Hydrogenolysis of 1-Aminopyrazoles: Synthesis of Primary and Secondary Alkylamines [1]

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The tautomerizable *N*-aminopyrazolone **9**, the *O*-methyl **1** and *N*-methyl derivatives **4** were condensed with carbonyl compounds to give the alkenylaminopyrazoles **12**, **2a-g** and **5c**, which, under mild conditions, were hydrogenated to the corresponding alkylamino derivatives. The subsequent hydrogenation of the latter ones gave different results according to the structure of the starting material. The 5-methoxy-1-alkylaminopyrazoles **3a-g** yielded the 5-methoxypyrazole **15** and the corresponding primary amines in good yields. On the contrary, *N*-methyl-1-alkylaminopyrazolone-5 **6c** gave 1-alkylpyrazolone-3 **8**.

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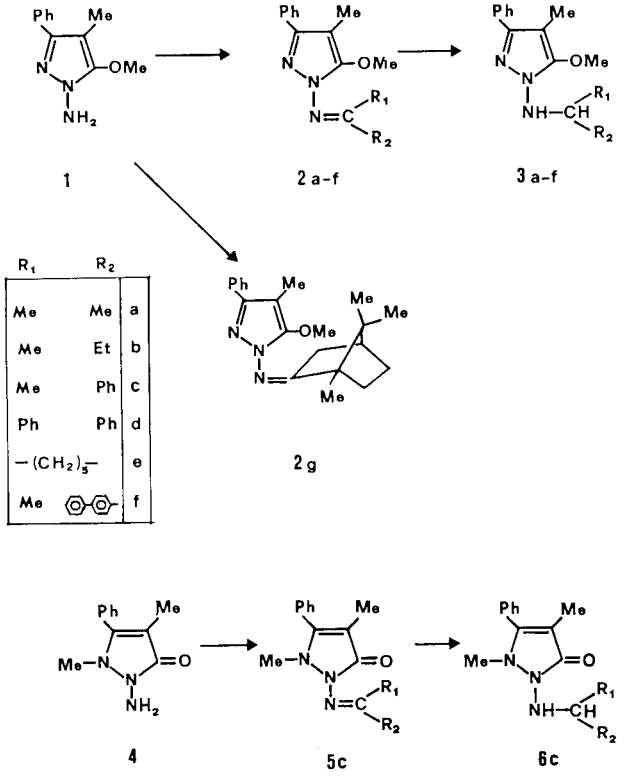
1-Amino-5-hydroxypyrazoles [2] have good nucleophile properties and can be transformed by direct or indirect alkylation into mono- or dialkyl- derivatives [2,3]. This applies to both those in the free tautomeric form and to *O*- or *N*-methyl derivatives which can be obtained by the former *via* methylation with diazomethane.

The labile nature of the nuclear nitrogen-aminic nitrogen bond which causes, simply by heating, their decomposition resulting in the formation of the respective pyrazoles, led us to use the tautomerizable 5-hydroxy-1-alkylaminopyrazoles as starting products for obtaining aliphatic amines in order to submit them to hydrogenolysis.

The research described here concerns derivatives of 1-amino-3-phenyl-4-methyl-5-hydroxypyrazole (**9**) in that this compound, among the many available, could be obtained with better yields and was found to be the most easily purifiable.

Scheme 1



Condensation of 1-aminopyrazole **1** with carbonylic compounds resulted in alkenylaminopyrazoles **2a-g** which, after undergoing hydrogenation, gave mono-alkylated compounds **3a-f**. Aminopyrazolone **4** behaved similarly yielding compounds **5c** and **6c**.

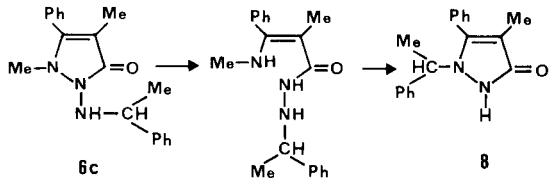
Subsequent detachment of the primary amines **12a-g** usually occurred when the hydrogen pressure reached about 3.5 atmospheres (50 psi) and depended on both the *p*H and the nature of the starting product.

Also the tautomerizable 1-aminopyrazole **9** yielded the corresponding alkenylaminopyrazole **12**. Hydrogenolysis of this compound, however, produced primary amines with rather low yields. Besides these, other products of decomposition and rearrangement have been identified. Further studies on this aspect are in progress and will be published elsewhere. It is likely that the labile nature of the pyrazole system in **9** is linked to the fact that the system can exist in several different tautomeric forms (the position of the equilibrium depends on the solvent, as can be seen by recording the pmr spectra) and only in the aromatic hydroxypyrazole form the nuclear nitrogen-nitrogen bond is stable toward hydrogenation.

Keeping this difficulty in mind along with the fact of the pyrazole recycling after its separation from the amine, we focused our attention on the *N*-methylpyrazolone **4**, easily obtainable from 1,4-dimethyl-5-phenylpyrazol-3-one through amination under basic conditions. This behaviour was in contrast to that occurring with 3-phenyl-4-methyl-5-hydroxypyrazole which almost exclusively produced the 4-amino derivative [4].

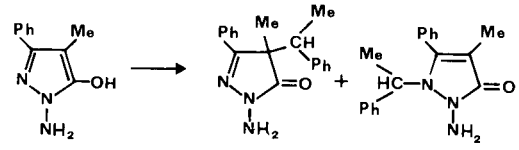
However, compound **6c** was not suitable because hydrogenation easily cleaved the nuclear nitrogen-nitrogen bond: under acid conditions it formed, probabily *via* an unstable aminohydrazide **7**, 1-alkylpyrazol-3-one, **8**.

Scheme 2



Structure **8** was demonstrated starting from 1-amino-3-phenyl-4-methyl-5-hydroxypyrazole (**9**). This, after alkylation with 1-phenylethyl bromide in sodium methoxide, gave a mixture of the two diastereoisomers 1-amino-3-phenyl-4-(1-phenylethyl)-4-methylpyrazol-5-one (**10**) and 1-amino-2-(1-phenylethyl)-3-phenyl-4-methylpyrazol-5-one (**11**), from which **8** can be obtained using nitrous acid.

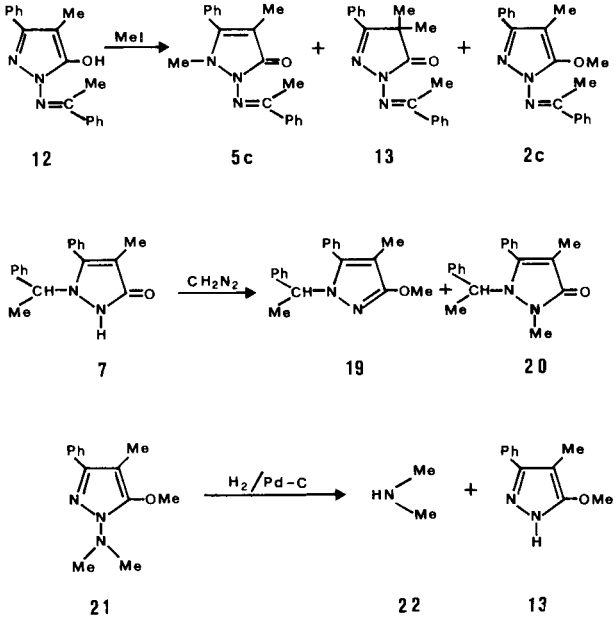
Scheme 3



By contrast the *O*-methylpyrazole of type **1** has an aromatic structure, and in fact products **2a-g** corresponding to this structure gave the best results in amine preparation.

Compounds **2a-g** could be prepared by methylation of the corresponding 1-alkenylamino-5-hydroxypyrazoles using methyl iodide under basic conditions. However this synthesis is not very suitable because a mixture of products is formed. Thus, from **12** we obtained **2c**, **5c** and **13**.

Scheme 4

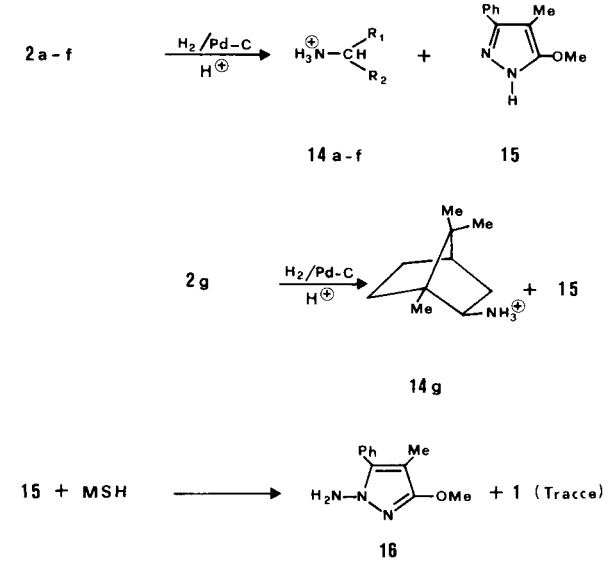


As already recorded, reduction of alkenylaminopyrazoles **2a-g** and **5c** was easily effected and it was usually possible to isolate the alkylaminopyrazoles **3a-f** and **6c**, though it was necessary to modify the reaction conditions according to the type of radical bonded to the nitrogen. In only one instance, that of the bornylamine, were we unable to isolate the intermediate 1-bornylaminopyrazole.

The yields of the amines (from 40-90%) recovered in the form of hydrochlorides were comparable with those obtained by other methods, even when one of the radicals was an aryl group. It was only in the case of R = biphenyl that the yield diminished to 15% and in the case of R_1 = R_2 = phenyl that we found only decomposition products (gas-mass analysis).

It was not possible to recycle the methoxypyrazole **15**, which usually resulted in high yields from the hydrogenolysis of compounds **2a-g** and **20** (see Table). Amination of **15** carried out by treating the sodium salt with MSH (*O*-mesitylenesulfonyl)hydroxylamine [5] produced 1-amino-3-methoxy-4-methyl-5-phenylpyrazole (**16**) and only traces of **1**.

Scheme 5



The compound **16** can be transformed into monoalkyl-derivatives **18** by condensation with acetophenone and subsequent reduction. But hydrogenolysis of **18**, under neutral conditions, gave rise to ethylbenzene, the methoxypyrazole **15** and 1-amino-3-methoxy-4-methyl-5-phenylpyrazole (**16**). If hydrogenolysis was carried out under acidic conditions 1-(1-phenylethyl)-5-methoxypyrazole (**19**) was isolated in addition to ethylbenzene and 5-methoxypyrazole **15**. Structure of **19** was confirmed since compound **8** with diazomethane led to a different *O*-methyl isomer.

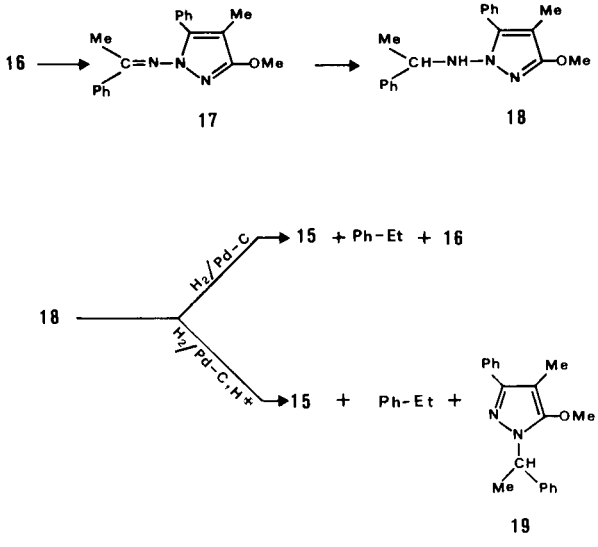
Table

Reduction of Alkenylaminopyrazoles 2a-g and 20

Reduction of	Amine	Yield % (Amine•HCl)	Pyrazole 15 Recovered %
2a	14a	40	77
2b	14b	44	70
2c	14c	49	87
2d	14d	--	--
2e	14e	53	63
2f	14f	15 [7]	47
2g	14g [a]	90	80
20	21	85	80

[a] *Exo*-bornylamine [α_D^{20} = -46.5° (ethanol), (lit -46.8°) [8].

Scheme 6



Secondary amines can be obtained by submitting 1-dialkylaminopyrazoles to catalytic hydrogenation. Thus, dimethylamine was obtained by hydrogenation of 1-dimethylamino-3-phenyl-4-methyl-5-methoxypyrazole **20**.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were measured as potassium bromide discs with a Perkin-Elmer 782 spectrometer. The pmr spectra (60 MHz) were recorded in deuteriochloroform (unless otherwise indicated) with a Perkin-Elmer R 600 instrument; chemical shifts are reported in ppm downfield from internal tetramethylsilane. The gcms analyses were carried out on a VG 70-250S instrument (*e.i.*, 70 eV). Flash chromatographic separations were carried out as described [6] on 230-400 mesh silica gel 60.

General Procedure for the Preparation of Alkenylaminopyrazoles **2a,b**.

A mixture of 1-aminopyrazoles **1** (5 mmoles), the ketone (50 mmoles) and anhydrous magnesium sulfate (200 mg) was stirred at room temperature for 4 hours. The magnesium sulfate was filtered off and the excess ketone removed by distillation under vacuum.

Reaction of 1-Aminopyrazole **1** with Acetone.

The residue was dissolved in the minimum amount of carbon tetrachloride and chromatographed using ether/petroleum ether 1/1.5 as eluent in order to eliminate the faster and the slower eluting impurities. The intermediate fraction was collected to afford 1-(isopropylidene)amino-3-phenyl-4-methyl-5-methoxypyrazole (**2a**) (74%) as an oil which was directly used for the following reaction of reduction; pmr: δ 2.18 (s, 3H, 4-Me), 2.24 (s, 6H, 2 x Me), 3.94 (s, 3H, O-Me), 7.33-7.61 (m, 5H, Ph).

Reaction of 1-Aminopyrazole **1** with Ethyl Methyl Ketone.

The residue was dissolved in the minimum amount of carbon tetrachloride and chromatographed using ether/petroleum ether 1/3 as eluent. Evaporation of the eluate afforded 1-[(1-methylpropylidene)amino]-3-phenyl-4-methyl-5-methoxypyrazole (**2b**) (74%) as an oil and directly used for the following reduction reaction; pmr: δ 1.25 (t, 3H, Me, J = 7.0 Hz), 2.17 (s, 3H, Me), 2.33 (s, 3H, Me), 2.52 (q, 2H, CH_2, J = 7.0 Hz), 3.93 (s, 3H, O-Me), 7.33-7.70 (m, 5H, Ph).

General Procedure for the Preparation of Alkenylaminopyrazoles **2c, 2f** and **2g**.

A solution of 1-aminopyrazole **1** (5.0 mmoles), the ketone (6.0 mmoles) and *p*-toluensulfonic acid (50.0 mg) in toluene (60 ml) was poured into a flask of a Soxhlet extractor and refluxed overnight. The cartridge of the Soxhlet was previously filled with Dryerite (anhydrous granular calcium sulfate). At the end of the reaction the solvent was removed.

Reaction of 1-Aminopyrazole **1** with Acetophenone.

The residue was treated with petroleum ether and refluxed for a few minutes. After cooling, the lower layer was recovered and kept at 100° under vacuum for a few hours to afford the raw 1-[(1-phenylethylidene)amino]-3-phenyl-4-methyl-5-methoxypyrazole (**2c**). This product crystallized very slowly from ethanol (53%) mp 40-42° (petroleum ether); pmr: δ 2.19 (s, 3H, 4-Me), 2.74 (s, 3H, Me), 3.99 (s, 3H, O-Me), 7.30-7.91 (m, 10H, 2 x Ph).

Anal. Calcd. for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.90; H, 6.51; N, 13.90.

Reaction of 1-Aminopyrazole **1** with 4-Biphenyl Methyl Ketone.

The residue was dissolved in the minimum amount of carbon tetrachloride and was chromatographed using ether/petroleum ether 1/3 as eluent. The faster eluting product was collected to afford 1-[1-(4-biphenylethylidene)amino]-3-phenyl-4-methyl-5-methoxypyrazole (**2f**) (70%), mp 111-113° (petroleum ether); pmr: δ 2.22 (s, 3H, 4-Me), 2.79 (s, 3H, Me), 4.04 (s, 3H, O-Me), 7.36-7.97 (m, 14H, Ar).

Anal. Calcd. for $C_{25}H_{23}N_3O$: C, 78.71; H, 6.08; N, 11.01. Found: C, 79.00; H, 6.18; N, 11.00.

Reaction of 1-Aminopyrazole **1** with (+)-Camphor.

The residue was kept at 50° and 0.02 mm to eliminate the excess of camphor, then it was dissolved in a minimum amount of carbon tetrachloride and chromatographed using ether/petroleum ether 4/100 as eluent. Evaporation of the eluate afforded 1-

[(2-bornylidene)amino]-3-phenyl-4-methyl-5-methoxypyrazole (**2g**) (60%) mp 56-58° (methanol) $[\alpha]_D^{20} = -20.5°$ (c = 2.68); pmr: δ 0.85 (s, 3H, Me), 0.98 (s, 3H, Me), 1.13 (s, 3H, Me), 1.20-2.10 (m, 6H, 3 x CH_2), 2.60-3.12 (m, 1H, CH), 4.01 (s, 3H, O-Me), 7.29-7.68 (m, 5H, Ph).

Anal. Calcd. for $C_{21}H_{27}N_3O$: C, 74.74; H, 8.07; N, 12.45. Found: C, 74.87; H, 8.11; N, 12.60.

General Procedure for the Preparation of Alkenylaminopyrazoles **2e**, **12** and **17**.

A solution of 1-aminopyrazole **1**, **9** or **16** (5.0 mmoles), the ketone (5.0 mmoles) and three drops of concentrated hydrochloric acid in ethanol (8.0 ml) was stirred overnight at room temperature. Then the solvent was removed by distillation.

Reaction of 1-Aminopyrazole **1** with Cyclohexanone.

The residue was washed three times with petroleum ether to afford 1-[(1-cyclohexylidene)amino]-3-phenyl-4-methyl-5-methoxypyrazole (**2e**) (90%) as an oil and directly used for the following reduction reaction; pmr: δ 1.40-2.00 (m, 6H, 3 x CH_2), 2.18 (s, 3H, 4-Me), 2.40-2.90 (m, 4H, 2 x CH_2), 3.92 (s, 3H, O-Me), 7.29-7.75 (m, 5H, Ph).

Reaction of 1-Amino-3-phenyl-4-methyl-5-hydroxypyrazole (**9**) with Acetophenone.

The residue was treated twice with petroleum ether and then with a minimum amount of ether/petroleum ether 1/1 solution to afford 1-[(1-phenylethylidene)amino]-3-phenyl-4-methyl-5-hydroxypyrazole (**12**) (80%) mp, 152-154° (ligroin); pmr spectrum shows the presence of two tautomeric forms: a) CH form δ 1.57 (d, 3H, 4-Me, J = 8.2 Hz), 2.48 (s, 3H, Me), 3.70 (q, 1H, CH, J = 8.2 Hz), 7.34-8.04 (m, 10H, 2 x Ph); b) OH/NH form 2.08 (s, 3H, 4-Me), 2.62 (s, 3H, Me), 7.34-8.04 (m, 10H, 2 x Ph).

Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.50; H, 5.93; N, 14.10.

Reaction of 1-Aminopyrazole **16** with Acetophenone.

The residue was chromatographed using ether/petroleum ether 6/100 as eluent. The faster eluting product was 1-[(1-phenylethylidene)amino]-3-methoxy-4-methyl-5-phenylpyrazole (**17**) (82%) as an oil and directly used for the following reduction reaction; pmr: δ 2.04 (s, 3H, 4-Me), 2.77 (s, 3H, Me), 4.00 (s, 3H, O-Me), 7.38-7.44 (m, 10H, 2 x Ph).

1-[(Diphenylmethylene)amino]-3-phenyl-4-methyl-5-methoxypyrazole (**2d**).

1-Aminopyrazole **1** (5.0 mmoles) was mixed with benzophenone (6.0 mmoles) and benzoic acid (100 mg) and the mixture introduced into a stoppered flask with a test tube inside containing concentrated sulfuric acid as drying agent. The flask was kept at 100° for 60 hours. At the end of the reaction the excess of benzophenone was removed by sublimation and the residue was dissolved in the minimum amount of ethyl ether and chromatographed using ether/petroleum ether 1/4 as eluent. Evaporation of the eluate afforded the product **2d** (73%) mp 100-102°; pmr: δ 2.14 (s, 3H, 4-Me), 4.03 (s, 3H, O-Me), 7.30-7.80 (m, 15H, 3 x Ph).

Anal. Calcd. for $C_{24}H_{21}N_3O$: C, 78.45; H, 5.76; N, 11.43. Found: C, 78.31; H, 5.76; N, 11.44.

1-[(1-Phenylethylidene)amino]-2,4-dimethyl-3-phenylpyrazolin-5-one (**5c**).

A solution of 1-aminopyrazolone **4** (5.0 mmoles) and benzoic acid (20 mg) in acetophenone (2.0 ml) was kept at 90° for 24 hours. The excess ketone was removed by distillation under vacuum and the residue was chromatographed using chloroform as the eluent. The faster eluting product was the unreacted acetophenone, while the slower was the reaction product **5c** (40%), mp 122-123° (petroleum ether); pmr: δ 1.94 (s, 3H, 4-Me), 2.59 (s, 3H, Me), 3.02 (s, 3H, N-Me), 7.30-8.10 (m, 10H, 2 x Ph); ir: 1672 cm^{-1}.

Anal. Calcd. for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.64; H, 6.37; N, 13.54.

The same product was also obtained by methylation of **12** with methyl iodide (see below).

General Procedure for Catalytic Hydrogenation of Alkenylaminopyrazoles **2a**, **2e** and **5c** at 50 psi.

Alkenylaminopyrazoles (5.0 mmoles) in methanol (200 ml) were stirred at room temperature under hydrogen at 50 psi in the presence of 10% palladium on charcoal (200 mg) until the starting material disappeared. The charcoal was then filtered off and the solvent removed.

1-Isopropylamino-3-phenyl-4-methyl-5-methoxypyrazole (**3a**).

Given that hydrogenation under neutral conditions was very slow, a stoichiometric amount of hydrochloric acid was added. The residue containing the crude reaction product was dissolved in the minimum amount of carbon tetrachloride and chromatographed using ether/petroleum ether 1/1.5 as eluent. The faster eluting product was **3a** (65%), mp 61-63° (sublimation at 50° and 0.02 mm); pmr: δ 1.07 (d, J = 6.2 Hz, 6H, 2 x Me), 2.13 (s, 3H, 4-Me), 3.72 (q, J = 6.2 Hz, 1H, CH), 3.99 (s, 3H, O-Me), 7.29-7.56 (m, 5H, Ph); ir: 3250 cm^{-1}.

Anal. Calcd. for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.41; H, 7.93; N, 16.95.

1-Cyclohexylamino-3-phenyl-4-methyl-5-methoxypyrazole (**3e**).

The residue containing the crude product was dissolved in the minimum amount of carbon tetrachloride and chromatographed using chloroform/methanol 100/0.5 as eluent. The faster eluting product was **3e** (60%), mp, 100-102°; pmr: δ 1.00-2.00 (m, 10H, 5 x CH_2), 2.12 (s, 3H, 4-Me), 3.60 (m, 1H, CH), 3.99 (s, 3H, O-Me), 7.29-7.80 (m, 5H, Ph); ir: 3223 cm^{-1} (NH).

Anal. Calcd. for $C_{17}H_{23}N_3O$: C, 71.55; H, 8.12; N, 14.72. Found: C, 71.47; H, 8.20; N, 14.74.

1-[(1-Phenylethyl)amino]-2,4-dimethyl-3-phenyl-5-methoxypyrazole (**6c**).

The residue containing the crude product was treated with a little amount of ethyl ether/petroleum ether 1/1 solution to afford a white precipitate of **6c** (73%), mp 132-135° (ligroin); pmr: δ 1.45 (d, 3H, Me, J = 6.6 Hz), 1.87 (s, 3H, 4-Me), 2.73 (s, 3H, N-Me), 4.85 (q, 1H, CH, J = 6.6 Hz), 5.06 (broad s, 1H, NH, deuterium oxide-exchangeable), 7.10-7.70 (m, 10H, 2 x Ph); ir: 3190 cm^{-1} (NH).

Anal. Calcd. for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67. Found: C, 74.11; H, 7.05; N, 13.60.

General Procedure for Catalytic Hydrogenation of Alkenylaminopyrazoles **2b-d,f** and **17** at Atmospheric Pressure.

Alkenylaminopyrazoles (5.0 mmoles) in methanol (50.0 ml) were stirred, at room temperature, under hydrogen at atmospheric pressure, in the presence of 10% palladium on charcoal (200 mg) until the starting material disappeared. The charcoal was then filtered off and the solvent removed.

1-[(1-Methylpropyl)amino]-3-phenyl-4-methyl-5-methoxypyrazole (**3b**).

The residue containing the crude product was dissolved in the minimum amount of carbon tetrachloride and was chromatographed using ethyl ether/petroleum ether 1/3 as eluent. Evaporation of the eluate afforded **3b** (65%), mp 43-46° (sublimation at 50° and 0.02 mm); pmr: δ 0.95 (t, 3H, Me), 1.05 (d, 3H, Me, J = 6.6 Hz), 1.02-1.07 (m, 2H, CH_2), 2.13 (s, 3H, Me), 3.20-3.70 (m, 1H, CH), 3.99 (s, 3H, O-Me), 4.75 (broad s, 1H, NH, deuterium oxide-exchangeable), 7.20-7.80 (m, 5H, Ph); ir: 3220 cm^{-1} (NH).

Anal. Calcd. for $C_{15}H_{21}N_3O$: C, 69.47; H, 8.16; N, 16.20. Found: C, 69.72; H, 8.20; N, 16.14.

1-[(1-Phenylethyl)amino]-3-phenyl-4-methyl-5-methoxypyrazole (**3c**).

The residue containing the crude product **3c** (90%) was crystallized from ethanol, mp 100-102°; pmr: δ 1.35 (d, 3H, Me, J = 6.4 Hz), 2.06 (s, 3H, 4-Me), 3.78 (s, 3H, O-Me), 4.75 (q, 1H, CH, J = 6.4 Hz), 7.33-7.55 (m, 10H, 2 x Ph); ir: 3220 cm^{-1} (NH).

Anal. Calcd. for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67. Found: C, 74.51; H, 7.04; N, 13.64.

1-[(1-Diphenylmethyl)amino]-3-phenyl-4-methyl-5-methoxypyrazole (**3d**).

The residue containing the crude product **3d** (84%) was crystallized from petroleum ether, mp 105-107°; pmr: δ 1.99 (s, 3H, 4-Me), 3.70 (s, 3H, O-Me), 5.23 (broad s, 1H, NH, deuterium oxide-exchangeable), 5.95 (s, 1H, CH), 7.31-7.45 (m, 15H, 3 x Ph); ir: 3180 cm^{-1} (NH).

Anal. Calcd. for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.27; N, 11.37. Found: C, 78.26; H, 6.29; N, 11.35.

1-[1-(4-Biphenylethyl)amino]-3-phenyl-4-methyl-5-methoxypyrazole (**3f**).

The residue containing the crude product **3f** was sublimed at 50° and 0.02 mm (90%), mp 91-93° (petroleum ether); pmr: δ 1.40 (d, 3H, Me, J = 6.2 Hz), 2.08 (s, 3H, 4-Me), 3.82 (s, 3H, O-Me), 4.80 (q, 1H, CH, J = 6.2 Hz), 7.31-7.61 (m, 14H, 3 x Ph); ir: 3240 cm^{-1} (NH).

Anal. Calcd. for $C_{25}H_{25}N_3O$: C, 78.30; H, 6.57; N, 10.96. Found: C, 78.36; H, 6.68; N, 10.95.

1-[(1-Phenylethyl)amino]-3-methoxy-4-methyl-5-phenylpyrazole (**18**).

The residue afforded the crude product **18** (80%), mp 92-93° (petroleum ether); pmr: δ 1.07 (d, 3H, Me, J = 6.6 Hz), 1.85 (s, 3H, 4-Me), 3.97 (s, 3H, O-Me), 4.60 (q, 1H, CH, J = 6.6 Hz), 7.30-7.43 (m, 10H, 2 x Ph); ir: 3220 cm^{-1} (NH).

Anal. Calcd. for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67. Found: C, 73.90; H, 6.74; N, 14.04.

1-(1-Phenylethyl)-4-methyl-5-phenylpyrazol-3-one (**8**).

A solution of compound **6c** (1.60 mmoles), hydrochloric acid (1.60 mmoles) in methanol (40 ml) was stirred for 5 hours at room temperature under hydrogen at atmospheric pressure, in the presence of 10% palladium on charcoal (200 mg). The charcoal was then filtered off and the solvent removed. The residue was treated with water, neutralized with sodium bicarbonate, and extracted with ether. Evaporation of the etheral solution afforded product **8** (70%), mp 208-209° (ethanol); pmr: δ 1.83 (d, 3H, Me, J = 7.4 Hz), 1.85 (s, 3H, 4-Me), 5.23 (q, 1H, CH, J = 7.4 Hz), 7.23-7.42 (m, 10H, 2 x Ph); ir 3200-2300 cm^{-1}.

Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.32; H, 6.34; N, 10.03.

Reaction Between 1-Amino-3-phenyl-4-methyl-5-hydroxypyrazole (**9**) and 1-Phenylethyl Bromide.

1-Aminopyrazole **9** (2.65 mmoles) was added to a solution of sodium methylate (2.65 mmoles) in methanol (10 ml). Anhydrous toluene (8 ml) and 1-phenylethyl bromide (3.40 mmoles) were added to the sodium salt afforded by the evaporation of the solvent. The solution was stirred at room temperature for 3 days. The precipitate (potassium bromide) was filtered off and the solvent was removed by distillation affording a residue containing the reaction products (90%). This residue was dissolved in the minimum amount of methanol and chromatographed. Elution was carried out first with ether and then with chloroform/methanol 100/3. Evaporation of the etheral eluate afforded a mixture of two diastereoisomers 1-amino-3-phenyl-4-methyl-4(1-phenylethyl)pyrazol-5-one (**10**) (47%). Analysis was carried out before separation of the isomers.

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.70; H, 6.53; N, 14.32. Found: C, 73.43; H, 6.75; N, 14.19.

These diastereoisomers were separated by chromatography using ethyl ether/petroleum ether: 3/1 as eluent. The faster running product was **10'**; pmr (deuteriomethanol): δ 1.71 (d, 3H, Me, J = 6.5 Hz), 1.85 (s, 3H, 4-Me), 5.47 (q, 1H, CH, J = 6.5 Hz), 7.31-7.48 (m, 10H, 2 x Ph); ir 3220-3350 cm^{-1} (NH_2). The slower running product was **10''**; pmr (deuteriomethanol): δ 1.54 (d, 3H, Me, J = 7.2 Hz), 1.71 (s, 3H, Me), 3.48 (q, 1H, CH, J = 7.2 Hz), 7.01-7.46 (m, 10H, 2 x Ph); ir 3220-3350 cm^{-1} (NH_2).

Evaporation of chloroform/methanol eluate afforded 1-amino-2-(1-phenylethyl)-3-phenyl-4-methylpyrazol-5-one (**11**) (23%) as an oil which was deaminated without further purification; (see next reaction); pmr (deuteriomethanol): δ 1.60 (d, 3H, Me, J = 6.9 Hz), 1.77 (s, 3H, 4-Me), 5.20 (q, 1H, CH, J = 6.9 Hz), 7.31-7.46 (m, 10H, 2 x Ph); ir: 1650 (CO), 3200-3320 (NH_2) cm^{-1}.

Deamination of 1-Amino-2-(1-phenylethyl)-3-phenyl-4-methylpyrazol-5-one (**11**).

Sodium nitrite (1.0 mmole), dissolved in the minimum amount of water, was added with stirring to compound **11** (1.0 mmole), dissolved in the minimum amount of glacial acetic acid and, after rubbing, a crystalline product precipitated, mp 208-209°. Melting point, ir and pmr spectra are identical to those of compound **8** afforded by reduction of **6c**.

Methylation of 1-[(1-Phenylethylidene)amino]-3-phenyl-4-methyl-5-hydroxypyrazole (**12**) with Methyl Iodide.

Methyl iodide (0.24 ml) was added to a solution of compound **12** (3.4 mmoles) in methanol (16 ml) containing sodium (80 mg). The solution was refluxed for two hours, then the solvent was removed by distillation. The residue was treated with chloroform, sodium iodide was removed by filtration and the solution was concentrated and was chromatographed using ethyl ether/petroleum ether 1/1 as eluent. The faster eluting product was 1-[(1-phenylethylidene)amino]-3-phenyl-4-methyl-5-methoxypyrazole (**2c**) (5.0%) identical (ir, pmr) to the compound previously described. The following eluting product was 1-[(1-phenylethylidene)amino]-3-phenyl-4,4-dimethylpyrazolin-5-one (**13**) (23%), mp 106-108° (petroleum ether); pmr: δ 1.62 (s, 6H, 2 x Me), 2.48 (s, 3H, Me), 7.38-7.94 (m, 10H, 2 x Ph); ir 1710 cm^{-1} (CO).

Anal. Calcd. for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.55; H, 6.50; N, 13.82.

Further elution, with the same solvent combination, but in a ratio 2/1, afforded 1-[(1-phenylethylidene)amino]-2,4-dimethyl-3-phenylpyrazolin-5-one (**5c**) (52%) identical (ir and pmr spectra) to the compound previously described.

General Procedure for Catalytic Reduction of Alkenylaminopyrazoles **2a-g** and 1-Dimethylamino-3-phenyl-4-methyl-5-methoxypyrazole (**20**) under 50 psi of Pressure.

Alkenylaminopyrazoles **2a-g** or 1-dimethylaminopyrazole **20** (5.0 mmoles) and concentrated hydrochloric acid (5.0 mmoles) in methanol (50 ml) were stirred at room temperature, under hydrogen at 50 psi of pressure, in the presence of 10% palladium on charcoal (200 mg) until the intermediate corresponding alkylaminopyrazoles or 1-dimethylaminopyrazole **20** disappeared. The charcoal was then filtered off and the solvent removed. Water and ether were added to the residue and, after stirring, the two phases were separated. The ethereal phase was extracted with water while the aqueous phase was extracted with ether. Evaporation of water afforded the amine hydrochlorides **14a-g** and dimethylamine while evaporation of ether afforded the pyrazole **15** (see Table).

Amination of 3-Phenyl-4-methyl-5-methoxypyrazole (**15**) with MSH [5].

A solution of pyrazole **15** in 25 ml of tetrahydrofuran was added, dropwise at 0° under stirring, to a suspension of sodium hydride (80% in paraffin, 20 mmoles) in 25 ml of tetrahydrofuran. The precipitation of sodium hydride disappeared along with an evolution of hydrogen gas during the addition. The solution was again cooled on an ice bath and added with a benzene solution of (*O*-mesitylenesulfonyl)hydroxylamine (MSH). The reaction mixture formed a milky precipitate when it was stirred for two hours at room temperature. After filtration of the precipitate, the solution was evaporated to dryness under reduced pressure to afford an oily residue of 1-amino-3-methoxy-4-methyl-5-phenylpyrazole (**16**) (80%), pyrazole **15** and 1-amino-3-phenyl-4-methyl-5-methoxypyrazole (**1**) in traces (tlc). The products were separated by chromatography and elution was carried out first with ethyl ether/petroleum ether 8/100 to afford product **16** and then with the same solvent combination but with a ratio 3/1 to afford compound **15**. Product **16** was crystallized from petroleum ether mp 79-80°; pmr: δ 1.92 (s, 3H, 4-Me), 3.60 (v broad s, 2H, NH_2 deuterium oxide-exchangeable), 3.93 (s, 3H, O-Me), 7.43 (s, 5H, Ph); ir: 3220-3315 cm^{-1} (NH_2).

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 64.82; H, 6.36; N, 20.42.

Catalytic Reduction of 1-[(1-Phenylethyl)amino]-3-methoxy-4-methyl-5-phenylpyrazole (**18**).

a) Under Neutral Conditions.

Alkylaminopyrazole **18** (1.30 mmoles) in methanol (60 ml) was stirred, at room temperature, under hydrogen at 90 psi in the presence of 10% palladium on charcoal (200 mg). The reaction was very slow, about ten days were required. The filtrate, after removal of the catalyst, was then evaporated to dryness and the residue analysed by a gcms spectrometry, revealing the presence of methoxypyrazole **15**, ethylbenzene, starting material **18** and aminopyrazole **16**.

b) Under Acidic Conditions.

Alkylaminopyrazole **18** (1.60 mmoles) and concentrated hydrochloric acid (1.60 mmoles) in methanol (50.0 ml) were stirred, at room temperature, under hydrogen at atmospheric pressure, in the presence of 10% palladium on charcoal (200 mg) for about two hours. The charcoal was filtered off and the solvent removed. The residue was analysed by a gcms spectrometry, revealing the presence of 1-(1-phenylethyl)-5-methoxypyrazole (**19**), ethylbenzene and 5-methoxypyrazole **15**. Then the residue was dissolved in the minimum amount of ethyl ether and chromatographed using ethyl ether/petroleum ether 1/8 as eluent. The faster eluting product was 1-(1-phenylethyl)-3-phenyl-4-methyl-5-methoxypyrazole (**19**) as an oil; pmr: δ 1.90 (d, 3H, Me, J = 7.1 Hz), 2.13 (s, 3H, 4-Me), 3.66 (s, 3H, O-Me), 5.52 (q, 1H, CH, J = 7.1 Hz), 7.22-7.72 (m, 10H, 2 x Ph).

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 77.68; H, 6.85; N, 9.50.

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