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RESEARCHES ON PYRAZOLES

LI. The Possibility of Opening the Pyrazole Ring by Sodamide*

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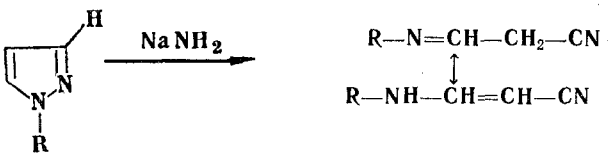
The pyrazole ring is opened by sodamide to give the corresponding β-iminonitriles.

Various compounds with the group –CH=N–N< in common can undergo nitrile splitting of the N–N bond, if, on the one hand, the latter is weakened by polarization due to a positive charge on the terminal nitrogen atom, and if, on the other hand, structural and experimental conditions facilitate elimination of the hydrogen atom of the CH group [1].

It would be expected that N-substituted pyrazoles having an unsubstituted hydrogen atom at position 3 in the ring could also undergo nitrile splitting. The reaction is not known to occur with pyrazoles themselves, but recently A. M. Siminov, B. K. Martsokha, and F. T. Pozharskii found that the pyrazole ring is opened by sodium hydroxide in xylene. Depending on the structure of the starting indazole, the products are nitriles, amides, or amidines of N-alkyl- and N-arylanthranilic acids [2-4]. It has been found that when 1-phenyl-, 1-amyl-, 1, 5-diphenyl-, and 1-phenyl-4-benzoylpyrazole are heated at 140° with sodamide in dry xylene, a nitrile rearrangement takes place

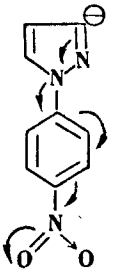


With 1-phenyl-4-benzoylpyrazole the yield of scission products (60%) was smaller, there was only slight reaction in the case of 1-phenylpyrazole, and 1, 5-diphenylpyrazole reacted with even greater difficulty. The readier reaction of 1-phenyl-4-benzoylpyrazole as compared with 1-phenylpyrazole is due to the presence of the electron-accepting $C_6H_5CO^-$ group which decreases the electron density at the ring and promotes readier deprotonation at position 3, than obtains with 1-phenylpyrazole. It was not possible to effect splitting of 1-phenyl-4-acetylpyrazole: a more crystalline substance, mp 200°, whose structure was not ascertained, was obtained. Apparently here reaction is complicated by reaction of the acetyl group with the sodamide. With 1, 5-diphenylpyrazole, rearrangement gives a smaller yield (25%) and proceeds more sluggishly than with 1-phenylpyrazole (48%). A possible explanation is that in the pyrazole anion formed by deprotonization, the charge is not, (because of conjugation of the aromatic system) localized at position 3, but distributed over the whole conjugated system. This decreases the polarization of the N–N bond, as well as its subsequent scission. Formal consideration of the case of 1-p-nitrophenylpyrazole leads one to expect that reaction will occur more easily than in the case of 1-phenylpyrazole. The strongly electron accepting NO_2 group should make for greater polarization of the N–N bond, and facilitate deprotonization at position 3.

In a series of experiments on the scission of 1-p-nitrophenylpyrazole under various conditions, only about 85% of the starting material was isolated, the identity of the latter being fully proven (mp, mixed mp, elementary analysis, UV spectrum).

Evidently this fact is connected with deprotonation of 1-p-nitrophenylpyrazole giving an anion I, with, as in the case of 1, 5-diphenylpyrazole, a strongly delocalized charge, i. e., as compared with 1-phenylpyrazole the anion is more stable, but less reactive, and N–N bond breaking does not occur.

Even at 100° 1-amylpyrazole underwent exothermic reaction with sodamide. It would appear that an electron-donor group at the nitrogen atom must hinder polarization and N–N bond breaking. But apparently participation of the electron pair of a N atom in formation of a 6π electron system already polarizes the N–N bond enough, and the lack of possible delocalization of the anion-ion at the conjugated system (as compared with arylpyrazoles) is the determining factor with regard to occurence of the reaction.



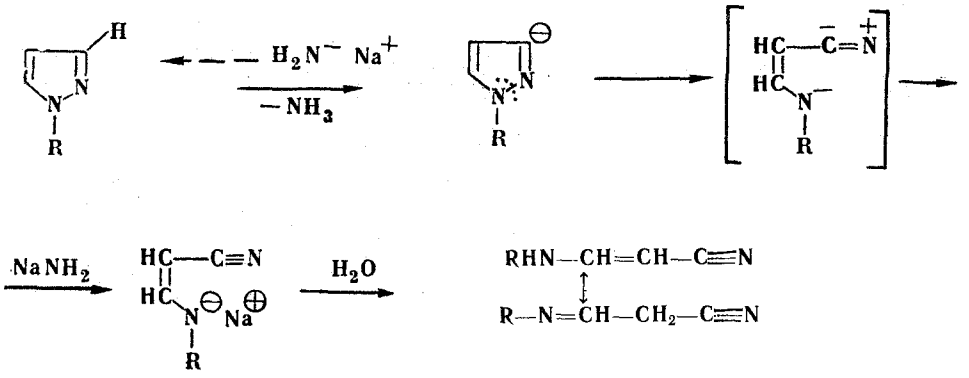
I

The existing results confirm the theory that the nitrile rearrangementsof pyrazoles unsubstituted at position 3, has an ionic mechanism, and is accompanied by heterocyclic splitting of the N–N bond.

Probably a proton is first split off through direct nucleophilic attack on a hydrogen atom by

*For Part L see [11].

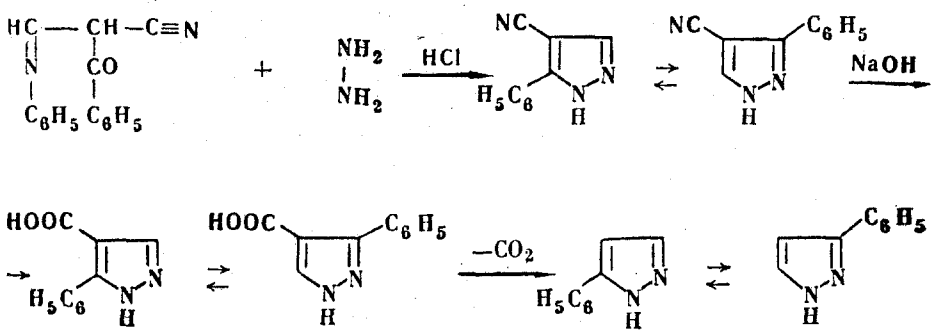
sodamide. Subsequently or simultaneously there is a redistribution of electron density, weakening the N–N bond, and



leading to its heterocyclic scission and formation of a sodio derivative, which gives the corresponding β-iminonitrile on treatment with water.

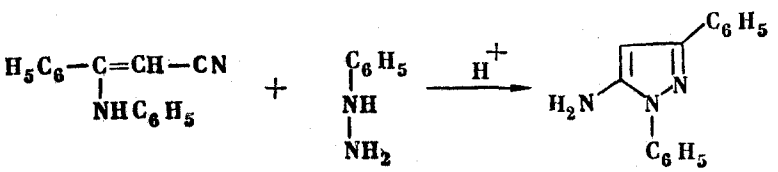
The structures of the β-iminonitriles were proved by synthesis from known starting materials.

3(5)-Phenylpyrazole-4-nitrile, hitherto undescribed in the literature, was prepared by condensing α-benzoyl-β-phenyliminopropionitrile with hydrazine hydrate, and hydrolysis of it gave the known 3(5)-phenylpyrazole-4-carboxylic acid. But our acid melted 22° higher than that described in the literature [5], so it was decarboxylated to the well known 3(5)-phenylpyrazole [6]



Complete identity with a specimen of authentic compound was proved by comparison of melting points and chromatographic characteristics.

The structure of β-phenyl-β-phenylaminoacrylonitrile was proved by synthesis of known 1,3-diphenyl-5-aminopyrazole [7]



All β-aryl-β-aminoacrylonitriles prepared are crystalline substances, insoluble in dilute alkalies and acids. They are soluble in concentrated hydrochloric acid, and when treated with alkoxides or sodamide give Na salts. β-amylaminoacrylonitrile is a pale yellow liquid with a very unpleasant smell.

Experimental

β-phenylaminoacrylonitrile. 4.32 g 1-phenylpyrazole (bp 110-112° (8 mm); n_D^{20} 1.5891 [8]), 1.17 g powdered sodamide, and 50 ml dry xylene were placed in a flask fitted with a reflux condenser and stirrer, and heated for 5 hr in an oil bath at 150°. The reaction mixture was cooled to room temperature, and sodium salt which separated filtered off on a suction filter, thoroughly washed with dry ether, and decomposed with 10 ml cold water. The precipitate was filtered

off, and recrystallized from benzene-petrol ether. Yield 2.1 g (48.8%), mp 127-128°, R^*_f 0.28 (Al_2O_3; benzene-chloroform 1 : 1) 0.45 (Al_2O_3, chloroform). Found: C 74.70, 74.93; H 5.79, 5.48%. Calculated for $C_9H_8N_2$: C 74.97; H 5.59%. UV spectrum (SF-4, in methanol): λ_{max} 282, 305 mμ; lgε 4.63, 4.62. IR spectrum (JASCO, paste with vaseline): 2210 cm^{-1} (CN group).

β-phenyl-β-phenylaminoacrylonitrile. This was prepared similarly to β-phenylaminoacrylonitrile, using 15 g 1,5-diphenylpyrazole (mp 56° [9]), and 3.8 g sodamide in 50 ml dry xylene. Yield 3.7 g (25%). Mp. 143-144°. R_f 0.46 (Al_2O_3, benzene-chloroform 1 : 1) 0.69 (Al_2O_3 chloroform). Found: C 82.18, 82.00; H 5.88, 5.55%. Calculated for $C_{15}H_{12}N_2$: C 81.88; H 5.48%.

UV spectrum (SF-4, in methanol): λ_{max} 248, 316 mμ; lgε 4.09, 4.04. IR spectrum (JASCO, paste with vaseline): 2200 cm^{-1} (CN group).

1,3-Diphenyl-5-aminopyrazole. 1.1 g β-phenylaminoacrylonitrile, 0.55 g phenylhydrazine, and 8 ml 4N HCl were refluxed for 15 min. Then 4 ml conc. HCl was added, and the refluxing continued for 30 min more. The reaction products were filtered through activated carbon, made alkaline with conc. ammonia, and the aminopyrazole precipitated recrystallized from 50% ammonia. Yield 0.8 g (66%) compound mp 130-130.3°. The preparation gives an undepressed mixed mp with an authentic specimen [7].

α-benzoyl-β-phenylaminopropionitrile. 2.48 g 4-benzoyl-1-phenylpyrazole (mp 128-128.5° [10]), 0.65 g sodamide, and 25 ml dry xylene were heated for 8 hr in an oil bath at 150°. The sodium salt which separated was filtered off with suction, washed with dry ether, and decomposed with 5 ml water. The solution was filtered, and the filtrate acidified to pH 3 with 2N hydrochloric acid. The resultant precipitate was recrystallized from benzenecyclohexane. Yield 1.5 g (60.5%) compound mp 157-158°, R_f 0.39 (Al_2O_3, chloroform-benzene 1 : 1); 0.61 (Al_2O_3, chloroform). Found: C 77.42, 77.62; H 4.96%. Calculated for $C_{16}H_{12}N_2O$: C 77.39; H 4.87%.

UV spectrum (SF-4, in methanol): λ_{max}, 250, 325 mμ; lgε 4.10, 4.60. IR spectrum (JASCO, paste with vaseline): 2240 cm^{-1} (CN group).

3(5)-Phenylpyrazole-4-nitrile. 1.3 g α-benzoyl-β-aminopropionitrile was dissolved in 15 ml 2N hydrochloric acid, and refluxed for 15 min with 0.18 g hydrazine hydrate. The mixture was cooled to room temperature and made alkaline with 2N NaOH. The precipitate was filtered off with suction, washed with water, and recrystallized from benzene. Yield 0.5 g (58.1%) nitrile mp 133-134°. Found: C 70.85, 70.95; H 4.25, 4.39%. Calculated for $C_{10}H_7N_3$: C 70.99; H 4.17%.

3(5)-Phenylpyrazole-4-carboxylic acid. 0.5 g 3(5)-phenylpyrazole-4-nitrile, 0.5 ml 40% NaOH, and 5 ml methanol was refluxed for 11 hr. The methanol was then distilled off, the residue cooled to room temperature, and acidified with conc. HCl to pH 4. The precipitate was filtered off with suction, washed with water, and recrystallized from methanol. Yield 0.45 g (80%) acid mp 282°, the literature gives [5] 260°.

Decarboxylation of 3(5)-phenylpyrazole-4-carboxylic acid. 0.45 g 3(5)-phenylpyrazole-4-carboxylic acid was put in a flask fitted with a reflux condenser, and heated for 10 min at 300°. The dry residue was recrystallized from petrol ether, to give 0.15 3(5)-phenylpyrazole mp 78° [9]. Mixed mp with authentic compound undepressed, and they were shown to be identical chromatographically. R_f 0.64 (Al_2O_3, benzene-acetone 3 : 2), 0.66 (Al_2O_3, ethyl acetate-chloroform 3 : 1).

1-Amylpyrazole. 22 g tetraethoxypropane, 10.2 amylhydrazine hydrochloride, 10 ml ethanol, 5 ml water were refluxed for 2 hr in a flask. The products were made alkaline with sodium carbonate, and extracted with ether. After distilling over sodium there was obtained 12 g (87%) 1-amylpyrazole, bp 193-194°, n_D^{20} 1.4635; d_4^{20} 0.9024. Found: C 69.73, 69.63; H 10.43, 10.37%. Calculated for $C_8H_{14}N_2$: C 69.52; H 10.21%.

β-amylaminoacrylonitrile. 6 g powdered sodamide and 100 ml dry xylene were heated for 10 min at 140°, then cooled to 100°, and 20.3 g 1-aminopyrazole added, after which heating was continued for 5 hr at 140°. The xylene was evaporated off under reduced pressure on a water bath, and residue cooled to room temperature and treated with 20 ml water. This was followed by extraction with ether, washing of the ether extract with water, and drying over magnesium sulfate. The ether was distilled off and the residue vacuum-distilled. A second distillation gave 6.2 g 1-amylpyrazole (the starting material) bp 190-193° at atmospheric pressure, and 3.8 g (18.7% on the reacted 1-amylpyrazole) β-amyl-

*A variation of chromatography with a thin unfixed layer of alumina was used. An alumina powder layer approx. 1 mm thick was placed on matt-surface glass plates 13 × 18 cm, using a metal roller. Methanol solutions of 5-20 mg of the substances under investigation were run on to the alumina 10 mm from the plate edge, and 10-15 mm apart. Separation was carried out in a closed vessel, the edge of the slightly inclined plate being touched with 25-30 ml solvent. When the liquid front had moved forward 15 cm, for example, the plate was taken out, dried, and exposed to iodine vapor. Brockman alumina for chromatography activity II was used.

aminoacrylonitrile bp 160-162° (15 mm), n_D^{20} 1.5050; d_4^{20} 0.9143. Pale yellow liquid with a very unpleasant smell, R_f 0.31 (Al_2O_3, benzene-chloroform 1 : 1), 0.55 (Al_2O_3, chloroform). Found: C 69.53, 69.18; H 10.35, 10.59%. Calculated for $C_8H_{14}N_2$: C 69.52; H 10.21%.

UV spectrum (SF-4, in methanol): λ_{max} 258-259 mμ; lgε 4.15. IR spectrum (JASCO, paste with vaseline): 2200 cm^{-1} (CN group).

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