, R'' = R''' = H, R' = NO_2
IX, R = p-$NO_2C_6H_4$, R'' = R''' = H, R' = NO_2
X, R = p-$NO_2C_6H_4$, R'' = R''' = CH_3, R' = NO_2
XI, R = p-$NO_2C_6H_4$, R' = R'' = R''' = H
XII, R = p-$NO_2C_6H_4$, R' = H, R'' = R''' = CH_3
XIII, R = 2,4-$(NO_2)_2C_6H_3$, R'' = R''' = H, R' = NO_2
XIV, R = Ph, R' = Br, R'' = R''' = H
XV, R = Ph, R' = Br, R'' = R''' = CH_3
XVI, R = Ph, R' = Cl, R'' = R''' = H

By using acetylnitrate, 5-chloro-3-methyl-1-phenylpyrazole (11) was selective nitrated to give 5-chloro-3-methyl-4-nitro-1-phenylpyrazole (II). Heating II with hydrazine gave 3-methyl-4-nitro-1-phenylpyrazol-5-ylhydrazine (III) in 68% yield. The condensation of III with various 1,3-dicarbonyl compounds gave the derivatives (IV-VI) of 1,5'-bipyrazole system in good yields. The treatment of III with ethyl 2-cyano-3-ethoxyacrylate gave a mixture of VII and its corresponding acyclic intermediate which was, however, converted into VII by refluxing in acetic acid.

Some electrophilic substitution reactions were carried out on compounds IV and V. Nitration of IV with acetyl nitrate at 0-5° gave VIII in 77% yield while employing the "mixed acids" at 20-25° IX was obtained in 72% yield. Similarly nitration of V resulted in 77% yield of the trinitro product (X). Selective nitration in the benzene ring of IV and V was achieved when the nitration with "mixed acids" was carried out at 0-5° and the corresponding *p*-nitrophenyl derivatives XI and XII were obtained. Using more vigorous conditions ("mixed acids" at 100°) led to the formation of tetranitro compound (XIII).

The bromination of IV and V gave respectively XIV and XV in which the pyrazole ring was brominated at the four position. The chlorination of IV was also effected and the 4-chloro derivative (XVI) was isolated from this reaction.

The results of these electrophilic substitution reactions of 1,5'-bipyrazoles point out the similarity of their behaviour towards these reactions when compared with *N*-arylpyrazoles (12). These compounds are also sensitive to the nature and the conditions of the reactions.

EXPERIMENTAL

The pmr spectra were taken on a 60 MHz Hitachi Perkin-Elmer model

R-20B using tetramethylsilane as an internal reference and deuteriochloroform as the solvent. Infrared absorption spectra were measured on a Perkin-Elmer model 180. Samples were examined as potassium bromide pellets. The melting points were observed on a Fisher-Johns apparatus and are uncorrected.

5-Chloro-3-methyl-4-nitro-1-phenylpyrazole (II).

To a solution of 30 g of 5-chloro-3-methyl-1-phenylpyrazole in 150 ml of acetic anhydride at 0°, 30 ml of fuming nitric acid was added dropwise in such a manner that the temperature was maintained at 0-5° during the addition of the acid. After the addition of nitric acid was over the temperature of the reaction mixture was allowed to gradually reach temperature of 25-30° and then maintained at this temperature for a period of 4 hours. At the end of this period the reaction mixture was poured over crushed ice, the precipitate was filtered and washed with water. After drying, the precipitate was crystallized from ethanol to give II, mp 115-116°, yield, 23.8 g (64%); pmr: δ 2.61 (s, CH_3), 7.50 (s, arom); ir: 1600, 1542 (NO_2), 1500, 1490, 1465, 1450, 1360 (NO_2), 1150, 1000, 860, 765, 690 cm^{-1}.

Anal. Calcd. for $C_{10}H_8ClN_3O_2$: C, 50.54; H, 3.39; N, 17.68. Found: C, 50.49; H, 3.46; N, 17.56.

3-Methyl-4-nitro-1-phenylpyrazole-5-ylhydrazine (III).

To a refluxing solution of 2.3 g of II in 15 ml of ethanol, 1.5 ml of hydrazine hydrate (85%) was slowly added and let reflux for an additional 15 minutes. The reaction mixture was cooled, the precipitate filtered off and crystallized from ethanol to give 3.6 g, (68%) of III, mp 150-151°; pmr: δ 2.49 (s, CH_3), 3.53 (s, NH_2), 7.42 (s, arom), 7.95 (br, N*H*); ir: 3358 (NH), 3325 and 3240 (NH_2), 1650, 1595, 1570, 1535 (NO_2), 1490, 1465, 1450, 1380, 1350 (NO_2), 1280, 1140, 970, 775 cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}N_5O_2$: C, 51.50; H, 4.75; N, 30.03. Found: C, 51.76; H, 4.82; N, 30.02.

3'-Methyl-4'-nitro-1'-phenyl-1,5'-bipyrazole (IV).

A mixture of 2.3 g of III, 1.64 g of 1,1,3,3-tetramethoxypropane in 12 ml of ethanol and 1 ml of hydrochloric acid was heated under reflux for an hour. The reaction mixture was poured over water, filtered and the product IV was crystallized from aqueous ethanol, yield 1.6 g (60%), mp 81-82°. This compound was identical with a sample obtained from the Ullmann arylation of II (1).

4'-Nitro-1'-phenyl-3,3'-5-trimethyl-1,5'-bipyrazole (V).

A mixture of 2.3 g of III, 1 g of 2,4-pentanedione in 12 ml of ethanol and 1 ml of hydrochloric acid was heated under reflux for an hour. The reaction mixture was treated as for IV above giving 1.8 g (62%) of V, mp 87-88° (aqueous ethanol); pmr: δ 1.90 (s, CH_3), 2.24 (s, CH_3), 2.68 (s, CH_3), 5.99 (s, H-4), 7.29 (s, arom); ir: 3080, 1600, 1580, 1570, 1515 (NO_2), 1500, 1460, 1435, 1365 (NO_2), 1330, 1135, 855, 770, 760, 690 cm^{-1}.

Anal. Calcd. for $C_{15}H_{15}N_5O_2$: C, 60.60; H, 5.09; N, 23.56. Found: C, 60.34; H, 5.14; N, 23.44.

3'-Methyl-4'-nitro-1',3,5-triphenyl-1,5'-bipyrazole (VI).

Using the same method as used for the preparation of IV and V, from 1.15 g of III, and 1.09 g of dibenzoylmethane, 1.75 g (90%) of VI, mp 124-125° (ethanol) was obtained; pmr: δ 2.64 (s, CH_3), 6.77 (s, H-4), 6.80-8.00 (m, arom); ir: 3060, 1600, 1580, 1520 (NO_2), 1500, 1475, 1460, 1435, 1375, 1362 (NO_2), 1135, 960, 860, 790, 760, 695 cm^{-1}.

Anal. Calcd. for $C_{25}H_{19}N_5O_2$: C, 71.25; H, 4.54; N, 16.62. Found: C, 71.21; H, 4.66; N, 16.70.

Ethyl 5-Amino-3'-methyl-4'-nitro-1'-phenyl-1,5'-bipyrazole-4-carboxylate (VII).

A mixture of III and 0.85 g of ethyl 2-cyano-3-ethoxyacrylate in 15 ml of ethanol was heated under reflux for an hour. The reaction mixture was poured over crushed ice and the precipitate was filtered off and dried. The precipiate was added to 10 ml of acetic acid and heated under reflux for an hour. The excess of acetic acid was evaporated off and the residue diluted with ether, filtered and crystallized from ethanol gave 1.2 g (69%) of VII, mp 83°; pmr: δ 1.34 (t, J = 7 Hz, $CO_2CH_2CH_3$), 2.68 (s, CH_3), 4.28 (q, J = 7 Hz, $CO_2CH_2CH_3$), 5.38 (s, NH_2), 7.33 (s, arom), 7.70 (s, H-3); ir: 3580 (NH), 3460, 3360 (NH_2), 3300, 3190, 2995, 1690 (CO), 1635, 1600, 1590, 1570, 1520, 1500 (NO_2), 1420, 1380, 1360, 1340, 1305 (NO_2), 1210, 1140, 940, 790, 690 cm^{-1}.

Anal. Calcd. for $C_{16}H_{16}N_6O_4$: C, 53.93; H, 4.53; N, 23.59. Found: C, 53.70; H, 4.50; N, 23.45.

4,4'-Dinitro-3'-methyl-1'-phenyl-1,5'-bipyrazole (VIII).

To a solution of IV (0.5 g in 4 ml of acetic anhydride) 1.5 ml of fuming nitric acid was added at 0-5°. The reaction mixture was left at this temperature for an hour and then poured over crushed ice. After a few hours the precipitate was filtered off and crystallized from a mixture of ethanol and chloroform to give 0.45 g (77%) of VIII, mp 165-166°; pmr: δ 2.70 (s, CH_3), 7.20-7.50 (m, arom), 8.21 (s, H-3), 8.42 (s, H-5); ir: 3120, 3090, 1605, 1555, 1525 (NO_2), 1510, 1500, 1410, 1358, 1312 (NO_2), 820, 770 cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}N_6O_4$: C, 49.68; H, 3.21; N, 26.74. Found: C, 49.60; H, 3.22; N, 26.50.

4,4'-Dinitro-3'-methyl-1'-*p*-nitrophenyl-1,5'-bipyrazole (IX).

Nitric acid was added to a solution of 0.5 g of IV in 5 ml of concentrated sulfuric acid at 20-25°. The reaction mixture was maintained at this temperature for 5 hours and then poured over crushed ice. The precipitate was filtered, washed thoroughly with water and crystallized from a mixture of chloroform and petroleum ether (bp 60-80°) to give 0.48 g (72%) of IX, mp 167-168°; pmr: δ 2.71 (s, CH_3), 7.41 (d, J = 9 Hz, H-2'' and H-6''), 8.25 (d, J = 9 Hz, H-3'' and H-5''), 8.25 (s, H-3), 8.57 (s, H-5); ir: 3140, 1620, 1600, 1550, 1525 (NO_2), 1510, 1410, 1348 (NO_2), 1315, 930, 860, 750 cm^{-1}.

Anal. Calcd. for $C_{13}H_9N_7O_6$: C, 43.46; H, 2.53; N, 27.29. Found: C, 43.37; H, 2.58; N, 27.30.

4,4'-Dinitro-1'-*p*-nitrophenyl-3,3',5-trimethyl-1,5'-bipyrazole (X).

By nitrating 0.2 g of V with 3 ml of concentrated sulfuric acid and 1.5 ml of nitric acid at 20-25°, 0.2 g (77%) of X, mp 202-203° (chloroform/-petroleum ether (bp 60-80°)) was obtained, pmr: δ 2.47 (s, CH_3), 2.58 (s, CH_3), 2.73 (s, CH_3), 7.49 (d, J = 9 Hz, H-2'' and H-6''), 8.28 (d, J = 9 Hz, H-3'' and H-5''); ir: 1620, 1590, 1580, 1535, 1525 (NO_2), 1500, 1440, 1410, 1380, 1360, 1345 (NO_2), 865, 850, 810 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}N_7O_6$: C, 46.52; H, 3.38; N, 25.32. Found: C, 46.54; H, 3.44; N, 25.08.

3'-Methyl-4'-nitro-1'-*p*-nitrophenyl-1,5'-bipyrazole (XI).

To a solution of 0.5 g of IV in 5 ml of concentrated sulfuric acid at 0-5°, 2.5 ml of nitric acid was added so as to maintain the temperature during the addition of nitric acid at 0-5°. After the addition of nitric acid was completed, the reaction mixture was poured over crushed ice, filtered, washed with water, dried and crystallized from a mixture of chloroform and petroleum ether (bp 60-80°) to give 0.52 g (89%) of XI, mp 133-134°; pmr: δ 2.71 (s, CH_3), 6.59 (t, J = 2.5 and 1.5 Hz, H-4), 7.25 (d, J = 9 Hz, H-2'' and H-6''), 8.18 (d, J = 9 Hz, H-3'' and H-5''), 7.77 (d, $J_{3,4}$ = 1.5 Hz, H-3), 7.82 (d, $J_{4,5}$ = 2.5 Hz, H-5); ir: 3150, 3130, 1620, 1600, 1530 (NO_2), 1500, 1400, 1345 (NO_2), 1310, 865, 780, 750 cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}N_6O_4$: C, 49.68; H, 3.21; N, 26.74. Found: C, 49.40; H, 3.24; N, 26.65.

4'-Nitro-1'-*p*-nitrophenyl-3,3',5-trimethyl-1,5'-bipyrazole (XII).

The treatment of 0.2 g of V with concentrated sulfuric and nitric acid at 0-5° (similar manner as used for the nitration of IV above) gave 0.21 g (89%) of XII, mp 146-147° [chloroform/petroleum ether (bp 60-80°)]; pmr: δ 2.08 (s, CH_3), 2.27 (s, CH_3), 2.70 (s, CH_3), 6.09 (s, H-4), 7.36 (d, J = 9 Hz, H-2'' and H-6''), 8.20 (d, J = 9 Hz, H-3'' and H-5''); ir: 3050, 1619; 1598, 1530 (NO_2), 1500, 1430, 1350 (NO_2), 870 cm^{-1}.

Anal. Calcd. for $C_{15}H_{14}N_6O_4$: C, 52.63; H, 4.12; N, 24.55. Found: C, 52.80; H, 4.31; N, 24.26.

4,4'-Dinitro-1'-(2'',4''-dinitrophenyl)-3'-methyl-1,5'-bipyrazole (XIII).

A mixture of 1 g of IV, 10 ml of concentrated sulfuric acid and 5 ml of nitric acid was heated on a water bath for a period of 4 hours. The reaction mixture after cooling was poured over crushed ice and the precipitate filtered off, washed with water and crystallized from aqueous ethanol to give 1.3 g (87%) of XIII, mp 87-88°; pmr: 2.70 (s, CH_3), 7.87 (d, $J_{5'',6''}$ = 9 Hz, H-6''), 8.09 (s, H-3), 8.58 (dd, $J_{5'',6''}$ = 9 Hz, $J_{3'',5''}$ = 3 Hz, H-5''), 8.69 (s, H-5), 8.87 (d, $J_{3'',5''}$ = 3 Hz, H-3''); ir: 3140, 3110, 1610, 1600, 1545 (NO_2), 1530, 1410, 1350 (NO_2), 1315, 920, 810, 790, 750 cm^{-1}

Anal. Calcd. for $C_{13}H_8N_8O_8$: C, 38.62; H, 1.99; N, 27.72. Found: C, 38.82; H, 2.19; N, 27.48.

4-Bromo-3'-methyl-4'-nitro-1'-phenyl-1,5'-bipyrazoles (XIV).

A solution of 0.5 ml of bromine in 2 ml of acetic acid was slowly added to a solution of 0.3 g of IV in 10 ml of acetic acid at room temperature and the mixture allowed to stir for an hour. The reaction mixture was diluted with water, treated with sodium bisulfite and the precipitate filtered. Upon crystallization from aqueous ethanol 0.3 g (77%) of XIV, mp 101-102° was obtained, pmr: δ 2.66 (s, CH_3), 7.00-7.50 (m, arom), 7.64 (s, H-3), 7.70 (s, H-5); ir: 3160, 3120, 1685, 1598, 1585, 1520, 1500 (NO_2), 1460, 1415, 1405, 1380, 1349 (NO_2), 1315, 990, 955, 930, 860, 770, 692 cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}BrN_5O_2$: C, 44.85; H, 2.90; N, 20.12. Found: C, 44.70; H, 2.88; N, 19.85.

4-Bromo-4'-nitro-1'-phenyl-3,3',5-trimethyl-1,5'-bipyrazole (XV).

By following the method used for the bromination of IV, 0.2 g of V gave 0.21 g (83%) of XV, mp 91-92° (aqueous ethanol); pmr: δ 1.99 (s, CH_3), 2.24 (s, CH_3), 2.68 (s, CH_3), 7.10-7.50 (m, arom); ir: 1602, 1581, 1500 (NO_2), 1490, 1460, 1430, 1370 (NO_2), 1335, 1320, 1145, 860, 810, 770, 765, 690 cm^{-1}.

Anal. Calcd. for $C_{15}H_{14}BrN_5O_2$: C, 47.89; H, 3.75; N, 18.62. Found: C, 48.16; H, 3.85; N, 18.46.

4-Chloro-3'-methyl-4'-nitro-1'-phenyl-1,5'-bipyrazole (XVI).

A solution of 0.5 ml of commercial sodium hypochlorite (±5%) was added with stirring to a solution of 0.3 g of IV in 10 ml of acetic acid. After an hour of stirring at room temperature the reaction mixture was diluted with water and the precipitate filtered off, washed with water and crystallized from aqueous ethanol giving 0.25 g (74%) of XVI, mp 89-90°; pmr: δ 2.68 (s, CH_3), 7.10-7.50 (m, arom), 7.63 (s, H-3), 7.68 (s, H-5); ir: 3160, 3080, 1610, 1590, 1540, 1520, 1505 (NO_2), 1465, 1440, 1350 (NO_2), 1325, 1150, 940, 860, 770, 698 cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}ClN_5O_2$: C, 51.41; H, 3.32; N, 23.06. Found: C, 51.60; H, 3.58; N, 22.95.

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