REACTIONS OF PHENYL-SUBSTITUTED HETEROCYCLIC COMPOUNDS

II. NITRATIONS AND BROMINATIONS OF 1-PHENYLPYRAZOLE DERIVATIVES[1]

MISBAHUL AIN KHAN[2]
Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland

AND

BRIAN M. LYNCH[3]
Departments of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland, and St. Francis Xavier University, Antigonish, Nova Scotia

AND

YUK-YUNG HUNG[4]
Department of Chemistry, St. Francis Xavier University, Antigonish, Nova Scotia

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ABSTRACT

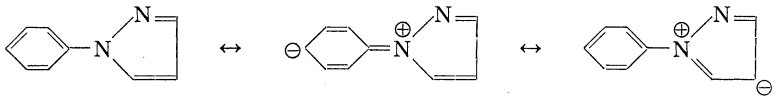
Nitrations of 1-phenylpyrazole (I), 1-*p*-biphenylylpyrazole (II), and 1,5-diphenylpyrazole by "acetyl nitrate" (nitric acid – acetic anhydride) occur selectively in the 4-position of the pyrazole ring, as do brominations of I and II in chloroform solution. These results are in agreement with R. D. Brown's calculations of localization energies for electrophilic substitution in pyrazole.

However, nitration of I by mixed acids at 12° yields 1-*p*-nitrophenylpyrazole, and bromination of I by bromine in concentrated sulphuric acid in the presence of silver sulphate yields 1-*p*-bromophenylpyrazole.

The variations in orientation of substitution can be rationalized if the reacting species of I in strongly acidic solvents is the conjugate acid, in which the pyrazole ring is deactivated by protonation.

INTRODUCTION

Electrophilic substitution in 1-phenylpyrazole (I) often leads to initial attack at the 4-position of the pyrazole ring (for example, bromination in inert solvents (1), Friedel–Crafts acylation (2, 3), chloromethylation (4), and mercuration (4)). However, nitration of 1-phenylpyrazole with mixed acids at 12° introduces the first nitro group into the para position of the phenyl ring, although further substitution occurs readily to yield 4-nitro-1-*p*-nitrophenylpyrazole (cf. Finar and Hurlock (5)).



I Ia Ib

The present paper suggests a simple interpretation of this variation in orientation, and applies this interpretation in establishing conditions for selective 4-nitration of 1-*p*-biphenylylpyrazole (II) and 1,5-diphenylpyrazole (III), for the controlled dinitration of III, for the 4-bromination of II, and for the 1-*p*-bromination of I.

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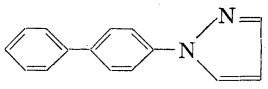
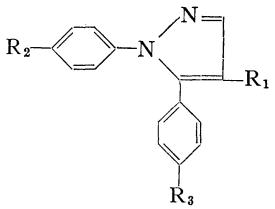
[2]*Graduate Research Assistant, 1961–1962. Present address: Florida State University, Tallahassee, Florida, U.S.A.*

[3]*Correspondence should be addressed to this author at the Department of Chemistry, St. Francis Xavier University, Antigonish, Nova Scotia.*

[4]*Graduate Research Assistant.*



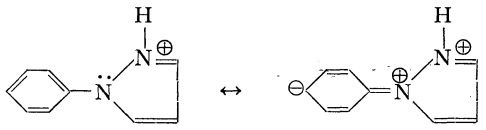
II



III: $R_1 = R_2 = R_3 = H$
V: $R_1 = NO_2$, $R_2 = R_3 = H$
VI: $R_2 = NO_2$, $R_1 = R_3 = H$
VII: $R_3 = NO_2$, $R_1 = R_2 = H$
VIII: $R_2 = R_3 = NO_2$, $R_1 = H$
IX: $R_1 = R_2 = NO_2$, $R_3 = H$

DISCUSSION

We suggest that the different orientation noted in the strongly acidic medium results from protonation of 1-phenylpyrazole to yield the conjugate acid (IV), in which the pyrazole ring would be deactivated towards attack by electrophils, while the +T effect of the 1-nitrogen atom would facilitate substitution at the para position of the phenyl group (cf. IV*a*). If this suggestion is correct, it should be possible to effect changes in the orientation of electrophilic substitution in 1-phenylpyrazole and its derivatives by varying the conditions of reaction so that either the neutral molecule or the conjugate acid is the reacting species.



IV IV*a*

Examples

(a) Selective 4-Nitrations

Although no interpretation along the lines of the above suggestion has been offered previously, an instance of the predicted control of orientation exists in the literature, in that nitration of 1-phenylpyrazole by nitric acid in acetic anhydride at 0° is reported to give 4-nitro-1-phenylpyrazole (in unstated yield) (6). In confirmation (see Experimental) we find that fair yields of 4-nitro-1-phenylpyrazole are obtained. It seems almost certain that this reaction involves attack of protonated acetyl nitrate (the effective reagent in nitrations by nitric acid in acetic anhydride, cf. Bordwell and Garbisch (7)) on the neutral molecule of 1-phenylpyrazole, while Finar and Hurlock's nitration in mixed acids involves attack by nitronium ion on the conjugate acid (IV).

Since the normally favored position of attack by an electrophilic reagent on the neutral molecule of a 1-phenylpyrazole derivative is the 4-position of the pyrazole ring (cf. refs. 1–4), it would be predicted that nitrations of 1-*p*-biphenylylpyrazole and of 1,5-diphenylpyrazole by nitric acid in acetic anhydride would yield 4-substituted derivatives. The results from the nitrations of these compounds are consistent with this prediction, although the structures of the products were not proved absolutely. The structure assigned to the nitro-1-*p*-biphenylylpyrazole, m.p. 170° (i.e., 1-*p*-biphenylyl-4-nitropyrazole), is based on correlations with the infrared and ultraviolet absorption of nitrophenylpyrazoles and other substituted 1-phenylpyrazoles. The positions of the strong bands at the N—O stretching frequencies, in conjunction with others at ca. 690 and 760 cm^{-1}, as observed with compounds possessing monosubstituted phenyl groups (8), can be used to distinguish

between the various nitrophenylpyrazoles (see Table I): the similarities between the nitro-1-*p*-biphenylylpyrazole, m.p. 170°, and 4-nitro-1-phenylpyrazole indicate very strongly that the compound is 1-*p*-biphenylyl-4-nitropyrazole. Furthermore, we have noted (9) that a strong band in the region 925–960 cm^{-1} is associated with the C—H vibrations of the pyrazole carbons, and its position in substituted 1-phenylpyrazoles in diagnostic of substitution in the pyrazole ring: absorption in the range 925–942 cm^{-1} is noted for compounds without substituents in the pyrazole ring, while absorption in the range 950–960 cm^{-1} is observed with compounds carrying such substituents. This generalization is valid for approximately 50 substituted 1-phenylpyrazoles prepared in the course of the present series of papers. This band appears at 952 cm^{-1} in the infrared spectra of the nitro-1-*p*-biphenylpyrazole, m.p. 170°, thus providing further support for the assigned structure.

TABLE I

Infrared absorption bands of nitroarylpyrazoles

Compound	Infrared absorption regions (cm^{-1}) (all strong bands)		
	650–1000 (C—H deformation)	1300–1400 (ν_{N-O} sym.)	1500–1560 (ν_{N-O} asym.)
1-*o*-Nitrophenylpyrazole	750, 754, 760, 941	1371	1545
1-*m*-Nitrophenylpyrazole	738, 762, 940	1355	1535
1-*p*-Nitrophenylpyrazole	765, 852, 928	1341	1527
4-Bromo-1-*p*-nitrophenylpyrazole	750, 855, 960	1340	1527
1-(2,4-Dinitrophenyl)-pyrazole	740, 780, 832, 910, 940	1345 br	1530, 1545, 1555
4-Nitro-1-phenylpyrazole	690, 751, 770, 820, 950	1325	1545
Nitro-1-*p*-biphenylylpyrazole, m.p. 170°	692, 748, 765, 820, 952	1325	1541

Evidence from ultraviolet absorption is also consistent with the assigned structure: the ultraviolet absorption spectra of the various nitrophenylpyrazoles are characteristic, as 4-nitro-1-phenylpyrazole is the only isomer having two absorption maxima of approximately equal intensity above 220 mμ. The presumed 1-*p*-biphenylyl-4-nitropyrazole also exhibits two maxima, displaced bathochromically about 30 mμ, as would be expected from the presence of an extra *p*-phenyl substituent (compare 1-phenylpyrazole, λ_{max} 252 mμ, log ε 4.13, and 1-*p*-biphenylylpyrazole, λ_{max} 280 mμ, log ε 4.50). The absorption maxima are listed in Table II.

The nitro-1,5-diphenylpyrazole, m.p. 150°, obtained by nitration of 1,5-diphenylpyrazole in acetic anhydride, is almost certainly 1,5-diphenyl-4-nitropyrazole (V). The

TABLE II

Ultraviolet absorption spectra of nitro-1-arylpyrazoles

Compound	λ_{max} (mμ)	log ε
1-*o*-Nitrophenylpyrazole	238, 300	4.18, 3.27
1-*m*-Nitrophenylpyrazole	250	3.88
1-*p*-Nitrophenylpyrazole	318*	4.29
4-Bromo-1-*p*-nitrophenylpyrazole	315	4.21
4-Nitro-1-phenylpyrazole	228, 295	4.11, 4.07
Nitro-1-*p*-biphenylylpyrazole, m.p. 170°	265, 315	4.06, 4.08

*In chloroform solution.

only likely positions of attack are the 4-position of the pyrazole ring, or the para positions of either the 1- or 5-phenyl groups, and both 1-*p*-nitrophenyl-5-phenylpyrazole (VI), m.p. 117° (10), and 5-*p*-nitrophenyl-1-phenylpyrazole (VII), m.p. 93° (11), are known compounds.

(b) Nitrations in Mixed Acids

Under these conditions, we have assumed that the reacting species of substituted 1-phenylpyrazoles will be the appropriate conjugate acids. Attempted nitration of 1-*p*-biphenylylpyrazole, using the conditions employed for 1-phenylpyrazole (5), yielded mixtures from which no single substances were isolated. The infrared spectra of the mixtures showed broad, strong absorption in the 1350–1370 and 1530–1550 cm^{-1} regions, indicative of polysubstitution (compare the infrared absorption of 1-(2,4-dinitrophenyl)-pyrazole, Table I).

Nitration of 1,5-diphenylpyrazole was more successful: a dinitro-1,5-diphenylpyrazole, m.p. 185°, was obtained by reaction at 0°. This product is assigned tentatively as 1,5-di(*p*-nitrophenyl)pyrazole (VIII). In agreement with this assignment, nitration of 1-*p*-nitrophenyl-5-phenylpyrazole by mixed acids at 0° also yielded the dinitro-1,5-diphenylpyrazole, m.p. 185°, while similar nitration using nitric acid in acetic anhydride at 0° yielded a different dinitro-1,5-diphenylpyrazole, m.p. 147°, presumably 4-nitro-1-*p*-nitrophenyl-5-phenylpyrazole (IX).

(c) 4-Brominations

Balbiano (1) found that the initial product of bromination of 1-phenylpyrazole was 4-bromo-1-phenylpyrazole, while Brain and Finar (12) showed that further reaction took place readily to yield 4-bromo-1-*p*-bromophenylpyrazole. In the present work, in order to have authentic samples of these compounds for detailed comparison with 1-*p*-bromophenylpyrazole (cf. following section), we have repeated the preparations of these compounds using bromine in chloroform solution.

1-*p*-Biphenylylpyrazole underwent bromination in chloroform to yield 1-*p*-biphenylyl-4-bromopyrazole, m.p. 182°, whose structure was established by comparison with authentic samples prepared by two unambiguous routes. One used the sequence 4-bromo-1-phenylpyrazole → 4-bromo-1-*p*-nitrophenylpyrazole → 1-*p*-aminophenyl-4-bromopyrazole → 1-*p*-biphenylyl-4-bromopyrazole, and the other used the free-radical phenylation of 4-bromo-1-phenylpyrazole by benzoyl peroxide (cf. Lynch and Khan (13)). The presence of strong infrared absorption bands at 690 and 760 cm^{-1}, characteristic of a monosubstituted phenyl ring (cf. ref. 8), and at 952 cm^{-1}, assignable to a 1-phenylpyrazole carrying a pyrazole C-substituent (cf. ref. 9), provided additional evidence for the assigned structure of the bromination product of 1-*p*-biphenylylpyrazole.

(d) Selective 1-p-Bromination of 1-Phenylpyrazole

Derbyshire and Waters (14) have shown that solutions of bromine in concentrated sulphuric acid become extremely effective brominating agents on addition of silver sulphate; evidence summarized by Arotsky and Symons (15) indicates that $AgBr_2^+$, rather than protonated hypobromous acid or free bromine cations, is probably the effective electrophilic reagent in such solutions. Use of this Derbyshire–Waters reagent for the bromination of 1-phenylpyrazole gave good yields of 1-*p*-bromophenylpyrazole, m.p. 70°, identical (m.p., mixed m.p., superimposable ultraviolet and infrared spectra) with an authentic sample prepared by an unambiguous synthesis from *p*-bromophenylhydrazine and 1,1,3,3-tetramethoxypropane, and differing in melting point, ultraviolet and infrared absorption from other possible bromination products, i.e., 4-bromo-1-phenylpyrazole or 4-bromo-1-*p*-bromophenylpyrazole. Key differences in the infrared spectra of the three brominated

compounds include pyrazole C—H deformation bands at 952 and 955 cm^{-1} respectively for 4-bromo-1-phenylpyrazole and 4-bromo-1-*p*-bromophenylpyrazole, and at 935 cm^{-1} for authentic 1-*p*-bromophenylpyrazole and the bromo-1-phenylpyrazole, m.p. 70°, obtained using the Derbyshire–Waters reagent. The positions of these bands confirm that the bromo-1-phenylpyrazole, m.p. 70°, and, of course, authentic 1-*p*-bromophenylpyrazole, carry no C-substituents on the pyrazole ring (cf. ref. 9). Full details of the infrared spectra are given in the Experimental section.

Once again, the change in orientation noted in the sulphuric acid medium is readily interpreted in terms of protonation of 1-phenylpyrazole to the conjugate acid (IV), which undergoes bromination by $AgBr_2^+$ at the para position of the phenyl ring.

An Interpretation of 4-Substitution in the Neutral Molecule of 1-Phenylpyrazole: The Relevance of Localization Energies

Although initial 4-substitution is noted for many electrophilic substitutions in the neutral molecule of 1-phenylpyrazole (cf. above), no interpretation of this orientation has been offered previously. The preference for 4-substitution cannot result from inter-ring conjugation: although conjugative electron transfer by a +T mechanism is possible from the pyrazole ring to the para position of the phenyl ring (structure I*a*), charge transfer to the 4-position can involve only the heterocyclic ring (structure I*b*).

However, it is possible that differences in the electron densities at the 4-position and the para position account for the preferred 4-substitution. We explored this possibility by determining the pK_a values of isomeric acids having their functional groups at either the 4- or 1-*para*-substituted positions of 1-phenylpyrazole, since it is known that the electron density at a given position of a molecule influences the ionization constants of acids or bases whose functional groups are attached to that position (for a discussion of many instances of this influence, see Brown, McDaniel, and Hafliger (16)). The relevant pK_a values were: (*a*) in water at 25°: 4-amino-1-phenylpyrazole cation, 3.22±0.05; 1-*p*-aminophenylpyrazole cation, 3.42±0.20; anilinium ion, 4.58; (*b*) in 1:1 ethanol–water at 25°: 1-phenylpyrazole-4-carboxylic acid, 5.22±0.03; *p*-1-pyrazolylbenzoic acid, 5.32±0.03; benzoic acid, 5.67. Thus, in 1-phenylpyrazole, both the 4-position and the para position of the phenyl ring appear electron deficient with respect to a benzene position, and the results indicate that the electron density at the 4-position is slightly lower than that at the para position of the phenyl ring, since the 4-substituted acids are slightly stronger than the 1-*para*-substituted isomers. Consequently, we must discard the hypothesis that 4-substitution is a result of attack at the position of highest electron density; some other factor must control the orientation.

In this regard, Brown's molecular-orbital calculations for pyrazole (17) are of interest, since the localization energies for electrophilic substitution at various positions in pyrazole suggest that the 4-position is the most reactive; further, for reasonable choices of the relative electronegativity parameter h (defined by $h = (\alpha_N - \alpha_C)/\beta$, where α_N and α_C are the Coulomb integrals of nitrogen and carbon, and β is the standard resonance integral (approximately −20 kcal)), the localization energy for the 4-position in pyrazole is less than that for a benzene position. Typical values, in multiples of $-\beta$, are: benzene, 2.54; pyrazole, 2.10 ($h = 1/2$), 2.25 ($h = 1$). Accepting a current suggestion (18) that the bonds linking aromatic nuclei are essentially single, with minimal inter-ring conjugation, we propose that 1-phenylpyrazole should be regarded simply as a 1-substituted pyrazole with an inductively electron-attracting substituent, where the ease of localization of an electron pair at the 4-position approximates that for pyrazole; consequently, 4-substitution

is to be expected. Similarly, 1-*p*-biphenylylpyrazole is regarded as virtually independent biphenyl and pyrazole nuclei, and the ease of localization of an electron pair at the 4-position of the pyrazole ring is still product controlling (the localization energies for electrophilic substitution at the 2- or 4-positions of biphenyl (-2.38β and -2.44β respectively) are greater than that for the 4-position of pyrazole). For 1,5-diphenylpyrazole, where the three rings cannot be coplanar, we consider that the 5-phenyl group will have little effect on the localization energy, so 4-substitution is still favored.

Conclusions

Our assumption that the state of protonation of 1-phenylpyrazole derivatives controls the orientation of their electrophilic substitution reactions appears valid, as it satisfactorily predicts the results reported in this paper. It is realized, of course, that the attacking electrophilic reagents differ, in addition to the changes in the predominant substrate species. However, the products from the substitutions effected by both highly selective reagents (e.g., molecular bromine) and by the more reactive, less selective reagents (such as nitronium ion, or "positive bromine") are those of *selective* attack at a single position (*either* the 4- *or* the 1-*para*-position). This rules against any correlation between the nature of the attacking electrophilic reagent and the orientation of substitution, since such a correlation would be expected to reveal itself in a tendency of the more reactive reagents to attack both reactive positions (the 4- and the 1-*para*-position) to give mixtures of products. This is neither in agreement with our results, nor with the experience of previous workers.

EXPERIMENTAL

General

Analyses are by the Schwarzkopf Microanalytical Laboratory, Woodside, N.Y., U.S.A. Melting points were observed using a Fisher–Johns melting point apparatus, and are uncorrected. Infrared spectra were recorded using a Unicam SP 100 spectrophotometer equipped with a SP 130 grating accessory; samples were examined using the potassium chloride disk technique. Ultraviolet spectra refer to solutions in 95% ethanol, and were recorded using a Beckman DK-2A spectrophotometer. A Radiometer Model 4 pH meter was used for the potentiometric titrations.

Substituted 1-Phenylpyrazoles

The following compounds were prepared in excellent yields by the standard condensation of the appropriate substituted hydrazine with 1,1,3,3-tetramethoxypropane in ethanolic hydrochloric acid (cf. Jones (19) and Finar and Hurlock (5)): 1-phenylpyrazole, m.p. 11°, b.p. 246°, n_D^{25} 1.5957; 1-*o*-nitrophenylpyrazole, m.p. 89°; 1-*m*-nitrophenylpyrazole, m.p. 94–95°; 1-*p*-nitrophenylpyrazole, m.p. 170°; 1-(2,4-dinitrophenyl)-pyrazole, m.p. 107°; *p*-1-pyrazolylbenzoic acid, m.p. 268–270° (decomp.) (anal. calc. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28%; found: C, 63.82; H, 4.47%); 1-*p*-bromophenylpyrazole, m.p. 70° (anal. calc. for $C_9H_7N_2Br$: C, 48.45; H, 3.16%; found: C, 48.70; H, 3.34%) (ultraviolet absorption: λ_{max} 262 mμ, log ϵ 4.29; infrared absorption: strong bands in the 650–1800 cm^{-1} region at 752, 810, 824, 935, 1050, 1075, 1125, 1205, 1340, 1398, 1495, 1525, and 1600 cm^{-1}); Brain and Finar (12) refer to 1-*p*-bromophenylpyrazole but quote no physical constants. 4-Nitro-1-phenylpyrazole, m.p. 127°, was prepared from sodium nitromalonaldehyde hydrate and phenylhydrazine (5, 6). 1-Phenylpyrazole-4-carboxylic acid, m.p. 220°, was prepared from 4-formyl-1-phenylpyrazole (20) by oxidation with alkaline potassium permanganate. 4-Amino-1-phenylpyrazole, m.p. 104°, and 1-*p*-aminophenylpyrazole, m.p. 45°, were obtained by reduction of the appropriate nitrophenylpyrazole with tin and hydrochloric acid. 1,5-Diphenylpyrazole, m.p. 55°, was prepared by condensation of hydroxymethyleneacetophenone and phenylhydrazine (21), and 1-*p*-nitrophenyl-5-phenylpyrazole, m.p. 117°, was prepared by a similar condensation using *p*-nitrophenylhydrazine (21).

1-p-Biphenylylpyrazole

This compound was obtained by condensation of *p*-hydrazinobiphenyl and 1,1,3,3-tetramethoxypropane, and also by the following route: 1-*p*-aminophenylpyrazole (10.7 g) was diazotized in 10 *N* hydrochloric acid at 0°, and the solution of the diazonium salt was stirred at 7° with benzene, after buffering to pH 5 with sodium acetate, and was allowed to reach room temperature. After 3 hours, evolution of nitrogen had ceased, and the benzene layer was separated and chromatographed on alumina. Evaporation of the eluate, followed by crystallization from ethanol, yielded 7.8 g (53%) of 1-*p*-biphenylylpyrazole, m.p. 126°. Anal. Calc. for $C_{15}H_{12}N_2$: C, 81.80; H, 5.50; N, 12.72%. Found: C, 82.00; H, 5.55; N, 13.00%.

Nitrations in Acetic Anhydride

(a) 1-Phenylpyrazole

A solution of nitric acid (*d* 1.52, 1.5 ml) in acetic anhydride (4 ml), prepared at 15–20°, was cooled to −5° and added to 1-phenylpyrazole (3 g) in acetic anhydride (6 ml) at −5° over 30 minutes. The reaction mixture was allowed to reach room temperature, and was poured onto ice. The precipitate was collected and crystallized from ethanol, yielding 4-nitro-1-phenylpyrazole, m.p. and mixed m.p. 125–127°, having ultraviolet and infrared absorption identical with authentic material. The yield of crystallized product was 2.1 g (53%). Reactions on a larger scale generally gave lower yields, although unreacted 1-phenylpyrazole was recovered.

(b) 1-p-Biphenylylpyrazole

Nitration of 1-*p*-biphenylylpyrazole (0.5 g) under the conditions of part (*a*) gave the presumed 1-*p*-biphenylyl-4-nitropyrazole (0.25 g, 42%), m.p. 170°, after crystallization from ethanol. Anal. Calc. for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18%. Found: C, 67.67; H, 4.41%. For ultraviolet and infrared absorption see tables.

(c) 1,5-Diphenylpyrazole

Nitration of 1,5-diphenylpyrazole (2 g) under the general conditions of part (*a*), except that the temperature of reaction was maintained at 0°, gave the presumed 1,5-diphenyl-4-nitropyrazole (ca. 1 g, 43%), m.p. 150°, after chromatography on alumina and crystallization from benzene. Anal. Found: C, 68.32; H, 4.04%.

(d) 1-p-Nitrophenyl-5-phenylpyrazole

Nitration of 1-*p*-nitrophenyl-5-phenylpyrazole (1 g) under the conditions of part (*c*) gave the presumed 4-nitro-1-*p*-nitrophenyl-5-phenylpyrazole (0.3 g, 26%), m.p. 147°, after chromatography on alumina and repeated recrystallization from ethanol. Anal. Calc. for $C_{15}H_{10}N_4O_4$: C, 58.06; H, 3.25%. Found: C, 57.71; H, 3.32%.

Nitrations in Mixed Acids

(a) 1-p-Biphenylylpyrazole

With mixed acids at 0°, using the conditions employed by Finar and Hurlock (5) for 1-phenylpyrazole, 1-*p*-biphenylylpyrazole yielded amorphous products, sparingly soluble in ethanol and in benzene, having infrared absorption indicative of polysubstitution (cf. Discussion), and giving bluish-violet colors on addition of aqueous sodium hydroxide to their solutions in acetone (Janovsky test, indicative of polynitro-substituted 1-phenylpyrazoles (cf. ref. 5)).

(b) 1,5-Diphenylpyrazole

1,5-Diphenylpyrazole (2 g) was dissolved in the minimum volume of sulphuric acid (*d* 1.84) and cooled to 0°. A mixture of nitric acid (*d* 1.42, 4 ml) and sulphuric acid (*d* 1.84, 5 ml) was added at 0°. The resultant mixture was maintained at 0° for 18 hours and then poured onto ice. The precipitate was collected and crystallized repeatedly from ethanol, yielding the presumed 1,5-di(*p*-nitrophenyl)pyrazole (1.5 g, 55%), m.p. 185°. Anal. Calc. for $C_{15}H_{10}N_4O_4$: N, 18.06%. Found: C, 58.57; H, 3.41; N, 17.94%.

(c) 1-p-Nitrophenyl-5-phenylpyrazole

Nitration of 1-*p*-nitrophenyl-5-phenylpyrazole (1 g) under the conditions of part (*b*), followed by chromatography on alumina and crystallization from ethanol, similarly yielded the presumed 1,5-di(*p*-nitrophenyl)-pyrazole (0.5 g, 44%), m.p. 185°, identical (mixed m.p.) with the product obtained in part (*b*).

Brominations in Chloroform Solution

(a) 1-Phenylpyrazole

Bromine (61 g) was added dropwise to 1-phenylpyrazole (50 g) in chloroform (1000 ml) at 0°. The resulting solution was shaken with an excess of sodium carbonate solution and dried over sodium carbonate. Removal of the solvent, followed by crystallization of the product from ethanol, gave 4-bromo-1-phenylpyrazole (50 g, 65%), m.p. 83° (lit. (12), 81.5–82.5°). Ultraviolet absorption: λ_{max} 263 mμ, log ϵ 4.24. Infrared absorption: strong bands in the 650–1800 cm^{-1} region at 690, 758, 845, 952, 1042, 1202, 1250, 1340, 1386, 1410, 1465, 1502, 1530, and 1600 cm^{-1}.

Further bromination, under conditions similar to the above, of either 4-bromo-1-phenylpyrazole or 1-*p*-bromophenylpyrazole yielded 4-bromo-1-*p*-bromophenylpyrazole, m.p. 81° (lit. (12), 84.5–85°) (mixed m.p. with 4-bromo-1-phenylpyrazole, ca. 72°). Ultraviolet absorption: λ_{max} 270 mμ, log ϵ 4.29. Infrared absorption: strong bands in the 650–1800 cm^{-1} region at 810, 825, 855, 955, 1080, 1340, 1385, 1400, 1500 cm^{-1}.

(b) 1-p-Biphenylylpyrazole

Bromination as for 1-phenylpyrazole, using 1-*p*-biphenylylpyrazole (10 g), yielded 1-*p*-biphenylyl-4-bromopyrazole (7.5 g, 55%), m.p. 182°, after crystallization from ethanol, identical in all respects with authentic samples as prepared below. Anal. Calc. for $C_{15}H_{11}BrN_2$: Br, 26.72%. Found: Br, 26.89%. Ultraviolet absorption: λ_{max} 284 mμ, log ϵ 4.42. Infrared absorption in the 650–1800 cm^{-1} region (cm^{-1}, intensity): 650 w, 690 s, 760 vs, 838 s, 952 vs, 1008 w, 1018 w, 1042 m, 1080 w, 1120 w, 1155 w, 1202 w, 1250 w, 1342 s, 1385 s, 1405 m, 1425 m, 1460 w, 1490 vs, 1535 s, 1610 m.

Syntheses of 1-p-Biphenylyl-4-bromopyrazole

(a) Via 4-Bromo-1-p-nitrophenylpyrazole

To 4-bromo-1-phenylpyrazole (10 g) in sulphuric acid (*d* 1.84, 20 ml) was added, at 0°, a mixture of nitric acid (*d* 1.42, 15 ml) and sulphuric acid (*d* 1.84, 20 ml). The reaction mixture was kept overnight at 0°, poured onto ice, and collected. After crystallization from ethanol, 4-bromo-1-*p*-nitrophenylpyrazole (4.8 g, 40%), m.p. 168° (lit. (22), 168–169°), was obtained. Anal. Calc. for $C_9H_6BrN_3O_2$: C, 40.31; H, 2.24; N, 15.69%. Found: C, 40.57; H, 2.33; N, 15.90%. For ultraviolet and infrared absorption, see tables.

The 4-bromo-1-*p*-nitrophenylpyrazole was reduced quantitatively to 1-*p*-aminophenyl-4-bromopyrazole, m.p. 83°, by tin and hydrochloric acid. The amine was diazotized and the diazo solution used to arylate benzene, employing the conditions noted above for the synthesis of 1-*p*-biphenylylpyrazole. Chromatography on alumina, followed by crystallization from ethanol, yielded 1-*p*-biphenylyl-4-bromopyrazole, m.p. 182°. Anal. Calc. for $C_{15}H_{11}BrN_2$: C, 60.22; H, 3.68%. Found: C, 60.03; H, 4.04; Br, 26.79%.

(b) By Free-radical Phenylation of 4-Bromo-1-phenylpyrazole

Benzoyl peroxide (10 g) was allowed to decompose in 4-bromo-1-phenylpyrazole at 90° for 66 hours. After removal of free benzoic acid (4.0 g) with sodium hydrogen carbonate solution, excess of substrate was removed by steam distillation followed by distillation under reduced pressure. The residue was chromatographed on alumina and crystallized repeatedly from ethanol, yielding 1-*p*-biphenylyl-4-bromopyrazole, m.p. 180°, having ultraviolet and infrared absorption identical with that of sample prepared as in part (*a*).

Derbyshire–Waters Bromination of 1-Phenylpyrazole

1-Phenylpyrazole (10.8 g) and bromine (5.2 ml) were dissolved in a mixture of sulphuric acid (*d* 1.84, 90 ml) and water (10 ml). Finely powdered silver sulphate (17 g) was added, and the mixture was shaken mechanically for 3 hours. Silver bromide was filtered off and the filtrate was poured onto ice. The precipitate was collected and extracted with boiling benzene. 1-*p*-Bromophenylpyrazole, m.p. 67–68°, crystallized on slow evaporation of the benzene. Crystallization from dilute methanol yielded 10.5 g (62%) of 1-*p*-bromophenylpyrazole, m.p. 70°, identical in all respects with an authentic sample (m.p., mixed m.p., superimposable ultraviolet and infrared spectra).

Ionization Constants

Ionization constants of the carboxylic acids were determined by potentiometric titration in 1:1 ethanol–water, and those of the conjugate acids of the aminophenylpyrazoles by differential ultraviolet spectrophotometry of the appropriate ionic species in buffers of varying pH.

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