A STUDY OF PYRAZOLES

LVIII. Reactivity of Pyrazolo[2,3-a]Pyridine

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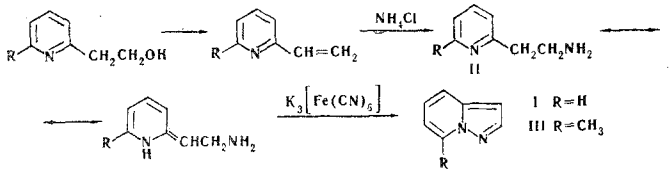
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 6, pp. 1076–1082, 1967

UDC 547.821'772:541.67+543.422.4.6+543.544+542.944.1'951

The reactivity of pyrazolo[2,3-a]pyridine in electrophilic substitution reactions has been studied. It has been shown that electrophilic attack is directed to position 3 (equivalent to position 4 of the pyrazole nucleus). The position of entry of the substituents was shown by chemical methods and was confirmed by a study of PMR spectra.

In the synthesis of pyrazolo[2,3-a]pyridine (I) precisely by Bower's method [1, 2] we found that the compound contains a considerable amount of the initial 2-(2'-aminoethyl)pyridine (II) as an impurity.



In order to obtain substance I in the pure state, we distilled the reaction mixture through a column of 20 theoretical plates; its constants are given in the table. We obtained 7-methylpyrazolo[2,3-a]pyridine (III) by an analogous method (table).

The yields of the pure substance are far lower than given by Bower, amounting to only 3–6.5%.

Pure pyrazolo[2,3-a]pyridine is a fairly stable substance which darkens somewhat on storage in the light. It is sparingly soluble in water and in acids weaker than sulfuric or hydrochloric. The base can be extracted with benzene from 20% H_3PO_4, and this is a good method for its separation from the initial aminopyridine. It possesses a weak characteristic odor, somewhat resembling N-alkylpyrazoles but less unpleasant. It is readily soluble in all organic solvents except petroleum ether.

It has been shown chromatographically that it undergoes no change at all in an attempt at hydrolysis with concentrated hydrochloric acid (100° C, 20 hr). A similar result was obtained in an attempt at alkaline hydrolysis (40% solution of sodium hydroxide in 50% ethanol).

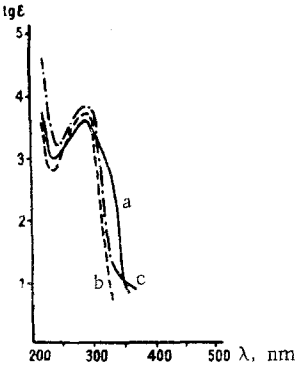


Fig. 1. UV spectra: a) pyrazolo-[2,3-a]pyridine in methanol (λ_{max} 285 nm, log ε 3.69); b) pyrazolo-[2,3-a]pyridine in 70% $HClO_4$ (λ_{max} 292 nm, log ε 3.79); c) its methiodide in methanol (λ_{max} 290 nm, log ε 3.86).

The dipole moment of pyrazolo[2,3-a]pyridine was measured and found to be 2.15 D [16]. As can be seen from a comparison of the values of the dipole moments

Constants of Pyrazolopyridines

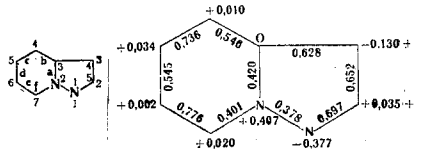
Property	Pyrazolo[2,3-a]pyridine	7-Methylpyrazolo[2,3-a] pyridine
Bp	108° (25 mm), 210.6° (756 mm)	98° (15 mm), 200.5° (756 mm)
n_D^{20}	1.6035	1.5892
d_4^{20}	1.1054	—
Mp of the picrate	152°	112°
Mp of the methiodide	215°	—
UV spectrum	λ_{max} 295 nm, lg ε 3.86	λ_{max} 286 nm, lg ε 4.00
pK_a*	2.47	2.71
μ, D	2.15 D	—
R_f**	0.53	0.79
R_f***	0.33	0.63

*For the method of measuring pK_a, see [3]

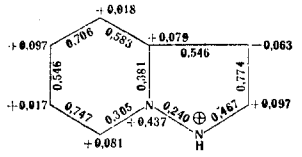
**Benzene–methanol (9:1) system, Al_2O_3 of Brockmann activity grade II

***Benzene–chloroform (1:1) system, Al_2O_3 of Brockmann activity grade II

the difference between the values of μ for pyrazolo[2, 3-a]pyridine (2.15 D), pyrazole (2.06 D), and N-methylpyrazole (2.28 D) [4] is very small, which convincingly confirms its structure.



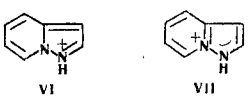
IV



V

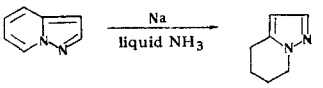
We have carried out a calculation of electron densities and bond multiplicities for pyrazolo[2, 3-a]pyridine and also for the compound protonated in position 2 of the pyrazole nucleus. The calculations were carried out by LCAO MO method in Hückel's approximation. The initial parameters for the heteroatoms were selected in accordance with the recommendations of Brown et al [5]. All the calculations were carried out on a ETsVM-20 electronic computer. As can be seen from the calculation of the electron densities of model IV, the distribution of charges in the pyrazole nucleus is the same as usual [6], i.e., the maximum electron density is at position 3 (corresponding to position 4 of the pyrazole nucleus). In the case of the protonated model V, the maximum electron density remains at the same position. This distribution of the electron density in the pyrazole nucleus of pyrazolopyridine presupposes an orientation of substituents analogous to that for pyrazoles, i.e., electrophilic substitution reactions must take place at position 3. With regard to nucleophilic attack, positions 2 and 7 will most probably be the most sensitive.

We were interested in the possible mechanism of the protonization of the basic molecule. The electron density calculation permitted the assumption of the protonization of the basic compound at position 1 with retention of the pyrazole structure VI, but a double bond migration with the formation of structure VII could also take place.



VI VII

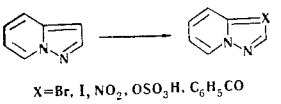
If the protonated molecule had the structure VI, the characteristic UV spectrum of the basic compounds should be preserved in its general outlines, while a bond rearrangement with the formation of structure VII should substantially change the nature of the spectrum. This also relates to the spectra of the methiodide. However, the UV spectrum of I in 70% $HClO_4$ and the spectrum of the methiodide of I practically coincided with the spectrum of pyrazolo[2, 3-a]pyridine in methanol (Fig. 1). Moreover, the pyrazolopyridine methiodide had the typical behavior of pyrazole methiodides [7]. Its pyrolysis led to the smooth splitting out of CH_3I and the formation of the initial compound (I). The IR spectra of I and its methiodide were also almost identical (Figs. 2 and 3). Thus, structure VI must evidently be assigned to the protonated molecule. From our point of view the reduction of the pyridine nucleus was of interest: it gave us a typical dialkylpyrazole. Thus, when the reduction was carried out with sodium in liquid ammonia, we obtained 1, 5-tetramethylenepyrazole with the characteristic properties and constants of 1,5-disubstituted pyrazoles. The PMR spectrum confirmed this structure (Fig. 4).



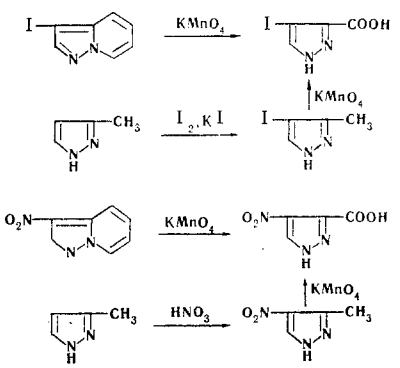
ELECTROPHILIC SUBSTITUTION REACTIONS OF THE PYRAZOLOPYRIDINE (I)

Bromination, iodination, nitration, sulfonation, and acylation gave the corresponding 3-derivatives of pyrazolo[2, 3-a]pyridine.

We proved the structure of the compounds obtained by the electrophilic substitution reactions on the basis of the reactions of 3-iodo- and 3-nitropyrazolo[2, 3-a]pyridine.



X=Br, I, NO_2, OSO_3H, C_6H_5CO



The oxidation of 3-iodopyrazolo[2, 3-a]pyridine gave 4-iodopyrazole-3-carboxylic acid, the melting point of which agreed with that of the acid that we obtained by direct synthesis. A mixture gave no depression of the melting point [8]. A comparison of the melting points and chromatographic characteristics showed the complete identity of the compound and the authentic sample. Similarly, the oxidation of 3-nitropyrazolo[2, 3-a]pyridine gave 4-nitropyrazole-3-carboxylic acid, the melting point of which agreed with that of the authentic substance and corresponded to the figure given in the literature [9]; their chromatographic characteristics also coincided.

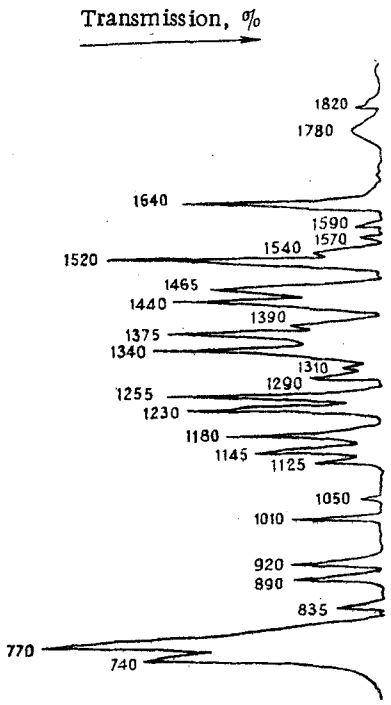


Fig. 2. IR spectrum of pyrazolo[2,3-a]pyridine (I) (UR-10, thin layer).

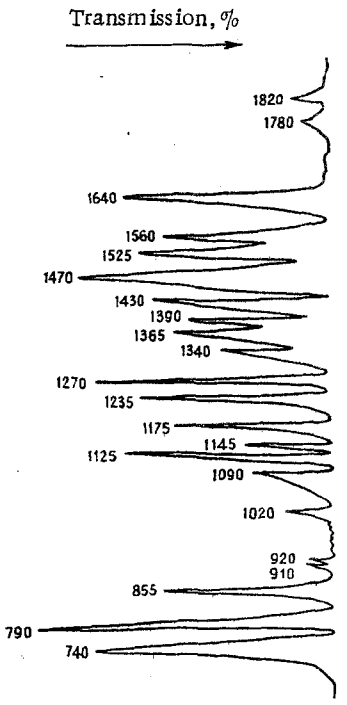


Fig. 3. IR spectrum of the methiodide of (I) (UR-10, in paraffin oil).

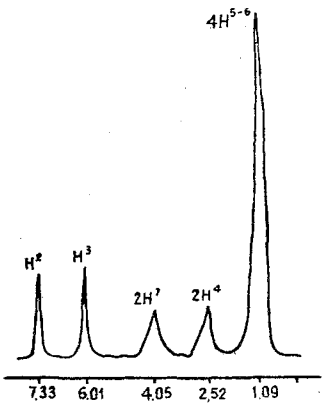


Fig. 4. PMR spectrum of 1,5-tetramethylmethylenepyrazole in CCl_4.

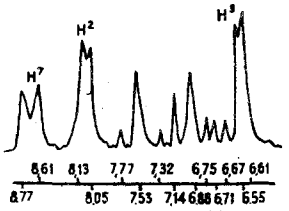


Fig. 5. PMR spectrum of pyrazolo[2, 3-a]-pyridine in $(CH_3)_2SO$.

PMR spectra (the proton magnetic resonance spectra were taken on a JNM-2 instrument at a frequency of 39.55 MHz). The proton magnetic resonance spectrum of the initial pyrazolopyridine was recorded in dimethyl sulfoxide (Fig. 5) and in nitromethane (Fig. 6). In both cases, the solvent simultaneously acted as an internal standard. The presence of the peak of the H^3 proton in a very strong field is similar to that of the peak of the H^4 proton of the pyrazole nucleus [10] in 1-phenylpyrazole. The H^2 and H^7 protons, which have similar locations with respect to the heteroatom, are in a strong field and have spin-spin interaction with the H^3 and H^6 protons, respectively ($J_{H_2-3} = 2.4$ Hz; $J_{H_6-7} = 6.3$ Hz). The assignments of the chemical shifts of the H^4, H^5, and H^6 protons were made in accordance with Paudler's data [11]. The spectrum of 7-methylpyrazolo[2, 3-a]pyridine (Fig. 7) lacks the peak of the H^7 proton and has a pronounced 3-proton peak of the methyl group in a strong field.

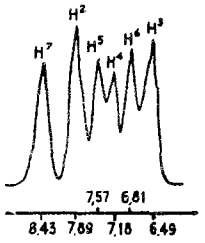


Fig. 6. PMR spectrum of pyrazolo[2, 3-a]-pyridine in CH_3NO_2.

The characteristics of the PMR spectra for 3-substituted pyrazolopyridines confirm the position of entry of the electrophilic agent by the chemical method (Fig. 8).

Thus, in the spectrum of 3-iodopyrazolopyridine (with dimethyl sulfoxide as solvent and standard) the peak corresponding to the H^3 proton disappeared. The assignment of the peaks in the spectrum of 1, 5-tetramethylenepyrazole (with carbon tetrachloride as solvent and hexamethylenesiloxane as internal standard) agrees well with the data for the chemical shifts of 1, 5-substituted pyrazoles [12, 13] (Fig. 4).

EXPERIMENTAL

Pyrazolo[2, 3-a]pyridine (I). Over the course of 1 hr, 31 g (0.25 mole) of 2-(2'-aminoethyl)pyridine [bp 98° C (10 mm), n_D^{20} 1.5420 [14]] was added to a solution of 344 g (1.04 mole) of potassium ferricyanide and 88.4 g (1.05 mole) of sodium bicarbonate in 1 *l* of water in a 2-liter flask fitted with a stirrer, condenser, and dropping funnel. Then the mixture was heated at 60° C in the water bath for 15 hr. After cooling, 190 ml of 40% sodium hydroxide was added to the reaction mixture and it was carefully extracted with chloroform (10 × × 150 ml); the extracts were dried with anhydrous sodium sulfate, the chloroform was distilled off, and the residue was extracted with boiling benzene. The oil that remained after the benzene had been driven off was distilled in vacuum, a fraction with bp 80°–110° C (14 mm) being collected. The fractions with this boiling point from a series of experiments were combined and distilled through a column of 20 theoretical plates. In this way 721 g of 2-(2'-aminoethyl)pyridine gave 41 g (6.4%) of pure pyrazolopyridine (for constants, see table). **Picrate:** mp 152° C (from methanol). Found, %: C 44.85; 44.76; H 2.88; 2.86. Calculated for $C_7H_8N_2 \cdot C_6H_3N_3O_7$, %: C 44.95; H 2.62.

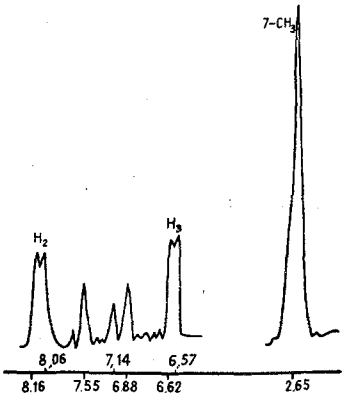


Fig. 7. PMR spectrum of 7-methylpyrazolo[2, 3-a]-pyridine in dioxane.

Pyrazolopyridine methiodide. A mixture of 1 g (8.5 mM) of pyrazolopyridine and 3 g (21 mM) of methyl iodide in 5 ml of absolute ether was heated at 100° C in a sealed tube for 12 hr. The precipitate of methiodide was washed on the filter with absolute ether and dissolved in absolute methanol. The solution was boiled with activated carbon and filtered, and then dry ether precipitated 2.1 g (99.5%) of the methiodide with mp 215° C. Found, %: C 37.38; 37.30; H 3.67; 3.64. Calculated for $C_8H_9IN_2$, %: C 36.96; H 3.48.

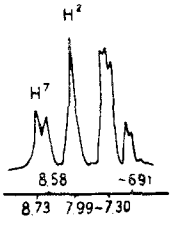


Fig. 8. PMR spectrum of 3-iodopyrazolo[2, 3-a]-pyridine in $(CH_3)_2SO$.

Pyrolysis of the methiodide I. In a flanged flask, 0.3 g of the methiodide was heated in vacuum to 200° C. The decomposition product (0.18 g) had bp 76°–80° C (10 mm), n_D^{20} 1.6060, R_f on alumina identical with that of the initial **I**. **The picrate,** mp 152° C (from methanol) gave no depression of the melting point with the picrate of I.

6-(2'-Aminoethyl)-2-methylpyridine (with the participation of S. N. Dashkevich). A mixture of 109 g (1 mole) of 2-methyl-6-vinylpyridine [bp 75°–76° C (24 mm), n_D^{20} 1.5410 [15]], 107 g (1 mole) of ammonium chloride, 300 ml of water, and 90 ml of propanol was heated in a flask with a stirrer and a reflux condenser in the water bath for 11 hr. After 100 ml of ethanol had been distilled off, the reaction mixture was cooled and made strongly alkaline with 40% sodium hydroxide, and then another 30 g of solid alkali was added. The oil was extracted with chloroform and the extracts were dried with anhydrous sodium sulfate. After the chloroform had been driven off, the residue was distilled in vacuum giving 40 g (42%) of 6-(2'-aminoethyl)-2-methylpyridine, mp 110° C (12 mm), n_D^{20} 1.5368, d_4^{20} 0.9870. Found, %: C 70.29; 70.40; H 8.70; 8.81. Calculated for $C_8H_{12}N_2$, %: C 70.57; H 8.87.

7-Methylpyrazolo[2,3-a]pyridine (III). Over one hour, 26 g (0.265 mole) of 6-(2'-aminoethyl)-2-methylpyridine was added to a mixture of 344 g (1.04 mole) of potassium ferricyanide, 88.4 g (1.05 mole) of sodium bicarbonate, and 1 *l* of water in a 2-liter flask fitted with a stirrer, condenser, and dropping funnel, and then the mixture was heated at 60° C for 15 hr. After cooling, the reaction mixture was treated with 190 ml of 40% sodium hydroxide solution and was carefully extracted with chloroform. The residue after the solvent had been driven off was distilled in vacuum. The fraction with bp 90°–110° C (20 mm) was treated with solid alkali and extracted with benzene. After the benzene had been driven off the residue was distilled in vacuum; to 1.8 g of the fraction with bp 100°–110° C (20 mm, n_D^{20} 1.5666) was added 20 ml of 10% phosphoric acid and it was carefully extracted with benzene. The benzene extract was dried with anhydrous sodium sulfate and distilled in vacuum giving 1.1 g of **III** (3.0%) (for constants, see table). **Picrate.** Found, %: C 46.75; 46.67; H 3.27; 3.25. Calculated for $C_8H_8N_2 \cdot C_6H_3N_3O_7$, %: C 46.53; H 3.07.

3-Nitropyrazolo[2,3-a]pyridine. To 0.6 g of the pyrazolopyridine were added an equivalent amount (0.25 ml) of 96% sulfuric acid and 0.4 ml of nitric acid (d 1.54). After the mixture had been heated under reflux for 30 min, 15 ml of water and then 4 g of sodium hydroxide were added with cooling, and the crystals that deposited were extracted with benzene. After part of the benzene had been evaporated off, the substance was precipitated with petroleum ether. Yield 0.66 g (73%), mp 146° C (from benzene by the addition of petroleum ether). Found, %: C 51.98; 51.91; H 3.34; 3.31. Calculated for $C_7H_5N_3O_2$, %: C 51.53; H 3.09. UV spectrum (SF-4, methanol): λ_{max} 350 nm; log ε 4.19. R_f 0.39 (Al_2O_3; benzene–chloroform 2:1); 0.67 (Al_2O_3; benzene–methanol, 9:1).

3-Bromopyrazolo[2,3-a]pyridine. A solution of 1 g of the pyrazolopyridine in 15 ml of methanol saturated with potassium bromide was treated with an equivalent amount of sodium acetate. The mixture was cooled with ice and water, and 0.3 ml of bromine in 5 ml of methanol also saturated with potassium bromide was added to it very slowly. The methanol was distilled off and the residue was treated with water. The crystals of bromide not dissolving in the water were extracted by boiling with petroleum ether. Yield 1.1 g (66%) mp 55° C (from petroleum ether). Found, %: C 42.50; 42.08; H 2.64; 2.68. Calculated for $C_7H_5BrN_2$, %: C 42.68; H 2.55. UV spectrum (SF-4, methanol); λ_{max} 295 nm, log ε 3.81; R_f 0.71 (Al_2O_3 [in all experiments alumina of Brockmann activity grade II was used]; benzene–methanol, 9:1); 0.33 (Al_2O_3; benzene–chloroform, 1:1).

3-Iodopyrazolo[2,3-a]pyridine. A solution of 1.37 g of iodine and 1.47 g of KI in 10 ml of acetic acid was added to a solution of 1 g of the pyrazolopyridine and 1.2 g of sodium acetate in 10 ml of acetic acid, and the mixture was boiled for 30 min. After cooling, it was made alkaline with 40% sodium hydroxide solution and the crystals that deposited were separated off and extracted with boiling benzene; the extracts were shaken several times with solid hyposulfite to eliminate the excess of iodine and were filtered through a layer of alumina. After the benzene had been evaporated, 1.3 g (63%) of 3-iodopyrazolopyridine was obtained with mp 55° C (from petroleum ether). Found, %: C 34.20; 34.05; H 2.10; 2.01%. Calculated for $C_7H_5IN_2$, %: C 34.45; H 2.05%. UV spectrum (SF-4, methanol): λ_{max} 297 nm, log ε 3.74. R_f 0.63 (Al_2O_3; benzene–methanol, 9:1); 0.30 (Al_2O_3; benzene–chloroform, 1:1).

Pyrazolo[2,3-a]pyridine-3-sulfonic acid. In drops, 3 ml of 20% oleum was added to 1 g of the pyrazolopyridine cooled with ice and water, and the mixture was heated in the boiling water bath under reflux for 6 hr. After cooling, it was diluted with water to 15 ml and neutralized with barium carbonate, and then the precipitate was filtered off and washed with water. The filtrate and the wash waters were evaporated to dryness. This gave 1.1 g of the barium salt of the pyrazolopyridinesulfonic acid. Found, %: C 31.07; 30.95; H 2.23; 2.16%. Calculated for $C_{14}H_{10}BaN_4O_6S_2$, %: C 31.67; H 2.38%. When the barium salt was treated with an equivalent amount of sulfuric acid the free sulfonic acid was liberated in the form of a very hygroscopic substance with mp 65°–69° C (not sharp).

UV spectrum (SF-4, methanol): λ_{max} 288 nm, log ε 3.96.

3-Benzoylpyrazolo[2,3-a]pyridine. A mixture of 0.3 g of the pyrazolopyridine and 1 ml of benzoyl chloride was heated in a flask with a reflux condenser and stirrer at 155° C in an oil bath for 7.5 hr. After cooling, the reaction mixture was poured into a beaker and boiled with concentrated potassium carbonate solution. The oil was extracted with benzene and boiled with activated carbon, and after the evaporation of part of the benzene petroleum ether precipitated a heavy oil which solidified on trituration. Yield 0.6 g (91%) of 3-benzoylpyrazolopyridine with mp 79° C (from benzene by the addition of petroleum ether). Found, %: C 74.91; 74.85; H 4.62; 4.54%. Calculated for $C_{14}H_{10}N_2O$, %: C 75.65; H 4.53%. UV spectrum (SF-4, methanol): λ_{max} 325 nm, log ε 4.66. R_f on alumina, 0.42 (benzene–chloroform, 1:1); 0.57 (benzene–methanol, 9:1).

1,5-Tetramethylenepyrazole. A three-necked flask with a reflux condenser was charged with 1 g of the pyrazolopyridine in 20 ml of liquid ammonia. The flask was cooled externally with a mixture of acetone and dry ice and 1 g of sodium in the form of wire was added to the reaction mixture until a permanent blue coloration appeared. After this, the ammonia was evaporated off and then 5 ml of water and 2 g of sodium hydroxide were added and the mixture was extracted with ether. The ethereal extract was dried with anhydrous sodium sulfate, the ether was driven off, and the residue was distilled in vacuum. Yield 0.5 g (51%), bp 140° C (10 mm), n_D^{20} 1.5195. UV spectrum (SF-4, methanol): λ_{max} 252 nm, log ε 3.36. R_f 0.27 on alumina (benzene–methanol, 9:1). **Picrate:** mp 105° C (from absolute ether). Found, %: C 44.19; 44.39; H 3.56; 3.55%. Calculated for $C_7H_{10}N_2 \cdot C_6H_3N_3O_7$, %: C 44.44; H 3.72%.

4-Nitropyrazole-3-carboxylic acid. A mixture of 0.5 g of 3-methyl-4-nitropyrazole (mp 138° C [9]), 0.76 g of potassium permanganate, 0.7 g of alkali, and 40 ml of water was heated in the water bath with stirring for 4 hr. The manganese dioxide that deposited was filtered off with suction and carefully washed with hot water. After cooling, the filtrate was acidified and the precipitate was filtered off. This gave 0.2 g (36%) of 4-nitropyrazole-3-carboxylic acid, mp 204° C, which agrees with literature data [9]. R_f on paper ["rapid" type chromatographic paper of the Volodarskii Mill] 0.76 (methanol–10% formic acid, 1:1); 0.09 (tert-butanol–petroleum ether–2 N ammonia, 25:5:2).

Oxidation of 3-nitropyrazolo[2,3-a]pyridine. A mixture of 0.9 g of 4-nitropyrazolopyridine, 3 g of potassium permanganate, and 40 ml of water was heated at 50°–70° C for 3 hr. The manganese dioxide was filtered off and carefully washed with hot water. The filtrate and the wash waters were evaporated. The precipitate that deposited on acidification with 2 N hydrochloric acid was filtered off. This gave 0.4 g (49%) of 4-nitropyrazole-3-carboxylic acid with mp 202° C (from acetone). A mixture with an authentic sample gave no depression of the melting point. R_f on paper 0.76 (methanol–10% formic acid, 1:1); 0.09 (tert-butanol–petroleum ether–2 N ammonia, 25:5:2).

4-Iodopyrazole-3-carboxylic acid. A mixture of 0.4 g of 4-iodo-3-methylpyrazole (mp 105° C [9]), 1.1 g of potassium permanganate, 2.3 g of alkali, and 20 ml of water was heated in the water bath with stirring for 3 hr, and then the manganese dioxide was filtered off and

washed with hot water and the filtrate was evaporated to dryness. The residue was treated with 2 N hydrochloric acid and the iodopyrazole-3-carboxylic acid that deposited (0.2 g) was filtered off, mp 197° C (decomp. from acetone). R_f on paper 0.64 (methanol–formic acid, 1:1); 0.06 (tert-butanol–petroleum ether–2 N ammonia, 25:5:2).

Oxidation of 3-iodopyrazolo[2, 3-a]pyridine. A mixture of 0.5 g of the iodopyrazolopyridine, 1.58 g of potassium permanganate, and 50 ml of water was heated in the boiling water bath for 4 hr and treated subsequently as described above. This gave 0.25 g (53%) of 4-iodopyrazole-3-carboxylic acid. A mixture with an authentic sample gave no depression of the melting point (200° C). R_f on paper 0.65 (methanol–formic acid, 1:1); 0.06 (tert-butanol–petroleum ether–2 N ammonia, 25:5:2).

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8 January 1966

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