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STERIC EFFECTS IN THE NUCLEOPHILIC ADDITION OF PYRAZOLES UNSUBSTITUTED AT A NITROGEN ATOM TO THE DOUBLE BOND OF MALEIC ANHYDRIDE

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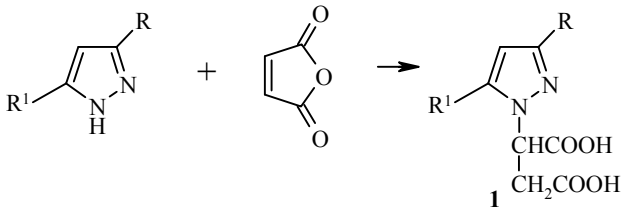
Only one isomer, 5-methyl-3-phenyl-1-pyrazolylsuccinic acid, is formed on addition of 3(5)-methyl-5(3)-phenylpyrazole to the double bond of maleic anhydride.

Keywords: pyrazoles, steric effects.

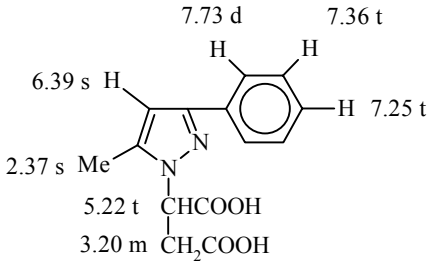
Pyrazoles unsubstituted at a nitrogen atom add to the double bond of maleic anhydride forming pyrazolylsuccinic acids **1** without an alkaline catalyst [1].



1

Unsymmetrical 3,5-disubstituted pyrazoles on alkylation, acylation, or addition to an activated double bond (cyanoethylation) practically always give a mixture of both possible isomers [2-5], although 1,5-dimethyl-3-phenylpyrazole is obtained preferentially in the case of methylation of 3(5)-methyl-5(3)-phenylpyrazole [3,5].

On reacting 3(5)-methyl-5(3)-phenylpyrazole with maleic anhydride the quantity of isomers formed was not established reliably in [1]. We readily solved this problem by analysis of the ^{1}H NMR spectrum of the obtained pyrazolylsuccinic acid **2**, which showed the presence of only one isomer with a good correlation of intensities, and even in the crude product before recrystallization there were no signals for a second isomer (see Experimental).



2

Moscow K. A. Timiryazev Agricultural Academy, Moscow 127550, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1493-1495, October, 2003. Original article submitted May 25, 1999; revision submitted October 8, 2002.

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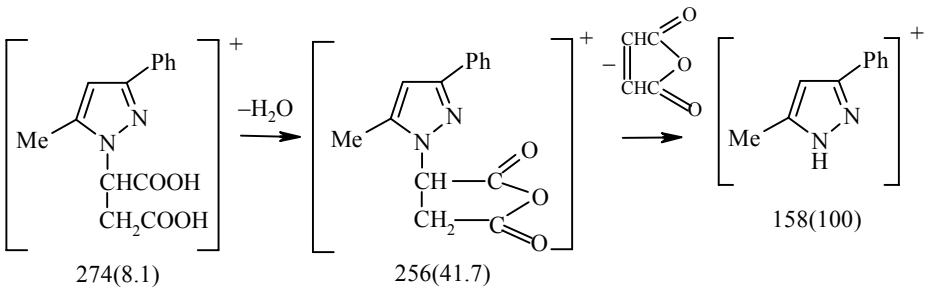
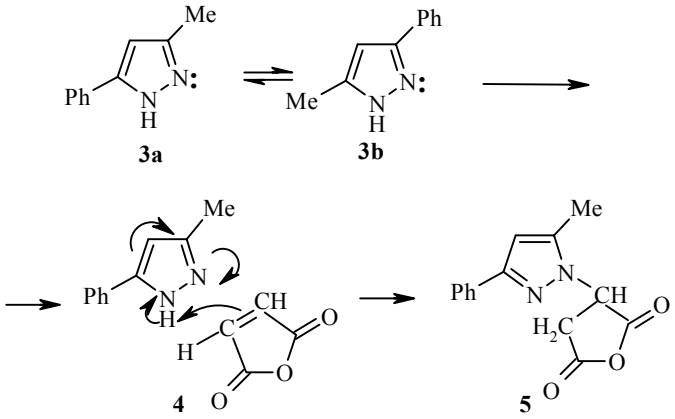
In the mass spectrum (by direct insertion) of compound **2** loss of a molecule of water occurs and then of maleic anhydride. Subsequent decomposition of the maleic and pyrazole fragments then occurs, which is additional confirmation of structure **2**.



We presume that the reaction between pyrazole and maleic anhydride is a process of nucleophilic addition to the activated double bond of maleic anhydride.



Isomer **3a** makes a link of the electron pair of the nitrogen atom in position 2 with the carbon atom of the anhydride with reduced electron density to form the intermediate compound **4**, which is stabilized by transfer of proton from the nitrogen atom in position 1 of the pyrazole to the anhydride carbon atom and redistribution of bonds in the pyrazole nucleus, leading to the addition product **5**.

As a result of steric hindrance caused by the phenyl group in position 3 isomer **3b** reacts far more slowly, which is the reason for the formation of only one isomer **5**.

The selectivity of the addition might also have been explained by the different basicity of forms **3a** and **3b**, of which **3a** must be more basic and consequently possess a greater nucleophilicity than **3b**. But the basicity of pyrazoles has practically no influence on the ease of addition. The weakly basic 4-bromo- and 4-chloro-3,5-dimethylpyrazoles react as readily as 3,5-dimethylpyrazole [1].

The structure of compound **5** is indirectly confirmed by the presence of the CH_3 signal (2.34 ppm) in the ^1H NMR spectrum. As a rule the signal of the CH_3 group in position 3 is observed for 1-substituted pyrazoles at 2.15-2.30, and in position 5 at 2.3-2.5 ppm.

Previously we were unsuccessful in adding maleic anhydride to 4-iodo-3,5-dimethylpyrazole due to extensive resinification. It turned out that in acetic acid the reaction proceeds smoothly in a yield of over 50%. On carrying out the reaction with 3,5-diphenylpyrazole we discovered that the reaction is reversible and at temperatures above 150°C the added anhydride is split off once again, as indicated by a significant drop in yield. The more severe conditions for carrying out the reaction in this case are explained by steric difficulties.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker AM-300 instrument in DMSO-d_6. The UV spectra were recorded on a Specord M-40 instrument, and the IR spectra on a Perkin-Elmer instrument.

5-Methyl-3-phenyl-1-pyrazolylsuccinic Acid (2). A mixture of 3(5)-methyl-5(3)-phenylpyrazole (1.46 g, 10 mmol), maleic anhydride (1.2 g, 12 mmol), and water (0.1 ml) in dioxane (8 ml) was boiled under reflux for 12 h. The reaction mixture was poured into water (70 ml), boiled for 30 min with activated carbon (0.5 g), and filtered through a heated paper filter. The filtrate was kept for 1 h in the refrigerator. The precipitated crystals were filtered off and crystallized once more from water (60 ml water per 1 g substance). After drying, succinic acid **2** (1.60 g, 58%) was obtained; mp 181°C [1].

3,5-Diphenyl-1-pyrazolylsuccinic Acid. A mixture of 3,5-diphenylpyrazole (2.2 g, 10 mmol), maleic anhydride (1.2 g, 12 mmol), water (0.2 ml), and dioxane (2 ml) was heated for 2 h in an open vessel on an oil bath at a mixture temperature of 140°C. The reaction mixture was dissolved in dioxane (40 ml), poured into water (200 ml), activated carbon (0.5 g) was added, and the mixture boiled under reflux. The hot solution was filtered through a heated paper filter and cooled for 1 h in the refrigerator. The precipitated crystals were filtered off, and crystallized once more from water–dioxane, 5:1, (200 ml mixture per 1.5 g of substance). 3,5-Diphenyl-1-pyrazolylsuccinic acid (1.62 g, 50%) was obtained having mp 188°C [1].

4-Iodo-3,5-dimethyl-1-pyrazolylsuccinic Acid. A mixture of 4-iodo-3,5-dimethylpyrazole (2.22 g, 10 mmol), maleic anhydride (1.08 g, 11 mmol), and acetic acid (6 ml) was heated on a boiling water bath for 30 min. The reaction mixture was evaporated on a rotary evaporator twice, diluted with water (8 ml), boiled for 15 min, and left for 1 h in the refrigerator. The precipitated crystals were separated and recrystallized from water (20 ml). To separate the contaminating 4-iodopyrazole the dried crystals were heated to boiling for 15 min with hexane (40 ml) under reflux, the hot mixture was filtered rapidly on a heated funnel with a glass filter, and the crystals were then washed with hot hexane (10 ml). Pure 4-iodo-3,5-dimethyl-1-pyrazolylsuccinic acid (2.54 g, 71%) was obtained; mp 191°C (decomp.). IR spectrum, ν, cm^{-1}: 1540, 1575, 1670, 1720, 1765. UV spectrum, λ_{max}, nm (log ε): 230 (3.78). ^{1}H NMR spectrum, δ, ppm: 2.12 (s, 3-CH_3); 2.31 (s, 5-CH_3); 3.08 (m, CH_2); 5.18 (m, CH). Found, %: C 31.7; H 2.9; N 8.2. $C_9H_{11}IN_2O_4$. Calculated, %: C 32.0; H 2.7; N 8.3.

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