1-Aminopyrazolin-5-ones. Synthesis and Reactivity (1)

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A synthesis of 1-aminopyrazolin-5-ones (I) by chloramine attack on the 2-benzylpyrazolones (IVd-e) has been accomplished. Nucleophilic substitution reactions of aminopyrazolones (I) are investigated; with 1,4-diketones, *N,N'*-pyrrolylpyrazolones (XVIIa-c) are obtained. Chlorination of acetylaminopyrazolones (VII) led to the corresponding 1-amino-5-chloropyrazoles (XXI) *via* the isolable pyrazolo[3,2-*b*]oxadiazoles (XIX).

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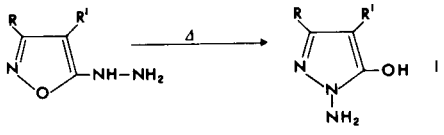
In connection with our interest in the thermally induced isomerisation of the isoxazol-5-ylhydrazines (2) and the corresponding rearrangement products (3) we now report a study of the preparation and reactivity of 1-aminopyrazolin-5-ones.

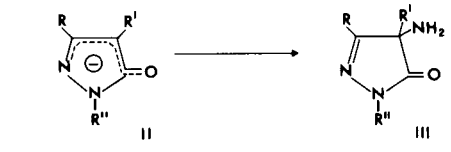


a) R=CH$_3$, R'=C$_6$H$_5$
b) R=C$_6$H$_5$, R'=CH$_3$
c) R=R'=C$_6$H$_5$

I

Scheme I

To this end, the development of a convenient synthesis of compounds I was desired. The availability of these compounds by transposition of isoxazolylhydrazines depends both on the reaction conditions and on the nature of ring substituents. For this reason, this pathway does not represent a convenient general method of synthesis. Direct amination of the corresponding pyrazol-5-ones in alkaline solution cannot be considered since the anion II is a nucleophilic polycentric species, leading exclusively to

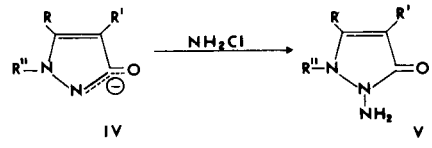


II III

a) R=CH$_3$, R'=C$_6$H$_5$, R''=H
b) R=C$_6$H$_5$, R'=CH$_3$, R''=H
c) R=R'=C$_6$H$_5$, R''=H
d) R=CH$_3$, R'=C$_6$H$_5$, R''=CH$_3$
e) R=C$_6$H$_5$, R'=CH$_3$, R''=CH$_3$
f) R=R'=C$_6$H$_5$, R''=CH$_3$

Scheme II

4-aminopyrazolin-5-ones (III). On the contrary, 1-alkylpyrazolin-3-ones (IV) give rise to nucleophilic attack through the nitrogen atom at position 2 to give 1-aminopyrazolin-5-ones (V).

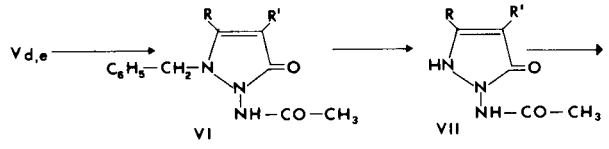


IV V

a) R=CH$_3$, R'=C$_6$H$_5$, R''=CH$_2$
b) R=C$_6$H$_5$, R'=CH$_3$, R''=CH$_2$
c) R=R'=C$_6$H$_5$, R''=CH$_2$
d) R=CH$_3$, R'=C$_6$H$_5$, R''=C$_6$H$_5$–CH$_2$
e) R=C$_6$H$_5$, R'=CH$_3$, R''=C$_6$H$_5$–CH$_2$

Scheme III

Consequently, we decided to prepare aminopyrazolin-5-ones (I) starting from *N*-benzyl derivatives V, profiting by their known property to undergo hydrogenolysis under mild conditions. However, the use of this method is not without problems, since on catalytic hydrogenation, 1-amino-2-benzylpyrazolones (V) first undergo deamination to give benzylpyrazolones IVd,e before debenzylation. By introducing an electron withdrawing group on the amino group, the >N-NH- bond becomes more stable and does not undergo hydrogenolysis. Thus, 1-acetylamino-2-benzylpyrazolin-5-ones (VI) can be debenzylated to give 1-acetylaminopyrazolin-5-ones (VII), which by alkaline hydrolysis give 1-aminopyrazolones I.



VI VII

a) R=CH$_3$, R'=C$_6$H$_5$
b) R=C$_6$H$_5$, R'=CH$_3$

Scheme IV

In the solid state and in hydrogen bonded solvents, compounds I exist in the hydroxypyrazole form I_A.

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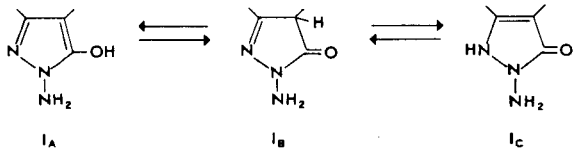
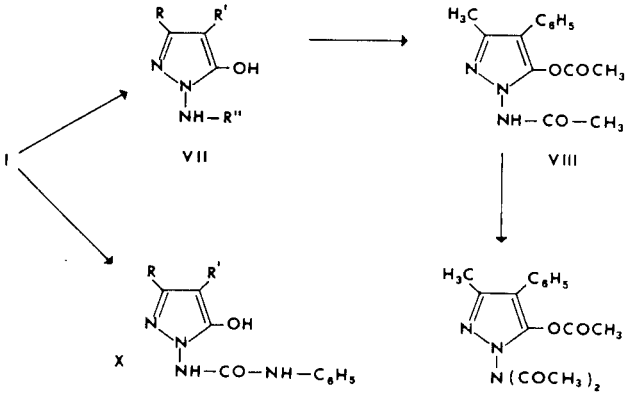


Scheme V

Although the amino group shows a reduced nucleophilic reactivity in comparison with analogous hydrazine systems, due to the electron withdrawing effect of the pyrazole ring system, nucleophilic reactions are still possible. Thus, with acyl halides or with anhydrides, *N*-acyl derivatives VII are easily obtained. However, under more drastic conditions, increasing the ratio acylant/substrate, it is possible to introduce two (VIII) or three (IX) acidic moieties in the molecule. The phenylisocyanate compounds I also react readily to give the corresponding ureas X.



a) R = CH_3, R' = C_6H_5, R'' = $COCH_3$

b) R = C_6H_5, R' = CH_3, R'' = $COCH_3$

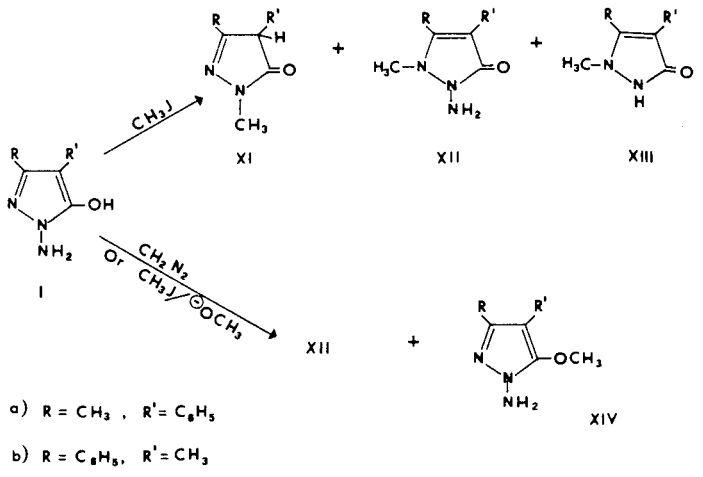
c) R = CH_3, R' = C_6H_5, R'' = $COCH_2Cl$

d) R = CH_3, R' = C_6H_5, R'' = $COCH_2Br$

Scheme VI

On the contrary, with alkyl halides the reaction proceeds slowly and it becomes necessary to operate at higher temperature, leading to a considerable deamination of the starting material. The main product of the reaction with methyl iodide is not the expected 1-amino-2-methylpyrazolin-5-one (XII), identified only by tlc, but rather the 1-methylpyrazolin-5-one (XI) along with a small amount of 1-methylpyrazolin-3-one (XIII) and other products in traces. Compound XIII is derived by thermal deamination of XII. The products obtained show that the nucleophilic attack is carried out by the nitrogen in the 2-position.

In alkaline medium, methylation proceeds at a higher rate; the same mixture of isomers XII and XIV was obtained as in the case of methylation with diazomethane (2a). When the mobile hydrogen is substituted by a methyl group, the alkylation with methyl iodide leads to a mixture

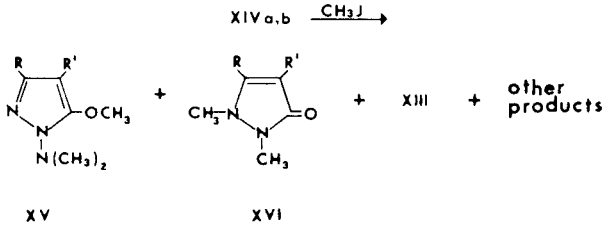


a) R = CH_3, R' = C_6H_5

b) R = C_6H_5, R' = CH_3

Scheme VII

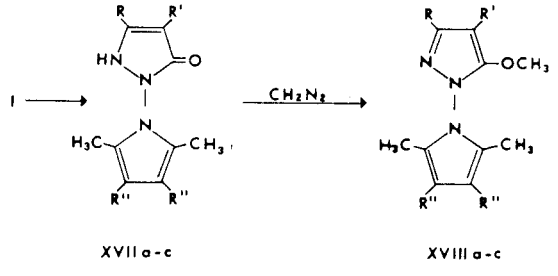
of dimethylaminopyrazole (XV), as the main product, 1,2-dimethylpyrazolin-3-one (XVI), the pyrazolone XIII and other minor products.



Scheme VIII

The *N,N*-dimethyl derivative XVb can be prepared more conveniently by reductive alkylation (2b).

The amino group of I reacts with 1,4-dicarbonyl compounds to give pyrrolylpyrazolones (XVIIa-c) by heating at 100°.



a) R = CH_3, R' = C_6H_5, R'' = H

b) R = C_6H_5, R' = CH_3, R'' = H

c) R = CH_3, R' = C_6H_5, R'' = $COOC_2H_5$

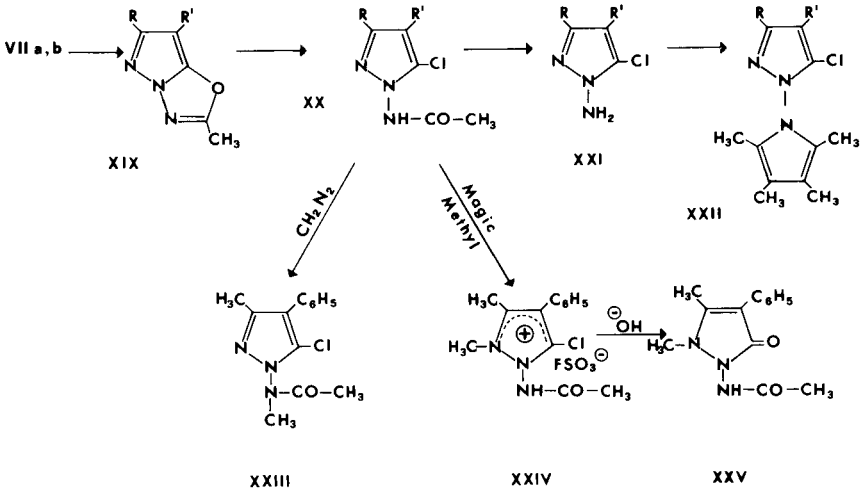
Scheme IX

Although compounds XVII exist in the oxo form in the solid state, as indicated by the presence of a band at 1650-1640 cm^{-1} in the ir spectrum, attributable to a conjugated carbonyl group, when treated with diazomethane,

Table

Compound No.	Lit. Reference	Yield %	Compound No.	Lit. Reference	Yield %
IIIa	2a	10	Va	2a	40
IIIb	2b	traces	Vb	2a	traces
IIIc	2b	50	Vc (a)	—	65 (b)
IIId	2a	50	Vd (c)	—	75 (b)
IIIe	2b	40	Ve (d)	—	33
IIIf	2b	55			

(a) This compound was also obtained with the method described below. (b) Based on the reacted starting material. (c) Ir: ν max 3260, 3160 (NH_2) and 1620 (CO) cm^{-1}. (d) Ir: ν max 3290, 3170 (NH_2) and 1640 (CO) cm^{-1}.



Scheme X

they give exclusively methoxy derivatives (XVIIIa-c). On the contrary, compounds XVII, when treated with halogenating agents, do not give the corresponding chloro derivatives (XXII), which can be prepared from 1-amino-5-chloropyrazoles (XXI) and 1,4 diketones.

1-Aminopyrazoles (XXIa,b) are prepared in good yields by reaction of the acetylaminopyrazolones VII with phenylphosphonic dichloride followed by hydrolysis of the 1-acetylamino-5-chloropyrazoles (XXa,b). As in the case of 5-chloropyrazoles (4), the halogen atom is very stable; both alkaline and acidic hydrolysis lead exclusively to the loss of the acetyl group.

The formation of the chloropyrazoles XXa,b involves the pyrazolooxadiazoles XIX, which are the exclusive products if the chlorination of VII is carried out with phosphorus oxychloride and triethylamine; these products are also isolated in low yield when phenylphosphonic dichloride reacts for a very short time. Therefore, the chloro derivative XX is formed by attack of hydrogen chloride on the oxadiazole, as confirmed by treatment of compound XIX with gaseous hydrogen chloride.

The chloropyrazole XX can be alkylated both on the extranuclear nitrogen atom or on the nitrogen atom at the 2 position to give XXIII or XXIV, with diazomethane or methyl fluorosulfonate, respectively. The chlorine atom of XXIV is reactive, giving rise to the pyrazolone XXV on reaction with alkali. Compound XXV can also be prepared from XIIa by acetylation.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were measured for dispersions in potassium bromide with a Perkin-Elmer 357 spectrometer. ^1H nmr spectra (60 MHz) were recorded with a Perkin-Elmer R 20 b instrument; chemical shifts are reported in ppm downfield from internal tetramethylsilane. Uv spectra were measured for solution in methanol with a Perkin-Elmer 124 spectrophotometer. Silica gel plates (Riedel-De Haen 37341) were used for analytical tlc. Extracts were dried over sodium sulphate. Light petroleum refers to the fraction with bp 30-50°.

1-Benzyl-5-methyl-4-phenylpyrazolin-3-one (IVd).

A solution of 5-methyl-4-phenylpyrazolin-3-one (sodium salt) (30 mmoles) in anhydrous tetrahydrofuran (350 ml) and benzyl bromide (3 ml) was refluxed for 1 hour. After evaporation of the solvent *in vacuo* the residue was purified by treatment with 2*N* sodium hydroxide. The solution was filtered and acidified to afford compound IVd, yield 65%, mp 240-241° (from ethanol); ir: ν max 3200-2100 br (OH) cm^{-1}.

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.56; H, 6.21; N, 10.77.

1-Benzyl-4-methyl-5-phenylpyrazolin-3-one (IVe).

This compound was prepared similarly starting from 4-methyl-5-phenylpyrazolin-3-one, yield 40%, mp 183-185° (from ethanol); ir: ν max 3200-2000 br (OH) cm^{-1}.

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.59; H, 6.06; N, 10.85.

General Procedure for Amination of Pyrazolones IIa-f and IVa-e with Chloramine.

To a solution of pyrazolones IIa-e (2a), IIf (5), IVa-c (2a), IVd,e (sodium salt) (4.0 mmoles) in dimethylformamide (20 ml), ethereal chloramine (4.8 mmoles) was added slowly with stirring and the resulting mixture was kept at room temperature for 12 hours. The solvent was evaporated *in vacuo*. In the case of compounds Vc,d, treating the residue with 1*N* sodium hydroxide, only starting material was recovered from the alkaline solution. The residue was dissolved in 1.5*N* hydrochloric acid and the solution, exracted with ether, was neutralised. Compounds IIIa-f or Va-e were collected by filtration or by extraction with chloroform. Yields are reported in the table.

1-Amino-3,4-diphenyl-5-methoxypyrazole and 1-Amino-3,4-diphenyl-2-methylpyrazolin-5-one (Vc).

To a suspension of 1-amino-3,4-diphenylpyrazolin-5-one (12 mmoles) in methanol:ether 1:1 (100 ml), ethereal diazomethane (36 mmoles) was added. After 12 hours the solvents were rotary evaporated and the oily residue was dried over phosphorus pentoxide *in vacuo*, and then dissolved in a minimum amount of ethanol and chromatographed on silica gel column. Elution was carried out first with ether, until the eluate did not leave a residue by evaporation, and then with ethanol. The crude product obtained by evaporation of the ethereal eluate afforded the methoxy derivative, yield 32%, mp 129-130° (from ligroin); ir: ν max 3320, 3200 (NH_2) cm^{-1}; uv: λ max 236 (log ϵ 4.23), 250 sh (4.14) nm; nmr (deuteriochloroform): δ 3.79 (s, 3H, OCH_3), 4.80 (br. s exch., 2H, NH_2), 7.13-7.52 (m, OH, $2C_6H_5$).

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.45; H, 5.66; N, 15.85. Found: C, 72.17; H, 5.47; N, 15.60.

The crude product obtained by evaporation of the ethanolic eluate afforded compound Vc, yield 35%, mp 165-167° (from cyclohexane); ir: ν max 3300, 3170 (NH_2), 1620 (CO) cm^{-1}; uv: λ max 230 sh (log ϵ 4.12), 297 (3.97) nm; nmr (deuteriochloroform): δ 3.14 (s, 3H, NCH_3), 4.13 (exch. br. s, 2H, NH_2), 7.04-7.52 (m, OH, $2C_6H_5$).

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.45; H, 5.66; N, 15.85. Found: C, 72.71; H, 5.41; N, 15.76.

1-Acetylamino-2-benzyl-3-methyl-4-phenylpyrazolin-5-one (VIa).

A solution of compound Vd (2.15 mmoles) in glacial acetic acid (15 ml) and acetic anhydride (2.6 mmoles) was heated at 100° for 1 hour. The solvent was distilled *in vacuo* and the residue kept over potassium hydroxide overnight. 1*N* Sodium hydroxide was added and the solution was repeatedly extracted with ether. Neutralization of the alkaline phase afforded compound VIa (yield 32%), mp 214-216° (from ethanol/water); ir: ν max 3140 (NH), 1720 (CO) and 1630 (CO) cm^{-1}.

Anal. Calcd. for $C_{19}H_{19}N_3O_2$: C, 71.00; H, 5.96; N, 13.07. Found: C, 71.21; H, 6.10; N, 12.92.

1-Acetylamino-2-benzyl-4-methyl-3-phenylpyrazolin-5-one (VIb).

This compound was prepared similarly starting from compound Ve (yield 45%); mp 215-217° (from ethanol/water); ir: ν max 3160 (NH), 1730 (CO) and 1650 (CO) cm^{-1}; nmr (deuteriochloroform): δ 1.85 and 1.91 (s, 6H, $2CH_3$), 4.56 (s, 2H, CH_2), 6.62-7.60 (m, OH, $2C_6H_5$), 11.23 (exch. br. s, 1H, NH).

Anal. Calcd. for $C_{19}H_{19}N_3O_2$: C, 71.00; H, 5.96; N, 13.07. Found: C, 70.93; H, 6.00; N, 13.13.

Catalytic Hydrogenation of 1-Acetylamino-2-benzylpyrazolin-5-ones (VIa,b).

A mixture of compounds VIa,b (1.2 mmoles), acetic acid (2 ml), palladium on charcoal (100 mg) and ethanol (50 ml) were shaken under hydrogen at room temperature and atmospheric pressure. After the take up of the calculated amount of hydrogen, the catalyst was filtered and the solvent evaporated *in vacuo* to give, in almost quantitative yield, 1-acetylaminopyrazolin-5-ones (VIIa,b) (see below).

1-Acetylamino-3-methyl-4-phenylpyrazolin-5-one (VIIa).

A solution of compound Ia (30 mmoles) and acetic anhydride (36 mmoles) in acetic acid (115 ml) was heated at 100° for one hour. The solvent was evaporated *in vacuo* and the residue was kept over potassium hydroxide overnight. Water (50 ml) was added and the solid compound VIIa was collected (yield 90%), mp 217-219° (from water); ir: ν max 3350-2200 br (2NH) and 1725 (CO) cm^{-1}; uv: λ max 274 nm (log ϵ 4.04); nmr (DMSO-d_6): δ 1.99 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 7.12-7.65 (m, 5H, C_6H_5), 10.15 and 10.78 (exch. br. s, 2H, NH and NH or OH).

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.61; H, 5.68; N, 18.37.

1-Acetylamino-4-methyl-3-phenylpyrazolin-5-one (VIIb).

This compound was prepared similarly starting from compound Ib (yield 60%), mp 104-106° (from water); ir: ν max 3460 (H_2O), 3200 (NH), 3100-2600 br (NH), 1680 (CO) cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}N_3O_2 \cdot H_2O$: C, 57.83; H, 6.02; N, 16.87. Found: C, 58.16; H, 5.83; N, 16.89.

1-Diacetylamino-5-acetoxypyrazole (IX).

When the preceding reaction was carried out employing acetic anhydride (5 ml for 5 mmoles of Ia) as a solvent, treatment of the residue with 0.1*N* sodium hydroxide and extraction with ether afforded compound IX (yield 55%), mp 85-87° (sublimation at 60° and 0.02 mm); ir: ν max 1785 and 1740 (CO) cm^{-1}; uv: λ max 235 nm (log ϵ 4.12); nmr (deuteriochloroform): δ 2.19 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.40 (s, 6H, $2CH_3$), 7.32 (s, 5H, C_6H_5).

Anal. Calcd. for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.83; H, 5.47; N, 13.18.

Hydrolysis of 1-Acetylamino-3-methyl-4-phenylpyrazolin-5-one (VIIa).

A mixture of compound VIIa (0.5 mmole) and anhydrous hydrazine (2 ml) was heated at 100° for 90 minutes. The hydrazine was removed *in vacuo* and the residue was dissolved in water. The solution was acidified (*p*H 5) with 6*N* hydrochloric acid and the white 1-amino-3-methyl-4-phenylpyrazolin-5-one (Ia) was collected, yield 62%, mp 174-176° [lit. (2a) mp 177-178°].

Reaction of 1-Amino-3-methyl-4-phenylpyrazolin-5-one (Ia) with Acyl Halides.

A suspension of compound Ia (5.0 mmoles), chloroacetyl chloride (5.0 mmoles) and sodium carbonate (5.0 milliequivalents) in anhydrous tetrahydrofuran (80 ml) was stirred overnight at room temperature. The solvent was evaporated *in vacuo* and water was added to give solid 1-chloroacetylamino-3-methyl-4-phenylpyrazolin-5-one (VIIc), yield 62%, mp 206-207° (from water); ir: ν max 3170 (NH), 3050-2500 br (NH) and 1700 (CO) cm^{-1}; nmr (DMSO-d_6): δ 2.21 (s, 3H, CH_3), 4.26 (s, 2H, CH_2), 7.15-7.55 (m, 5H, C_6H_5).

Anal. Calcd. for $C_{12}H_{12}ClN_3O_2$: C, 54.25; H, 4.55; Cl, 13.34; N, 15.81. Found: C, 54.08; H, 4.40; Cl, 13.42; N, 15.62.

Employing bromoacetyl bromide and operating as above, 1-bromoacetylamino-3-methyl-4-phenylpyrazolin-5-one (VIId) was obtained, yield 60%, mp 201-204° (from ethanol); ir: ν max 3180 (NH), 3100-2500 br (NH) and 1695 (CO) cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}BrN_3O_2$: C, 46.47; H, 3.90; Br, 25.76; N, 13.55. Found: C, 46.14; H, 3.75; Br, 25.52; N, 13.55.

1-(3-Methyl-4-phenylpyrazol-5-on-1-yl)-3-phenylurea (Xa).

A suspension of Ia (5.0 mmoles) and phenylisocyanate (5.0 mmoles) in benzene (30 ml) was heated at 100° for 30 minutes in a sealed tube. The precipitate was collected and washed with benzene to give compound Xa,

yield 70%, mp 230-233° (from DMF/water); ir: ν max 3400-2500 br (2NH and NH or OH) and 1690 (CO) cm^{-1}.

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.38; H, 5.28; N, 17.97.

1-(4-Methyl-3-phenylpyrazol-5-on-1-yl)-3-phenylurea (Xb).

This compound was prepared similarly starting from compound Ib, yield 80%, mp 223-225° (from DMF/water); ir: ν max 3400-2500 br (2NH and NH or OH), 1710 and 1690 (CO) cm^{-1}.

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.57; H, 5.28; N, 18.31.

Reaction of 1-Aminopyrazolin-5-one (Ia,b) with Methyl Iodide.

a) A solution of Ia,b (5.0 mmoles) and methyl iodide (5.0 mmoles) in methanol (2 ml) was heated at 100° for six hours in a sealed tube. Tlc analysis of the reaction mixture showed the presence of 1-methylpyrazolin-5-one (XIa,b) (2a), 1-amino-2-methylpyrazolin-5-one (XIIa,b) (2a) and 1-methylpyrazolin-3-one (XIIIa,b) (2a).

b) A solution of Ia,b (5.0 mmoles), methyl iodide (5.0 mmoles) and sodium methoxide (5.0 mmoles) in methanol (2 ml) was heated at 100° for four hours in a sealed tube. Tlc analysis showed the presence of 1-amino-2-methylpyrazolin-5-one (XIIa,b) (2a) and 1-amino-5-methoxypyrazole (XIVa,b) (2a).

Reaction of 1-Aminopyrazoles (XIVa,b) with Methyl Iodide.

A solution of 1-aminopyrazole (10.0 mmoles) and methyl iodide (10.0 mmoles) in methanol (2 ml) was heated at 100° for six hours. The solvent was evaporated *in vacuo* and the residue, dissolved in chloroform, was extracted with 1*N* sodium hydroxide. The alkaline solution was neutralised and extracted with chloroform to afford, after evaporation: a) 1,5-dimethyl-4-phenylpyrazolin-3-one (XIIIa) (2a), yield 15%; and b) 1,4-dimethyl-5-phenylpyrazolin-3-one (XIIIb) (2a), yield 10%.

The former chloroform solution was evaporated and the residue was chromatographed on silica gel. Elution of the column with ether-light petroleum 1:3 gave: a) 1-dimethylamino-5-methoxy-3-methyl-4-phenylpyrazole (XVa); yield 25%; nmr (deuteriochloroform): δ 2.19 (s, 3H, CH_3), 2.81 (s, 6H, $N(CH_3)_2$), 3.73 (s, 3H, OCH_3), 7.27-7.48 (m, 5H, C_6H_5); and b) 1-dimethylamino-5-methoxy-4-methyl-3-phenylpyrazole (XVb), (2b) yield 30%.

Further elution with chloroform-methanol 95:5 gave the following products.

a) 4-Phenyl-1,2,3-trimethylpyrazolin-3-one (XVIa).

This compound was obtained in a yield of 45%, mp 102-104° (sublimation *in vacuo*) [lit. (6) mp 215°]; ir: ν max 1620 (CO) cm^{-1}; nmr (deuteriochloroform): δ 2.19 (s, 3H, CH_3), 3.20 and 3.31 (s, 6H, $2NCH_3$), 7.22-7.45 (m, 5H, C_6H_5).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.53; H, 7.11; N, 13.74.

b) 3-Phenyl-1,2,4-trimethylpyrazolin-3-one (XVIb).

This compound was obtained in a yield of 40%; mp 136-138° [lit. (7) mp 140-141°]; nmr (deuteriochloroform): δ 1.92 (s, 3H, CH_3), 2.93 and 3.39 (s, 6H, $2NCH_3$), 7.41 (m, 5H, C_6H_5).

c) Unresolved Product Mixture.

An unresolved mixture of other products was obtained in 15-20% yield.

1-(2,5-Dimethylpyrrol-1-yl)-3-methyl-4-phenylpyrazolin-5-one (XVIIa).

A solution of compound Ia (5.0 mmoles) and acetonylacetone (5.0 mmoles) in methanol (20 ml) was heated at 80° for one hour in a sealed tube. After evaporation of the solvent, the residue was collected and dried to give compound XVIIa, yield 92%; mp 195-200° (from ethanol/water); ir: ν max 3200-2300 (NH) and 1630 (CO) cm^{-1}; uv: λ max 245 (log ε 4.01), 275 (log ε 4.02) nm; nmr (DMSO-d_6): δ 1.99 (s, 6H, $2CH_3$), 2.30 (s, 3H, CH_3), 5.80 (s, 2H, 2CH), 7.20-7.69 (m, 5H, C_6H_5), 11.30 (exch. br s, 1H, NH or OH).

Anal. Calcd. for $C_{16}H_{17}N_3O$: C, 71.89; H, 6.41; N, 15.72. Found: C, 72.27; H, 6.46; N, 15.60.

1-(2,5-Dimethylpyrrol-1-yl)-4-methyl-3-phenylpyrazolin-5-one (XVIIb).

This compound was prepared similarly starting from compound Ib. It was obtained as an oil and was purified and characterized as the methoxy derivative (see below).

1-(3,4-Dicarbethoxy-2,5-dimethylpyrrol-1-yl)-3-methyl-4-phenylpyrazolin-5-one (XVIIc).

A solution of compound Ia (3.2 mmoles) and 2,3-diacetylbutanoic acid diethyl ester (3.5 mmoles) in acetic acid (6 ml) was heated at 80° for 3 hours. The solvent was evaporated *in vacuo* and ether was added to the oily residue affording, by rubbing, product XVIIc as white crystals, yield 60%, mp 130-133° (from ethanol/water); ir: ν max 3200-2600 br (NH), 1700 (CO) and 1650 (CO) cm^{-1}; uv: λ max 262 (log ε 4.26) nm.

Anal. Calcd. for $C_{22}H_{25}N_3O_5$: C, 64.22; H, 6.12; N, 10.21. Found: C, 64.36; H, 6.09; N, 10.33.

Treatment of Compounds XVIIa-c with Diazomethane. General Procedure.

To the pyrrolylpyrazolin-5-ones (XVIIa-c) (5.0 mmoles) in ether (50 ml), ethereal diazomethane (10 mmoles) was added. After 24 hours the solvent was evaporated giving the following products.

a) 1-(2,5-Dimethylpyrrol-1-yl)-5-methoxy-3-methyl-4-phenylpyrazole (XVIIIa).

This compound was obtained in 96% yield, mp 108-110° (from methanol/water); ir: ν max 3060 and 3030 (CH arom.) cm^{-1}; uv: λ max 229 (log ε 4.20) nm; nmr (deuteriochloroform): δ 2.03 (s, 6H, $2CH_3$), 2.27 (s, 3H, CH_3), 3.58 (s, 3H, OCH_3), 5.81 (s, 2H, 2CH), 7.30-7.52 (s, 5H, C_6H_5).

Anal. Calcd. for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.93. Found: C, 72.84; H, 6.90; N, 15.17.

b) 1-(2,5-Dimethylpyrrol-1-yl)-5-methoxy-4-methyl-3-phenylpyrazole (XVIIIb).

This compound was obtained in 60% yield, mp 67-70° (sublimation at 60°, 0.02 mm); ir: ν max 3060 and 3030 (CH arom.) cm^{-1}; uv: λ max 242 (log ε 4.24) nm.

Anal. Calcd. for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.93. Found: C, 72.82; H, 6.87; N, 14.93.

c) 1-(3,4-Dicarbethoxy-2,5-dimethylpyrrol-1-yl)-5-methoxy-3-methyl-4-phenylpyrazole (XVIIIc).

This compound had mp 70-72° (from ethanol/water); ir: ν max 1710 (CO) cm^{-1}; nmr (deuteriochloroform): δ 1.31 (t, J = 7 Hz, 6H, $2CH_3$), 2.17 (s, 6H, $2CH_3$), 2.21 (s, 3H, CH_3), 3.59 (s, 3H, OCH_3), 4.29 (q, J = 7 Hz, 4H, $2CH_2$), 7.40 (s, 5H, C_6H_5).

Anal. Calcd. for $C_{23}H_{27}N_3O_5$: C, 64.93; H, 6.40; N, 9.88. Found: C, 64.66; H, 6.33; N, 9.97.

1-(2,5-Dimethylpyrrol-1-yl)-5-chloro-3-methyl-4-phenylpyrazole (XXIIa).

A solution of compound XXIa (5.0 mmoles) and acetonylacetone (5.0 mmoles) in glacial acetic acid was heated at 100° for one hour. The solvent was rotary evaporated and the residue was kept in a dessiccator (potassium hydroxide) overnight and then sublimed (60°, 0.02 mm) to give the product XXIIa, yield 70%, mp 110-111°; nmr (deuteriochloroform): δ 2.00 (s, 6H, $2CH_3$), 2.36 (s, 3H, CH_3); 5.86 (s, 2H, 2CH), 7.43 (s, 5H, C_6H_5).

Anal. Calcd. for $C_{16}H_{16}ClN_3$: C, 67.25; H, 5.64; N, 14.70. Found: C, 67.36; H, 5.58; N, 14.88.

1-(2,5-Dimethylpyrrol-1-yl)-5-chloro-4-methyl-3-phenylpyrazole (XXIIb).

This compound was prepared similarly starting from compound XXIb, yield 35%, mp 72-74° (sublimation at 50°, 0.02 mm); uv: λ max 246 (log ε 4.22) nm.

Anal. Calcd. for $C_{16}H_{16}ClN_3$: C, 67.25; H, 5.64; N, 14.70. Found: C, 67.10; H, 5.46; N, 14.58.

2,6-Dimethyl-7-phenylpyrazolo[3,2-*b*]-1,3,4-oxadiazole (XIXa).

To a cooled (ice-water bath) mixture of 1-acetylamino-3-methyl-4-phenylpyrazolin-5-one (21.6 mmoles) and phosphoryl chloride (15 ml), triethylamine (21.6 mmoles) was added, dropwise, with stirring. The reaction mixture was heated at 80° for one hour, the solvent was removed *in vacuo*, and the residue was poured into ice. The white precipitate was collected and purified by treatment with 2*N* sodium hydroxide. The insoluble phase was collected, washed with water and dried to give product XIXa, yield 86%, mp 117-119° (from ethanol/water); uv: λ max 252 (log ε 4.27) nm; nmr (deuteriochloroform): δ 2.54 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 7.20-7.55 (m, 5H, C_6H_5).

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.55; H, 5.31; N, 19.45.

2,7-Dimethyl-6-phenylpyrazolo[3,2-*b*]-1,3,4-oxadiazole (XIXb).

This compound was prepared similarly starting from compound VIIb by heating at 100° for 15 minutes, yield 60%, mp 106-108° (from ethanol/water).

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.45; H, 5.17; N, 19.50.

1-Acetylamino-5-chloro-3-methyl-4-phenylpyrazole (XXa).

A mixture of compound VIIa (4.0 mmoles) and phenylphosphonic dichloride (10.0 mmoles) was heated at 140° for one hour and, after cooling, it was poured into ice water. After decomposition of the excess of phenylphosphonic dichloride, the reaction mixture was made basic with sodium hydroxide and extracted with ether. Neutralization of the aqueous solution afforded compound XXa, yield 60%, mp 136-138° (from water); ir: ν max 3250 (NH), 1680 (CO) cm^{-1}; uv: λ max 237 (log ε 4.14) nm; nmr (deuteriochloroform): δ 1.91 and 2.19 (main branch) (br. s, 3H, CH_3) 2.29 (s, 3H, CH_3), 7.37 (s, 5H, C_6H_5), 8.70 and 9.56 (main branch) (exch. br. s, 1H, NH and OH) (branching attributable to tautomerism).

Anal. Calcd. for $C_{12}H_{12}ClN_3O$: C, 57.72; H, 4.85; Cl, 14.20; N, 16.83. Found: C, 57.60; H, 4.72; Cl, 14.35; N, 16.76.

When the above reaction was carried out under the same conditions but only for one minute, compound XIXa was obtained from the ethereal solution.

1-Acetylamino-5-chloro-4-methyl-3-phenylpyrazole (XXb).

This compound was prepared similarly starting from compound VIIb, yield 65%, mp 56-58° (sublimation at 50° and 0.02 mm); ir: ν max 3400-3100 br. (NH), 1690 (CO) cm^{-1}; uv: λ max 247 (log ε 4.18) nm.

Anal. Calcd. for $C_{12}H_{12}ClN_3O$: C, 57.72; H, 4.85; Cl, 14.20; N, 16.83. Found: C, 57.74; H, 4.90; Cl, 14.15; N, 16.69.

Reaction of 2,6-Dimethyl-7-phenylpyrazolo[3,2-*b*]-1,3,4-oxadiazole (XIXa) with Gaseous Hydrogen Chloride.

A solution of compound XIXa (0.5 mmole) in benzene saturated with gaseous hydrogen chloride (4 ml.) was heated at 80° for 5 hours. After evaporation of the solvent, the residue was treated with 1*N* sodium hydroxide. Neutralization of the alkaline solution afforded 1-acetylamino-5-chloro-3-methyl-4-phenylpyrazole (XXa), yield 50% (see above).

1-Amino-5-chloro-3-methyl-4-phenylpyrazole (XXIa).

A suspension of compound XXa (2.5 mmoles) in 6*N* hydrochloric acid (5 ml) was heated at 80° for 90 minutes. Neutralization of the cooled solution afforded compound XXIa, yield 78%, mp 67-70° (sublimation at 60° and 0.02 mm), ir: ν max 3295, 3205 (NH_2), cm^{-1}

Anal. Calcd. for $C_{10}H_{10}ClN_3$: C, 57.84; H, 4.85; N, 20.23. Found: C, 57.95; H, 4.74; N, 20.34.

1-Amino-5-chloro-4-methyl-3-phenylpyrazole (XXIb).

This compound was prepared similarly starting from compound XXb, yield 73%, mp 103-105° (sublimation at 80° and 0.02 mm); ir: ν max 3350, 3250, 3190 (NH_2) cm^{-1}; uv: λ max 249 (log ε 4.16) nm.

Anal. Calcd. for $C_{10}H_{10}ClN_3$: C, 57.84; H, 4.85; N, 20.23. Found: C, 58.16; H, 4.91; N, 20.39.

Reaction of 1-Acetylamino-5-chloro-3-methyl-4-phenylpyrazole (XXa) with Diazomethane.

Ethereal diazomethane (3.6 mmoles) was added to a suspension of compound XXa (3.6 mmoles) in ether (25 ml). After 24 hours the ethereal solution was extracted with 1*N* sodium hydroxide to remove the unreacted starting material and it was then rotary evaporated. The oily residue was chromatographed on a silica gel column and eluted with chloroform (the faster eluting product contained traces of the *O*-methyl derivative), affording an oily product which was further purified by sublimation at 50° and 0.02 mm to give 1-(*N*-acetyl-*N*-methylamino-5-chloro-3-methyl-4-phenylpyrazole (XXIII); ir: ν max 1705 (CO) cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}ClN_3O$: C, 59.21; H, 5.35; Cl, 13.44; N, 15.93. Found: C, 59.00; H, 5.16; Cl, 13.62; N, 16.08.

Reaction of 1-Acetylamino-5-chloro-3-methyl-4-phenylpyrazole (XXa) with Methyl Fluorosulphonate.

To a solution of compound XXa (1.6 mmoles) in chloroform (4 ml), methyl fluorosulphonate (0.13 ml) was added and the resulting mixture was kept at room temperature for 16 hours. The solvent was evaporated *in vacuo*. The deliquescent residue was identified as 1-acetylamino-5-chloro-3,4-dimethyl-4-phenylpyrazolium fluorosulphonate (XXIV) (quantitative yield); ir: ν max 3300-2000 br (NH), 1725 (CO) cm^{-1}; nmr (deuteriochloroform): δ 2.25 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.93 (s, 3H, NCH_3), 7.32 (s, 5H, C_6H_5), 9.30 (exch. br. s, 1H, NH).

Alkaline Hydrolysis of 1-Acetylamino-5-chloro-2,3-dimethyl-4-phenylpyrazolium Fluorosulphonate (XXIV).

Chloroform (30 ml) was added to a suspension of compound XXIV (1.6 mmoles) in 1*N* sodium hydroxide (30 ml). The reaction mixture was vigorously stirred for 1 hour. Neutralization of the alkaline solution afforded 1-acetylamino-2,3-dimethyl-4-phenylpyrazolin-5-one (XXV); mp 220-222° (from water); ir: ν max 3140 (NH), 1715 (CO), 1620 (CO); uv: λ max. 282 (log ε 4.14) nm.

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.76; H, 6.27; N, 17.22.

The same compound (yield 50%) was also obtained from 1-amino-2,3-dimethyl-4-phenylpyrazolin-5-one (Va) (2.5 mmoles), sodium carbonate (2.5 milliequivalents) and acetyl chloride (2.5 mmoles) in refluxing benzene (15 ml) for 90 minutes.

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