Acidity and Alkylation of 4-Phenyl-3,5-dihydroxypyrazole and Its Derivatives. *C versus O* and *N* Alkylation

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4-Phenyl-3,5-dihydroxypyrazole is a relatively strong acid, with a p*K*a of 3.70. The effect of substitution, both in the phenyl ring and on the heterocyclic ring, on the acidity was studied. Electron attracting groups on the phenyl group enhance the acidity. Selective replacement by an alkyl group of one or two of the heterocyclic hydrogens lowers the acidity. Meerwein reagent, as well as methyl iodide bring about alkylation on carbon, whereas diazomethane and diethyl sulfate do not. Michael addition proceeds through both carbon and nitrogen.

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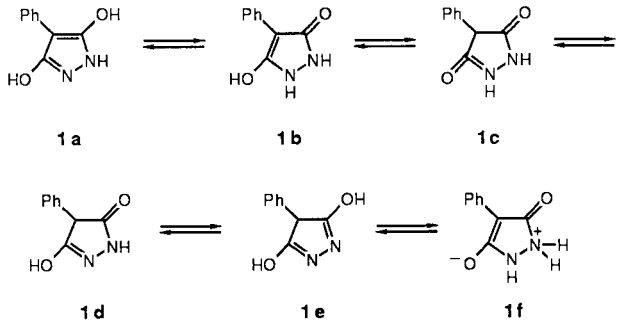
4-Phenyl-3,5-dihydroxypyrazole (**1**) which was first described [1] in 1969, is an important starting material in the recently described [2,3] preparation of pyrazolo[1,2-*a*]-pyrazolie derivatives. Dubau and Zinner suggested [4] that the dihydroxy form is the predominant tautomer on the basis of the ir study of this product, as compared to the aliphatic derivatives. The present work does not exclude this structure, however it is shown that probably in most polar and protic solvents, it dissociates to a large extent yielding the monoanion. The analogous isoxazole derivative, which is even a stronger acid showed similar properties [5]. The two oxygens take part in the stabilization of the anionic part of the paraionic pyrazolopyrazole derivatives [2].

The heterocyclic ring with the two oxygen functions at positions 3 and 5 has several tautomeric possibilities (structures **1a-f**). The monoanion as well as the dianion have numerous tautomeric forms for which many resonance structures can be written.

Scheme I

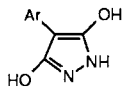


The participation of the aromatic ring in the stabilization of the anion is examined by the influence of substituents in the *para*-position on the acidity. In order to find what is the atomic sequence in the heterocyclic ring that contributes to the high acidity it is possible to fix some of the various tautomeric anionic forms by partial substitution of the exchangeable hydrogens by alkyl groups. Scheme II shows the dissociation constants found for the various derivatives of compound **1**. Substitution of the two nitrogen atoms reduces the acidity by the order of 10^5 (compound **6**). This fact suggests that the monoanion of **1** is stabilized by delocalization which involves the nitrogen atoms. The contribution of the NH group to the acidity is also shown in the relatively strong acidity of the monosubstitution product **5**. Blocking the possibility of conjugation with the phenyl group causes further decrease in the acidity. The uv absorption of the dianion of **1** resembles that of the monanion of both **5** and **6** where conjugation of the enolate with the aromatic ring is possible. The most pronounced difference in the λ max between the neutral and ionized species was observed in the 4-*p*-nitrophenyl derivative **4**. The facile dissociation in water, ethanol and other protic solvents could be followed by recording the change in λ max, effected by dilution of **4** in these solvents. It moves from 378 nm for a saturated ethanolic solution to 420 nm for a 1 x 10^{-4} *M* solution. In the latter concentration the product is probably completely dissociated to the monoanion. The dianion of **4** absorbs in ethanol at λ max 474 nm.

Compound **1** has three possible sites for monoalkylation, *e.g.* one of the oxygens, one of the nitrogens or the carbon at position **4**. There are six possible products of dialkylation and five of trialkylation. Methylation with diazomethane proceeded through alkylation of both oxygens yielding compounds **10** and **11**. The reaction with methyl iodide which was carried out in the presence of potassium carbonate as base in acetone did not lead to any of these products, probably because the first site which was substituted was the carbon, preventing the formation of **10** and **11**. Substitution on carbon was then followed by alkylation on either the nitrogens or on one of the oxygens resulting in products **12**, **13** and **14**. The Meerwein reagent attacks initially both the oxygens and the carbon leading to the 3,5-dimethoxy derivative **9** as well as to pro-

Scheme II

(λ max in H_2O)

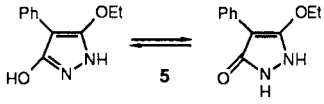


1 (Ar = Ph)
p*K*a 1 = 3.70, p*K*a 2 = 12.71
λ max (Neutral) 260 nm (ε = 5050)
(Monoanion) 258 nm (ε = 14200)
(Dianion) 280 nm (ε = 11000)

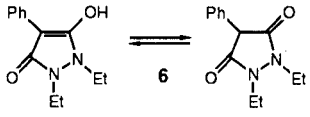
2 (Ar = *p*-Cl-C_6H_4)
p*K*a 1 = 3.34, p*K*a 2 = 12.50
λ max (Neutral) 257 nm (ε = 11380)
(Monoanion) 270 nm (ε = 16240)
(Dianion) 288 nm (ε = 14300)

3 (Ar = *p*-CH_3O-C_6H_4)
p*K*a 1 = 4.45, p*K*a 2 = 13.1
λ max (Neutral) 254 nm (ε = 8500)
(Monoanion) 259 nm (ε = 12900)
(Dianion) 273 nm (ε = 14150)

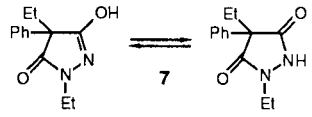
4 (Ar = *p*-O_2N-C_6H_4)
p*K*a 1 = 2.64, p*K*a 2 = 11.89
λ max (Neutral) 350 nm (ε = 8200)
(Monoanion) 405 nm (ε = 13200)
(Dianion) 468 nm (ε = 15500)



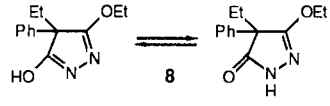
p*K*a = 6.2
λ max (Neutral) 257 nm (ε = 12200)
(Anion) 279 nm (ε = 10500)



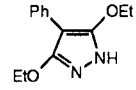
p*K*a = 8.8
λ max (Neutral) 257 nm (ε = 12000)
(Anion) 280 nm (ε = 16100)



p*K*a = 9.2
λ max (Neutral) 260 nm (ε = 7750)
(Anion) 270 nm (ε = 4700)



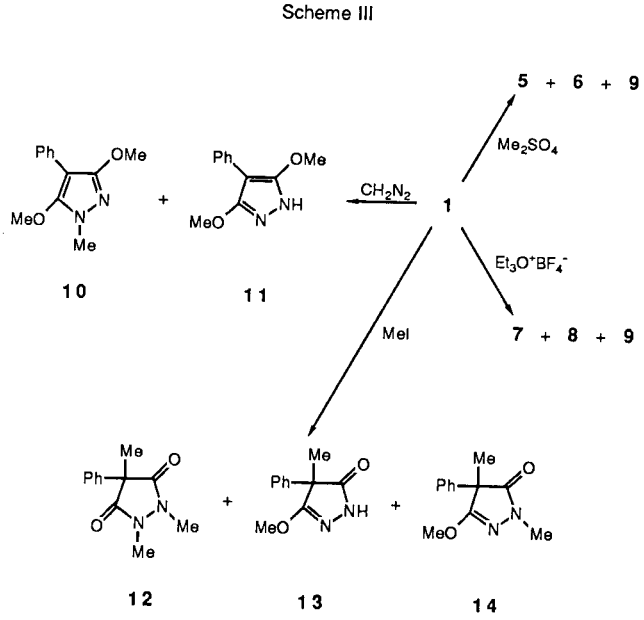
p*K*a = 10.5
λ max (Neutral) 253 nm (ε = 5400)
(Anion) 267 nm (ε = 4500)



p*K*a = 11.5
λ max (Neutral) 260 nm (ε = 10600)
(Anion) 273 nm (ε = 10000)

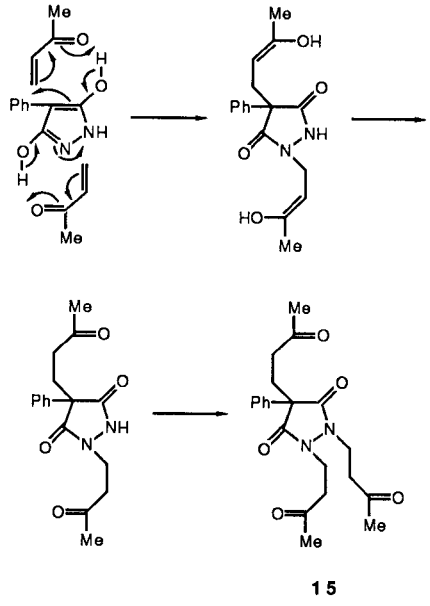
ducts **7** and **8**. Using diethyl sulfate as an alkylation agent in aqueous bicarbonate gave products of *O* and *N* alkylation. In addition to product **9**, the monoalkylation product **5** and the *N,N*-dialkylation product **6** were isolated.

Scheme III



Interaction of **1** with methyl vinyl ketone in a neutral medium resulted in a *tris* Michael addition product **15**. This non catalyzed Michael addition is illustrative of the nucleophilicity of the carbon at position 4, attack of which probably precedes that of the heteroatoms. A cyclic mechanism either concerted or non concerted, is proposed for the *C*-alkylation (Scheme IV).

Scheme IV



All the *C*-alkylated products **7**, **8** and **12-15** showed in their ir spectra carbonyl absorptions in the range of 1690-1720 cm^{-1}. The site of the alkylation could be easily determined by nmr spectroscopy. Products in which both

oxygens were substituted (**9-11**) did not show, of course, any carbonyl absorption in the ir spectrum. However products **5** and **6**, like the parent compound **1** do not show a distinctive carbonyl absorption. These products have a diffused NH OH absorption in the range of 3000-2500 cm^{-1}. Similar results have been reported [5] for the analogous 4-phenyl-3,5-dihydroxy-isoxazole. Compound **6** showed in the nmr spectrum two different N-CH_2CH_3 groups, suggesting a structure in which there should be one double bond in the heterocyclic ring, excluding a completely saturated pyrazoline-3,5-dione structure. The hydrogen atoms in the CH_2 of the ethyl groups in product **7** and **8** are magnetically nonequivalent. This is the result of their prochirality, as *C*-alkylation introduces a chiral center at position 4.

EXPERIMENTAL

Melting points were taken with a Thomas-Hoover apparatus and are uncorrected. Ir spectra were taken with a Perkin-Elmer Model 157. The uv spectra were taken with a Varian-Techtron Model 635. The nmr were taken either with a Brucker model WH-300 or with a Varian model T-60, with TMS as internal reference. Determination of dissociation constants were carried out either by studying the uv spectra in buffered solutions [6] or by potentiometric titration [7]. 4-Phenyl-3,5-dihydroxypyrazole (**1**), 4-(*p*-methoxyphenyl)-3,5-dihydroxypyrazole (**2**), 4-(*p*-chlorophenyl)-3,5-dihydroxypyrazole (**3**) and 4-(*p*-nitrophenyl)-3,5-dihydroxypyrazole (**4**) were prepared as described earlier [2].

Alkylation of 4-Phenyl-3,5-dihydroxypyrazole (**1**).

A) With Diazomethane.

To a solution of **1** (2.6 g) in tetrahydrofuran (30 ml) of an ether solution of diazomethane (0.07 mole) was added portionwise during 5 minutes. The solution was kept overnight at room temperature, acetic acid was added until the yellow color disappeared, and evaporated to dryness in vacuum. The residue was redissolved in ether (50 ml), washed once with 5% aqueous sodium bicarbonate (20 ml), twice with 0.05 *N* sodium hydroxide (10 ml) and with water (20 ml). The ether was removed in vacuum and the residue loaded on a silica gel column and eluted with ethyl acetate-petroleum ether mixture (2:3). Two products were obtained. First came 4-phenyl-1-methyl-3,5-dimethoxypyrazole (**10**). It was recrystallized from petroleum ether 60-80 (0.3 g, 10%) mp 63°; ir (Nujol): ν max 1600 cm^{-1} (C=N); uv (ethanol): λ max 260 nm (ϵ = 13840); ^{1}H nmr (deuteriochloroform): (δ) 7.33-7.10 m (Ph), 3.86 s (OCH_3), 3.70 s (OCH_3), 3.53 s (NCH_3); ^{13}C nmr (DMSO-d_6): (δ) 157.49, 150.80, 131.18-125.19 (Ph), 90.92, 61.19, 54.77, 32.24.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.35; H, 6.44; N, 12.51.

The next fraction was 4-phenyl-3,5-dimethoxypyrazole (**11**) which was recrystallized from cyclohexane (0.5 g, 14%), mp 120°; ir (Nujol): ν max 1595 cm^{-1} (C=N); uv (ethanol): λ max 260 nm (ϵ = 16200); ^{1}H-nmr (δ) 9.90 bs (NH), 7.73-7.10 m (Ph), 3.88 s (2 CH_3).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.93; H, 6.03; N, 13.55.

B) With Methyl Iodide.

To a solution of **1** (2.6 g) in acetone (150 ml), 35 ml of methyl iodide and potassium carbonate (7.7 g) were added and the mixture refluxed with stirring for 6 hours. After cooling to room temperature the solid was filtered off and the solvent removed in vacuum. The residue was mixed with ether (150 ml), filtered again and the etheral solution evaporated in vacuum. Three substances were isolated from the oily residue by column chromatography on silica gel, eluted with ethyl acetate-petroleum ether (2:3). The first to be eluted was 4-phenyl-1,4-dimethyl-3-methoxypyrazolin-5-one (**14**) which was an oil (0.3 g, 9%); ir (Nujol): ν max 1695 (CO); uv (ethanol): λ max 254 nm (ϵ = 4600); ^{1}H nmr (deuteriochloroform): (δ) 7.26 (Ph), 3.88 s (OCH_3), 3.26 s (NCH_3), 1.66 s (CCH_3).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.17; H, 6.56; N, 13.06.

Next to be eluted was 4-phenyl-4-methyl-3-methoxypyrazoline-5-one (**13**) (0.5 g, 15%) mp 132°, ir (Nujol): ν max 1720, 1690 cm^{-1} (CO); uv (ethanol): λ max 252 nm (ϵ = 4800); ^{1}H nmr (deuteriochloroform): (δ) 9.26 bs (NH), 7.36 (Ph), 3.83 s (OCH_3), 1.65 s (CCH_3).

Then came the main fraction of 4-phenyl-1,2,4-trimethylpyrazolidine-3,5-dione (**12**) which was an oil (1.5 g, 45%); ir (Nujol): ν max 1720, 1640 cm^{-1} (CO); uv (ethanol): λ max 258 nm (ϵ = 2800); ^{1}H-nmr (deuteriochloroform): (δ) 7.50-7.13 m (Ph), 3.20 s (2 NCH_3), 1.66 s (CCH_3).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.33; H, 6.66; N, 13.07.

C) With Meerwein Reagent.

Triethyloxonium tetrafluoroborate (12 g) was added portionwise during 5 minutes to a solution of **1** (2.6 g) in 100 ml 5% aqueous sodium bicarbonate with stirring. The solution was stirred for an additional 30 minutes at room temperature and the precipitate which was formed was collected by filtration and recrystallized from ethanol. It was found to be 4-phenyl-3,5-diethoxypyrazole (**9**) (0.5 g, 14%) mp 124°; ir (Nujol): ν max 1595 cm^{-1} (C=N); uv (ethanol): λ max 260 nm (ϵ = 10100); ^{1}H-nmr (deuteriochloroform): (δ) 10.16 s (NH), 7.90-7.16 (Ph), 4.21 q (2 CH_2), 1.36 s (2 CH_3).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.04; H, 6.70; N, 12.28.

The filtrate from the reaction mixture was extracted with chloroform (3 x 20 ml) and the combined organic layers were evaporated in vacuum and the oily residue was subjected to column chromatography on silica gel. The elution was carried out with a mixture of ethyl acetate and petroleum ether (3:1). Two additional products were obtained. The first to be eluted was 4-phenyl-4-ethyl-3-ethoxypyrazolin-5-one (**8**) (0.06 g, 2%), recrystallized from cyclohexane, mp 127°; ir (Nujol): ν max 1690, 1670 cm^{-1} (CO); uv (ethanol): λ max 253 nm (ϵ = 4200); ^{1}H-nmr (deuteriochloroform): (δ) 8.83 bs (NH), 7.50-7.16 (Ph), 4.33 (12 peaks, OCH_2), 2.16 (12 peaks, NCH_2), 1.36 t (CH_3), 0.93 t (CH_3).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.52; H, 6.78; N, 12.34.

The second to be eluted was 4-phenyl-2,4-diethylpyrazolin-3,5-dione (**7**) which was recrystallized from cyclohexane (0.28 g, 8%) mp 138°; ir (Nujol): ν max 1700-1600 cm^{-1} (CO); uv (ethanol): λ max 258 nm (ϵ = 3100); ^{1}H-nmr (deuteriochloroform): (δ) 9.45 bs (NH), 7.33-7.16 (Ph), 3.73 (12 peaks, NCH_2), 2.66 (12 peaks, CCH_2), 1.28 t (CH_3), 1.01 t (CH_3).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.14; H, 6.81; N, 12.15.

D) With Diethyl Sulfate.

Diethyl sulfate (15 ml) was added to a solution of **1** (2.6 g) in 250 ml of 5% aqueous sodium bicarbonate. The mixture was heated for 3 hours at 80° and left 24 hours at room temperature. The precipitate contained both *N,N*-dialkylation product **8** (see preceding article [8]) and the *O,O*-dialkylation product **9**. The latter was identical with the precipitate which was initially isolated in the reaction of **1** with triethyloxonium tetrafluoroborate (Meerwein reagent) which is described above. The yield of product **9** in this reaction was about 5% (0.16 g). The two products were separated by selective crystallization from ethanol. Product **8** precipitated first, while product **9** crystallized on concentration of the ethanolic filtrate of **8**.

The reaction mixture was acidified with acetic acid to *p*H 6.5, the precipitate collected by filtration and recrystallized from ethanol (0.7 g, 20%) mp 227°; the suggested structure is a mono alkylation product (**5**); uv (ethanol): λ max 257 nm (ϵ = 13000); ^{1}H-nmr (DMSO-d_6): (δ) 7.68-7.02 (Ph), 4.20 q (OCH_2), 1.35 t (CH_3).

Anal. Calcd. for $C_{11}H_{12}N_2O_2 \cdot 0.4H_2O$: C, 62.50; H, 6.05; N, 13.25. Found: C, 62.80; H, 5.71; N, 13.19.

E) With Methyl Vinyl Ketone.

A mixture of methyl vinyl ketone (2.5 ml) and **1** (0.45 g) was heated at the boiling point for 5 minutes and evaporated in vacuum to dryness. The residue was dissolved in chloroform (3 ml). The precipitate which was formed upon addition of ether (1 ml) was collected and recrystallized twice from chloroform-ether (0.15 g, 15%) mp 109°; ir (Nujol): ν max 1700 cm^{-1} (CO); ^{1}H-nmr (deuteriochloroform): (δ) 7.50-7.25 m (Ph), 3.88 t ($2CH_2$-N), 2.72 dt ($2CH_2CO$), 2.28-2.58 m (CCH_2CH_2CO), 2.13 s ($2CH_3$), 2.08 s (CH_3).

Anal. Calcd. for $C_{21}H_{26}N_2O_5$: C, 65.27; H, 6.78; N, 7.25. Found: C, 65.00; H, 6.83; N, 7.25.

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