Synthetic studies of hydrazine and guanidine: derivatives of 5-pyrazoles[1,2]

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The reactions of several substituted 5-chloropyrazoles with hydrazine hydrate and guanidine, respectively, were investigated in ethanol and dimethyl formamide media. In certain cases, only S_N2 reactions occurred, while in others the 5-hydrazino- and 5-guanidopyrazoles reacted still further to yield related compounds with two pyrazole rings. On the basis of the intermediates and the different condensation products isolated, reaction schemes are proposed for the reactions discussed.

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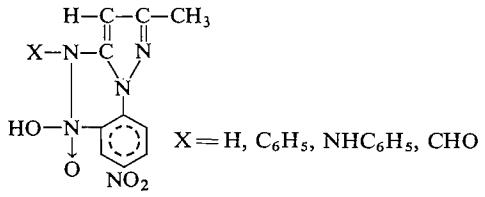
Introduction

Studies on the nucleophilic substitution of chlorine in several substituted 5-chloropyrazoles (**1**) by hydroxyl, alkoxyl, and other ions have shown that such reactions were possible whenever electron withdrawing groups were present in the 4-position (1–6). Furthermore, Rojahn and Fegeler (7) claimed that, although 1-phenyl-3-methyl-5-chloropyrazole (**2**) was inert, one or more nitro groups in the benzene nucleus would also labilize the chlorine to a remarkable degree. This conclusion was made as a result of a series of reactions between various nucleophiles and the nitration product of compound **2** (**3**), giving rise to a number of compounds to which the general formula **4** was assigned. Substrate **3**, melting at 181°, was claimed by Michaelis and Behn (8) to be 1(2,4-dinitrophenyl)-3-methyl-5-chloropyrazole. The present investigation elucidates the structure of compound **3** and describes the results of a systematic study of the nucleophilic reactions of substrates (**1**) with hydrazine hydrate and guanidine, respectively, in ethanol and dimethyl formamide media.



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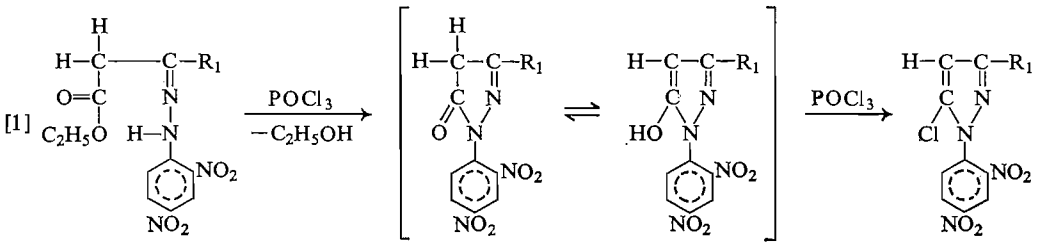
Results and Discussion

The substrates (**1**) required were prepared by chlorinating substituted 5-pyrazolones with phosphorus oxychloride according to a well known method (9–11). Application of the same method to the 2,4-dinitrophenylhydrazone of ethyl acetoacetate (**5**) and that of ethyl benzoylacetate (**6**) over a period of 8 to 10 h yielded, respectively, 1(2,4-dinitrophenyl)-3-methyl-5-chloropyrazole (**9**), m.p. 108–109.5°, and 1(2,4-dinitrophenyl)-3-phenyl-5-chloropyrazole (**10**). The preparation of compound **9** in this way leaves no ambiguity as to its structure. Thus compound **3** must be one of the two remaining possible isomers, 1(2-nitrophenyl)-3-methyl-4-nitro-5-chloropyrazole (**11**) or 1(4-nitrophenyl)-3-methyl-4-nitro-5-chloropyrazole (**12**). The nuclear magnetic resonance (n.m.r.) spectroscopic results shown in Table I indicate that the single nitro group in the 1-phenyl ring lies in the para position. Compound **3** is therefore 1(4-nitrophenyl)-3-methyl-4-nitro-5-chloropyrazole (**12**). This is analogous to the results found by previous investigators (12, 13) who nitrated 1-phenylpyrazole and 2-phenyl-1,2,3,2*H*-triazole by mixed acids and obtained the corresponding 1-*p*-nitro-4-nitro derivatives. Furthermore, the generalized conversion of all 1-phenylpyrazoles to their 1-*p*-nitro-4-nitro compounds via conjugated acids, as predicted by Lynch and Hung (14), well explains why the nitrations in compound **2** were oriented in the 1-para and 4-positions.

Chlorination of **5** and **6** over shorter periods also yielded the corresponding intermediate pyrazolones (**7** and **8**). The complete reaction proceeds as shown in eq. [1] with the hydrazine first undergoing a cyclization by the elimination of ethanol to form the corresponding pyrazolone.



5 $R_1 = CH_3$
6 $R_1 = C_6H_5$

7 $R_1 = CH_3$
8 $R_1 = C_6H_5$

9 $R_1 = CH_3$
10 $R_1 = C_6H_5$

The chlorination of the hydroxypyrazole then proceeds according to the usual manner. It is surprising that the phosphorus oxychloride attack on the carbonyl group occurs only after cyclization of the hydrazone.

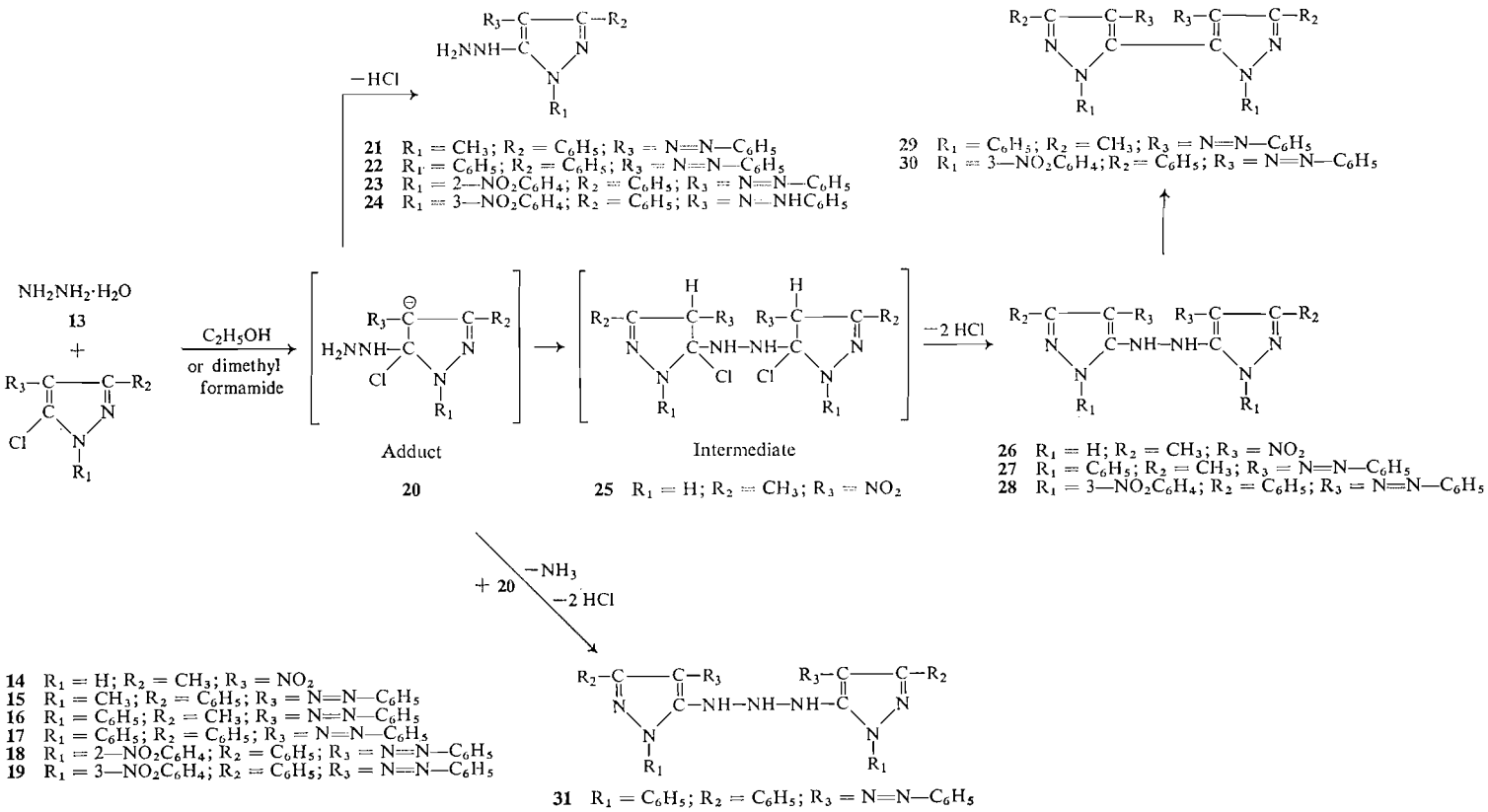
In the present work, the nucleophilic substitution reactions of substituted 5-chloropyrazoles (**14–19**) and hydrazine hydrate (**13**) are outlined in Scheme I. With 3-methyl-4-nitro-5-chloropyrazole (**14**) and **13** in ethanol, intermediate **25**, m.p. 128–129°, was isolated. When tested for the chloride ion, this intermediate gave a negative test. This excludes the possibility of the hydrochloride salt being formed. Compound **25** decomposed to **26** whose $R_f = 0.46$ when a dioxane–ethanol (1:2 vol) eluent was used. In addition, a compound with the same elemental analysis and an $R_f = 0.60$ in the same solvent mixture was isolated which is most probably the corresponding dimer. From **13** and **15** in ethanol, compound **21** only was obtained. The nucleophilicity of the end amino group in the latter compound is too weak to react with a second molecule of the chloropyrazole. The hydrazino group shows characteristic bands at 3350, 3240, and 3140 cm^{-1} which is in reasonable agreement with results obtained for methylhydrazine (15). From the reaction of 1-phenyl-3-methyl-4-benzazo-5-chloropyrazole (**16**) and **13** in dimethyl formamide, two products were isoisolated, 5,5′-bis(1-phenyl-3-methyl-4-benzazo-5-amino)-pyrazole (**27**) and 5,5′bis(1-phenyl-3-methyl-4-benzazo)-pyrazole (**29**). Thin-layer chromatography has shown beyond any doubt that **29** arises from the decomposition of **27** and not from the parent substrate. When 1(2-nitrophenyl)-3-phenyl-4-benzazo-5-chloropyrazole (**18**) and **13** were reacted together in the presence of dimethyl formamide in the molar ratio of 1:4, only 1(2-nitrophenyl)-3-phenyl-4-benzazo-5-hydrazinopyrazole (**23**) was obtained (ν_{NH_2} (Nujol) 3340 and 3380 cm^{-1}). Thin-layer chromatographic study of this reaction using benzene as an eluent indicates that **23** ($R_f = 0.18$) was gradually formed from a compound suspected to be 1(2-nitrophenyl)-3-phenyl-4-benzazo-5-chloro-5-hydrazino-2-pyrazoline ($R_f = 0.31$). By heating substrate **19** with **13** in a mixture of

TABLE I

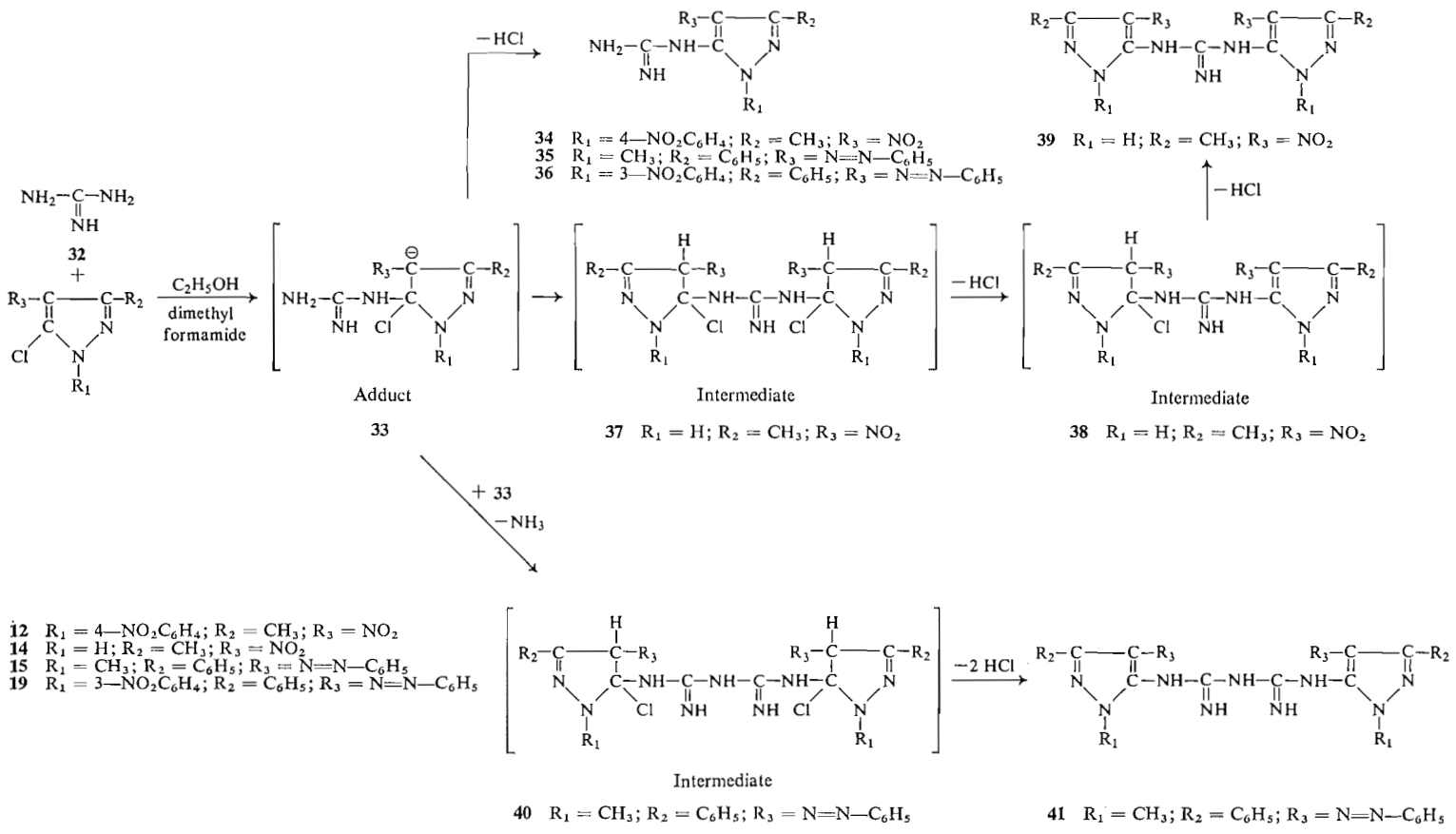
Nuclear magnetic resonance spectra of 1-phenyl-3-methyl-5-chloropyrazole and its dinitro derivatives in acetone-d_6

Compound	Group	Multiplicity*	Chemical shift†
1-phenyl-3-methyl-5-chloropyrazole (**2**)	3-CH_3	s	2.1
	4-H	s	6.25
	5 ϕ H	m	7.44
1-(2,4-dinitrophenyl)-3-methyl-5-chloropyrazole (**9**)	3-CH_3	s	2.12
	4-H	s	6.33
	3-H‡	d, $J = 2$	8.71
	5-H‡	q, $J = 9.2$	8.59
	6-H‡	d, $J = 9$	7.89
1-(4-nitrophenyl)-3-methyl-4-nitro-5-chloropyrazole (**12**)	3-CH_3	s	2.54
	4 ϕ H	q, symmetric	8.15

*s = singlet, d = doublet, q = quadruplet, m = multiplet, J in c.p.s.
†Chemical shift in p.p.m.
‡Hydrogen in 1-phenyl ring.



Scheme I



Scheme II

ethanol and dimethyl formamide, 5,5′-bis(1-(3-nitrophenyl)-3-phenyl-4-benzazo-5-amino)-pyrazole (**28**) is formed and partly decomposed to yield 5,5′-bis(1-(3-nitrophenyl)-3-phenyl-4-benzazo)-pyrazole (**30**). Here again, thin-layer chromatography adequately demonstrates that as the concentration of compound **28** increases and the temperature lies between 75 and 90°, the reaction takes a different course. Adduct **20** then preferably leads to the corresponding 5-hydrazinopyrazole (**24**). On the other hand, the action of **13** on substrate **17** gave rise to both 1,3-diphenyl-4-benzazo-5-hydrazinopyrazole (**22**) and *N*,*N*′-bis(1,3-diphenyl-4-benzazo-5-aminopyrazolyl)-amine (**31**). Chromatographic study of this reaction on thin-layer silica gel plates revealed that both compounds are formed simultaneously from the chloropyrazole. Therefore, direct competition between the simple dehydrohalogenation of adduct **20** and self-condensation of the same adduct through the elimination of ammonia followed by dehydrohalogenation must have occurred in this case.

Both 1(2,4-dinitrophenyl)-3-methyl- (**9**) and 1(2,4-dinitrophenyl)-3-phenyl-5-chloropyrazole (**10**) when heated with hydrazine hydrate (**13**) yielded the degradation product 2,4-dinitrophenylhydrazine. Similar nucleophilic displacements of the pyrazole ring by a hydroxyl or methoxyl group, induced by powerful attracting nitro groups in the ortho and para positions, have been previously reported (16). The former substrate (**9**) also gave a compound whose empirical formula corresponds to $C_6H_8O_3N_6$ and which according to its infrared and n.m.r. spectra could possibly be 2-nitro-4-aminoazoxyphenylhydrazine.

The methochloride salt of 1-methyl-3-phenyl-5-chloropyrazole and **13** in ethanol at room temperature yielded the corresponding 5-hydrazinopyrazole methochloride in two hydrated forms. The 1-phenyl-3-methyl isomer and **13** under the same conditions followed the same reaction path.

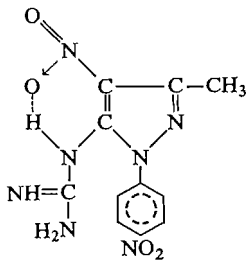
3-Phenyl-4-benzazo-5-chloropyrazole did not react with hydrazine hydrate in either ethanol or dimethyl formamide medium. 1-Phenyl-3-methyl-5-chloropyrazole with either an ortho or a para nitro substituent on the phenyl ring behaved likewise. 1(4-Nitrophenyl)-3-methyl-4-nitro-5-chloropyrazole (**12**) with **13** gave a brown polymeric substance whose melting point was above 300° and was not investigated further.

The nucleophilic substitution reactions of several substituted 5-chloropyrazoles (**12**, **14**, **15**, and **19**) with guanidine (**32**) are outlined in Scheme II. The reaction between **14** and **32** in ethanol proceeded slowly at 25° and two important intermediates were isolated, *N*,*N*′-bis-(3-methyl-4-nitro-5-chloro-2-pyrazolin-5-yl-guanidine (**37**) and *N*-(3-methyl-4-nitro-5-pyrazolyl)-*N*′-(3-methyl-4-nitro-5-chloro-2-pyrazolin-5-yl)-guanidine (**38**). Both products tested negatively for ionic chlorine thus excluding the possibility of the formation of the hydrochloride salt. Compound **38** was obtained by the partial dehydrohalogenation of **37** and subsequent dehydrohalogenation of **38** lead to *N*,*N*′-bis-(3-methyl-4-nitro-5-pyrazolyl)-guanidine (**39**).

Substrate **15** and guanidine (**32**) in ethanol did not lead to the corresponding 5-guanidopyrazole or any related compound. Instead **15** reverted back to the parent pyrazolone, 1-methyl-3-phenyl-4-benzazo-2-pyrazolin-5-one. However, in a mixture of ethanol and dimethyl formamide, both **35** and **41** were obtained. Thin-layer chromatographic study of this reaction indicates that both compounds are formed simultaneously from the chloropyrazole. It appears therefore that direct competition between the simple dehydrohalogenation of **33** and self-condensation of **33** through the elimination of ammonia followed by dehydrohalogenation must have occurred. The concentration of compound **41** does not increase at the expense of **35**.

1(3-Nitrophenyl)-3-phenyl-4-benzazo-5-chloropyrazole (**19**) and **32** in dimethyl formamide and ethanol yielded only 1(3-nitrophenyl)-3-phenyl-4-benzazo-5-guanidopyrazole (**36**). In addition to a broad band at 3340 cm^{-1}, attributed to the ν(C═N) of the guanidine group, a ν(N—H) band appears at 3430 cm^{-1}. The end amino group of the guanido group is not reactive enough to proceed to further nucleophilic attack of the substrate. **32** and **12** in ethanolic medium both at room and higher temperatures yielded the corresponding 5-guanidopyrazole **34** exclusively. An absorption band at 3490 cm^{-1} can be assigned to ν(N—H) of the imino group of the guanidine. This band is not present in the infrared spectrum of the nitration product, which nitration according to Wright (17) occurs on the nitrogen doubly bonded to the carbon of the guanidine. The infrared spectrum of compound **34** shows a broad band at 3190 cm^{-1}

which lends support to the chelated structure **42**. No evidence in support of the cyclic structure of the type proposed by Michaelis and Behn (8) (**4**) could be obtained from the infrared spectra.



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3-Phenyl-4-benzazo-5-chloropyrazole was stable towards guanidine in both media previously mentioned. This stability persisted even when a 2-nitrophenyl group was introduced in the 1-position. Similarly, 1-phenyl-3-methyl-5-chloropyrazole with either an ortho or a para nitro substituent in the 1-phenyl ring was equally inert. The methochlorides of 1-phenyl-3-methyl-5-chloropyrazole and its corresponding 1-methyl-3-phenyl isomer behaved likewise. On the other hand, 1(2,4-dinitrophenyl)-3-methyl-5-chloropyrazole (**9**) and 1(2,4-dinitrophenyl)-3-phenyl-5-chloropyrazole (**10**) degraded to 2,4-dinitrophenylguanidine. Crocker and Hall (16) reported a similar cleavage when 1(2,4-dinitrophenyl)-pyrazole was treated with either hot concentrated aqueous–methanolic sodium hydroxyde or boiling methanolic sodium methoxide. The degradation product identified was 2,4-dinitroanisole. It can be concluded therefore, that the electron density on carbon-1 of the phenyl ring is greatly diminished by the presence of the nitro groups, but this effect is not transmitted to carbon-5 of the pyrazole ring. Nucleophilic substitution of **13** and **32** as a result, occurs instead on carbon-1 of the phenyl ring. The two resonating forms of the adduct involved in the reactions with substituted-4-nitro-5-chloro pyrazoles can be represented by **43**, while **44** shows the two probable resonating forms of the adduct involved in the case of the substituted 4-benzazo-5-chloropyrazoles.

The successful isolation of the three intermediates previously described (**25**, **37**, and **38**) indicates that the simplest substitution reactions where 5-hydrazino- and 5-guanidopyrazoles only were obtained, are of the S_N2 type. However, this has not been substantiated by any kinetic studies.

Experimental

All melting points were taken in capillary tubes and were uncorrected. The carbon, hydrogen, nitrogen, and chlorine analyses were made by Micro-Tech Laboratories Inc., Skokie, Illinois. The infrared spectra were determined in Nujol and KBr on a Beckman apparatus, model IR–10, and the nuclear magnetic resonance spectra on a Varian apparatus, model A-60, with tetramethylsilane as an internal standard.

For the thin-layer chromatographic studies Eastman Chromagram sheets, type K301R2, coated with silica gel were used. The 20 cm × 20 cm sheets were cut into 2 cm × 9 cm strips and then activated in a vertical position in an oven at 110°–120°. The best chromatographic separation was obtained when volumes ranging from 1 to 1.5 μl of the reaction mixture were placed on a chromatogram at a point 3/4 in. from one end and then dried. The development was performed in a 125 ml wide mouth glass stoppered bottle containing eluent to a depth of 1 cm measured near the wall of the container.

Ethyl Benzoylacetate 2-Nitrophenylhydrazone

2-Nitrophenylhydrazine (35.5 g, 0.232 mole) was added to ethylbenzoyl acetate (67.0 g, 0.349 mole) and the resulting mixture was then heated while stirring at 95° for a period of 3 h. Upon cooling the reaction flask, a solid cake formed. The product after trituration and recrystallization in 99% ethanol yielded ethylbenzoylacetate 2-nitrophenylhydrazone as yellow needles, m.p. 104–105° (54.2 g, 71.4%), ν_{max} (Nujol) 3310 (NH), 1740 (C=O), 1615 (C=N), 1575 (phenyl), 1530, 1350 (NO_2), 1270 br, 1145 (C—O—C), 760, 735, 685 cm^{-1} (phenyl).

Anal. Calcd. for $C_{17}H_{17}O_4N_3$ (mol. wt, 327.3): C, 62.37; H, 5.23; N, 12.84. Found (mol. wt., Rast method, 311): C, 63.12; H, 5.24; N, 12.92.

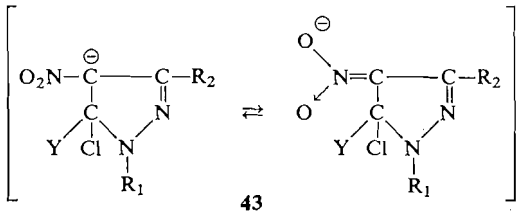
1(2-Nitrophenyl)-3-phenyl-2-pyrazolin-5-one

Ethyl benzoylacetate 2-nitrophenylhydrazone (53.0 g, 0.162 mole) was dissolved in glacial acetic acid (400 ml) and the solution was refluxed for 4 h during which time it changed from deep to light red. The resulting solution was then concentrated under reduced pressure until a yellow product separated which was then filtered and washed with ether to remove the unreacted ethylbenzoylacetate 2-nitrophenylhydrazone. The crude product crystallized from ethanol (95%) in cream colored needles, m.p. 164–465° (38.0 g, 83.4%), ν_{max} (Nujol) 1730 (C=O), 1605 (C=N), 1590 (phenyl), 1530, 1350 (NO_2), 775, 750, 740, 695 cm^{-1} (phenyl).

Anal. Calcd. for $C_{15}H_{11}O_3N_3$: C, 64.05; H, 3.94; N, 14.94. Found: C, 64.12; H, 4.12; N, 15.00.

Preparation of 1,3-Disubstituted 4-Benzazo-2-pyrazolin-5-ones

1,3-Disubstituted 2-pyrazolin-5-one (0.10 mole) was dissolved in a minimum amount of dioxane to which a freshly prepared solution of benzenediazonium sulfate (0.11 mole) was added slowly portionwise between 10–20°.



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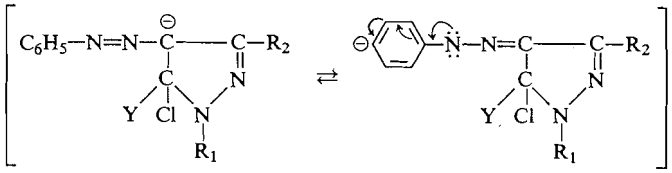

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$Y = NHNH_2,\ NH{-}\overset{\overset{NH}{\|}}{C}{-}NH_2$

An orange-colored solution was produced which gradually gave an orange to brick red precipitate. After the addition of benzenediazonium sulfate was complete, the mixture was further stirred at the above temperature for 45 min, then filtered and finally washed with a large amount of water and dried. The crude product was purified by recrystallization.

1(2-Nitrophenyl)-3-phenyl-4-benzazo-2-pyrazolin-5-one

This compound crystallized from benzene–dioxane in orange needles, m.p. 144–145° (76%), ν_{max} (Nujol) 1660 (C=O), 1600 (C=N), 1565 (phenyl), 1530, 1355 (NO_2), 780, 750, 690 cm^{-1} (phenyl).

Anal. Calcd. for $C_{21}H_{15}O_3N_5$: C, 65.45; H, 3.92; N, 18.17. Found: C, 65.72; H, 4.12; N, 17.48, 17.85.

Two distinct spots on a Chromagram thin-layer silica gel chromatogram were obtained when benzene was used as an eluent, ($R_f = 0.68$ and $R_f = 0.53$).

1(3-Nitrophenyl)-3-methyl-4-benzazo-2-pyrazolin-5-one

Obtained as yellow-orange needles from dioxane, m.p. 200–201° (74%), ν_{max} (KBr) 1660 (C=O), 1590 (phenyl), 1540 (NO_2), 1450 (phenyl), 1340 (NO_2), 880, 760, 730, 710 cm^{-1} (phenyl).

Anal. Calcd. for $C_{16}H_{13}O_3N_5$: C, 59.44; H, 4.05; N, 21.66. Found: C, 59.42; H, 4.20; N, 21.86.

1(4-Nitrophenyl)-3-phenyl-4-benzazo-2-pyrazolin-5-one

This compound was obtained as yellow-orange needles from dioxane, m.p. 241–242° (90%), ν_{max} (KBr) 1660 (C=O), 1590 (phenyl), 1540 (NO_2), 1505 (phenyl), 1360 (NO_2), 850, 785, 760, 745, 705, 695 cm^{-1} (phenyl).

Anal. Calcd. for $C_{21}H_{15}O_3N_5$: C, 65.45; H, 3.92; N, 18.17. Found: C, 65.52; H, 4.04; N, 17.80.

Reactions of Substituted 2,4-Dinitrophenylhydrazones with Phosphorus Oxychloride

Each of the following substituted 2,4-dinitrophenylhydrazones was heated with phosphorus oxychloride in a sealed tube according to the molar ratio, temperature, and time interval indicated below. The reaction tube was cooled, opened, and the contents which were partly viscous and partly gummy were poured over an ice-water mixture. When the ice melted, both a gum which settled to the bottom and a crystalline product were obtained. The crystalline product was separated from the gum by decantation and after filtration was recrystallized from 99% ethanol. The gummy product after standing in water for a few hours and upon trituration yielded an amorphous yellow solid. This solid was purified by crystallization in ethanol after treating the hot solution with activated charcoal.

Ethyl acetoacetate/$POCl_3$ (1.5/1 mole), 130–135°, 5 h gave 43% 1(2,4-dinitrophenyl)-3-methyl-2-pyrazolin-5-one (**7**) as yellow needles, m.p. 145–146°. This compound is identical with the known substance prepared by Khromov-Borisov (18), m.p. and mixture m.p. 144–145°. Also 37% 1(2,4-dinitrophenyl)-3-methyl-5-chloropyrazole (**9**) as colorless rods from ethanol (99%), m.p. 108–109.5°, ν_{max} (Nujol) 1615 (C=N), 1545 (phenyl), 1530 (NO_2), 1500 (phenyl), 1345 (NO_2), 900, 850, 835 cm^{-1} (phenyl).

Anal. Calcd. for $C_{10}H_7O_4N_4Cl$ (mol. wt., 282.6): C, 42.49; H, 2.50; N, 19.83; Cl, 12.54. Found (mol. wt., Rast method, 281): C, 42.55; H, 2.48; N, 19.86; Cl, 12.41.

Ethyl benzoylacetate/$POCl_3$ (2/1 mole), 120–130°, 4 h gave 33% 1(2,4-dinitrophenyl)-3-phenyl-2-pyrazolin-5-one (**8**), m.p. 162–163°. The compound is identical with the compound prepared by Khromov-Borisov (18), m.p. 160–161° and mixture m.p. 161–162°. Also 32% 1(2,4-dinitrophenyl)-3-phenyl-5-chloropyrazole (**10**) as yellow needles from 99% ethanol, m.p. 134–135°, ν_{max} (Nujol) 3120 (OH), 1610 (C=N), 1545 (phenyl), 1525 (NO_2), 1500 (phenyl), 1365, 1340 (NO_2), 895, 830, 810 cm^{-1} (phenyl).

Anal. Calcd. for $C_{15}H_9O_4N_4Cl \cdot \frac{1}{4}C_2H_5OH$: C, 52.26; H, 2.97; N, 15.73; Cl, 9.95. Found: C, 52.87; H, 2.92; N, 15.58; Cl, 9.75.

When the above chlorinations were carried on for an

TABLE II

Substituted 5-chloropyrazoles and hydrazine hydrate

Substrate	Reaction solvent	Mole ratio of substrate to hydrazine hydrate	Reaction temperature	Reaction time*	Intermediates and products	Yield† (%)	Melting point (°C)	R_f‡
14	ethanol	1:1.2	25°	1	5,5′-bis(3-methyl-4-nitro-5-amino-5-chloro)-2-pyrazoline (**25**)	28† (*b*)	128–129°	0.10‡ (*g*)
					+			
				2¼	5,5′-bis(3-methyl-4-nitro-5-amino)-pyrazole (**26**)	17† (*c*)	224–225°	0.46‡ (*g*)
					+			
					dimer of (**26**)	10† (*a*)	283–284°	0.60‡ (*g*)
15	ethanol	1:1.2	75–80°	16	1-methyl-3-phenyl-4-benzazo-5-hydrazinopyrazole (**21**)	33† (*a*)	162–163°	0.27‡ (*f*)
16	dimethyl formamide	1:1.5	47–78°	1¼	5,5′bis(1-phenyl-3-methyl-4-benzazo-5-amino)-pyrazole (**27**)	51† (*d*)	264–265°	0.90‡ (*f*)
					+			
			78–132°	26	5,5′-bis(1-phenyl-3-methyl-4-benzazo)-pyrazole (**29**)	23† (*a*)	126–127°	0.72‡ (*f*)
17	ethanol	1:1.1	75–80°	16	1,3-diphenyl-4-benzazo-5-hydrazino-pyrazole (**22**)	21† (*a*)	141–142°	0.35‡ (*e*)
					+			
					N,N′-bis(1,3-diphenyl-4-benzazo-5-aminopyrazolyl)-amine (**31**)	66† (*a*)	139–140°	0.52‡ (*e*)
18	dimethyl formamide	1:4.0	22–95°	1	1(2-nitrophenyl)-3-phenyl-4-benzazo-5-hydrazinopyrazole (**23**)	51† (*c*)	176–178°	0.18‡ (*e*)
19	ethanol – dimethyl formamide	1:1.1	34–75°	5	*N,N′*-bis(1-(3-nitrophenyl)-3-phenyl-4-benzazo-5-amino)-pyrazole (**28**)	20† (*b*)	181–182°	0.40‡ (*e*)
					+			
			34–75°	5	5,5′-bis(1-(3-nitrophenyl)-3-phenyl-4-benzazo)-pyrazole (**30**)	41† (*c*)	159–160°	0.75‡ (*e*)
					+			
			75–90°	6½	1(3-nitrophenyl)-3-phenyl-4-benzazo-5-hydrazinopyrazole (**24**)	18† (*b*)	188–189°	0.50‡ (*e*)

*In hours.
†Recrystallization solvent: ethanol (*a*), benzene (*b*), dioxane–ethanol (*c*), benzene–ethanol (*d*).
‡Eluent: benzene (*e*), chloroform (*f*), ethanol–chloroform 1:5 vol (*g*).

extended period, between 8 to 10 h, only the corresponding 5-chloropyrazoles (**9** and **10**) were obtained.

1(2-Nitrophenyl)-3-phenyl-4-benzazo-5-chloropyrazole

1(2-Nitrophenyl)-3-phenyl-4-benzazo-5-chloropyrazole was prepared by the method of Michaelis *et al.* (9–11). Treating a hot ethanolic solution of the crude product with activated charcoal and then cooling the resulting filtrate yielded yellow needlelike crystals, m.p. 131–132° (57%), $R_f = 0.83$ using ethanol – carbon tetrachloride (1:5 vol) as eluent, ν_{max} (Nujol) 1610 (C═N), 1530 (NO_2), 1585, 1500 (phenyl), 1340 (NO_2), 780, 770, 750 cm^{-1} (phenyl).

Anal. Calcd. for $C_{21}H_{14}O_2N_5$: C, 62.46; H, 3.49; N, 17.34; Cl, 8.78. Found: C, 62.78; H, 3.48; N, 17.60; Cl, 9.02.

Reactions of Substituted 5-Chloropyrazoles and Hydrazine Hydrate

Each of the substituted 5-chloropyrazoles listed in Table II were respectively dissolved in an appropriate solvent. Hydrazine hydrate was then added in the molar ratio given in the table. The resulting mixture was then stirred and the reaction followed by means of thin-layer chromatography while a temperature increase of 5° every 20 min up to the desired maximum was imposed. Whenever the formation of an intermediate or product was detected at its maximum concentration, a representative sample of the solution was withdrawn from the reaction flask, and the solvent evaporated under vacuum at 0° until the intermediates or products separated from the solution. The compounds were then separated by fractional crystallization and finally recrystallized from an appropriate solvent. The main course of the reaction was carried on until judged to be complete whereupon, the reaction mixture was then concentrated under vacuum until separation of the final product was accomplished. The product after filtration was then recrystallized from an appropriate solvent. In the event of a precipitate being formed during the course of the reaction, the reaction mixture was filtered immediately and the product purified by recrystallization. The reaction was then repeated without removing the precipitate and carried on according to the procedure described above. The intermediates and compounds isolated are listed in Table II while their elemental analyses and principal infrared absorption bands are given in Table III.

1(2,4-Dinitrophenyl)-3-methyl-5-chloropyrazole and Hydrazine Hydrate

The substrate 1(2,4-dinitrophenyl)-3-methyl-5-chloropyrazole (0.01 mole) heated with hydrazine hydrate (0.011 mole) in ethanol at 79° for 6 h yielded two degradation products: 54% 2,4-dinitrophenylhydrazine, m.p. and mixture m.p. with identical sample 197–198° (lit. m.p. 198°), $R_f = 0.52$ using ethanol – carbon tetrachloride (1:5 vol) as eluent.

Anal. Calcd. for $C_6H_6O_4N_4$: C, 36.37; H, 3.05; N, 28.28. Found: C, 36.54; H, 3.00; N, 27.95.

Also, 12% of a compound with empirical formula $C_6H_8O_3N_6$, possibly 2-nitro-4-aminoazoxyphenylhydrazine, m.p. 204–205°, $R_f = 0.03$ using ethanol – carbon tetrachloride (1:5 vol) as eluent, ν_{max} (Nujol) 3315, 3240 (NH), 1615 (phenyl), 1530 (NO_2), 1445 (phenyl), 1335 (NO_2), 1290 (N—N→O), 875, 830, 800 cm^{-1} (phenyl). Nuclear magnetic resonance (DMSO + TMS): 6.86 (5H, broadened singlet, O←N═N—NH_2, NH—NH_2), 7.86 (2H, doublet, 5-H, 6-H) and δ 8.49 (1H, quadruplet, 3-H).

Anal. Calcd. for $C_6H_8O_3N_6$: C, 33.96; H, 3.80; N, 39.61. Found: C, 33.86; H, 3.63; N, 39.80.

1(2,4-Dinitrophenyl)-3-phenyl-5-chloropyrazole and Hydrazine Hydrate

1(2,4-Dinitrophenyl)-3-phenyl-5-chloropyrazole (0.01 mole) and hydrazine hydrate (0.011 mole) in ethanol heated at 79° for 6 h gave 45% 2,4-dinitrophenylhydrazine, m.p. and mixture m.p. 197–198°, $R_f = 0.52$ using ethanol – carbon tetrachloride (1:5 vol) as eluent.

Anal. Calcd. for $C_6H_6O_4N_4$: C, 36.37; H, 3.05; N, 28.28. Found: C, 36.74; H, 3.22; N, 27.75.

Reaction of 1,3-Disubstituted 5-Chloropyrazole Methochlorides with Hydrazine Hydrate

Hydrazine hydrate (4.3 g, 0.085 mole) was slowly added to a solution of each of the methochloride salts (14.5 g, 0.057 mole) in ethanol (100 ml). The resulting yellow solution was then heated for 12 h between 70–75° and then left to cool overnight. A small amount of 1,3-disubstituted 5-chloropyrazole hydrochloride which crystallized from the solution was removed by filtration and the solvent was then stripped from the filtrate under reduced pressure. The 1,3-disubstituted 5-hydrazinopyrazole methochloride then remained as a viscous residue.

1-Methyl-3-phenyl-5-hydrazinopyrazole Methochloride

This compound was obtained as a pale-violet solid by treating the above residue with benzene (250 ml) followed by vigorous stirring. Recrystallization from chloroform gave white needles, m.p. 94–95° (6.4 g, 40%). A positive test was obtained for ionic chlorine. ν_{max} (Nujol) 3400, 3320 (NH), 3160 br (OH), 1675 (NH_2), 1610 (C═N), 1595, 765, 700 cm^{-1} (phenyl).

Anal. Calcd. for $C_{11}H_{15}N_4Cl \cdot 1.5\ H_2O$: C, 49.72; H, 6.83; N, 21.08; Cl, 13.34. Found: C, 50.03; H, 7.16; N, 20.69; Cl, 13.66.

The compound was also isolated as a hydrate with 1/2 molecule of water of crystallization, m.p. 138–139°.

Anal. Calcd. for $C_{11}H_{15}N_4Cl \cdot 0.5\ H_2O$: C, 53.33; H, 6.51; N, 22.62. Found: C, 53.24; H, 6.49; N, 22.05.

1-Phenyl-3-methyl-5-hydrazinopyrazole Methochloride

Treatment of the above residue with an ethanol–ether mixture gave a cream-colored precipitate. The compound was recrystallized from an ethanol–ether mixture as white clustered rods. A positive test for ionic chlorine was obtained, m.p. 209–210° (6.6 g, 41%), ν_{max} (Nujol) 3260, 3140, 1640 (NH), 1560, 1535, 735, 695 cm^{-1} (phenyl).

Anal. Calcd. for $C_{11}H_{15}N_4Cl$: C, 55.35; H, 6.33; N, 23.47; Cl, 14.85. Found: C, 55.13; H, 6.42; N, 23.91; Cl, 14.88.

Reactions of Substituted 5-Chloropyrazoles and Guanidine

The substituted 5-chloropyrazoles listed in Table IV were respectively dissolved in an appropriate solvent to which an ethanolic solution of guanidine was added according to the molar ratio given in Table IV. The mixture was then stirred and the reaction followed by means of thin-layer chromatography, while a temperature increase of 5° every 20 min was maintained until the desired temperature was reached. At the maximum concentration of the intermediate or product formed, a

TABLE III

Chemical analysis and infrared absorption data

Compound	Formula	Calculated (%)			Found (%)			ν_{max}(Nujol)*
		C	H	N	C	H	N	
21	$C_{16}H_{16}N_6$	65.74	5.52	28.75	65.53	5.50	28.63	3450 (NH), 3240 (NH), 1640 (NH), 1525, 1450 (phenyl), 1360 (C—N) arom., 770, 760, 720, 685 (phenyl).
22	$C_{21}H_{18}N_6$	71.17	5.19	23.71	71.16	5.15	23.27	3380, 3290 (NH), 1595 (C=N), 1585, 1490, 1450, 765, 750, 710, 685 (phenyl).
23	$C_{21}H_{17}O_2N_7 \cdot \frac{1}{2}C_2H_5OH$	62.55	4.77	23.21	63.56	4.60	23.38	3390, 3340 (NH), 1630 (NH), 1545 (NO_2), 1500, 780, 750, 685 (phenyl).
24	$C_{21}H_{17}O_2N_7$	63.15	4.29	24.55	63.46	4.29	24.55	3380, 3290 (NH), 1610 (C=N), 1585 (phenyl), 1520 (NO_2), 1480, 1450 (phenyl), 1340 (NO_2), 860, 795, 725, 710, 690 (phenyl).
25	$C_8H_{12}O_4N_8Cl_2$†	27.06	3.41	31.55	26.69	3.57	31.87	3360, 3300 (NH), 1605 (C=N), 1510, 1340, 825 (NO_2).
26	$C_8H_{10}O_4N_8$	34.05	3.57	39.70	34.62	3.83	39.14	3360, 3310 (NH), 1600 (C=N), 1555, 1345, 825 (NO_2).
Dimer of **26**	$C_{16}H_{20}O_8N_{16}$	34.05	3.57	39.70	34.30	3.88	39.37	3370, 3310, 1645 (NH), 1585 (C=N), 1515, 1325 (NO_2), 1165 (CH_3).
27	$C_{32}H_{28}N_{10}$	69.55	5.11	25.46	70.32	4.93	25.60	No NH, 1595 (C=N), 1585, 1495, 740, 675 (phenyl).
28	$C_{42}H_{30}O_4N_{12} \cdot 1.5\,H_2O$	63.55	4.19	21.17	63.66	4.21	21.16	3350 (NH), 1530 (NO_2), 1450 (phenyl), 1345 (NO_2), 885, 795 (phenyl).
29	$C_{32}H_{26}N_8$	73.54	5.01	21.45	73.02	5.44	21.50	No NH, 1595 (C=N—), 1500, 1450 (phenyl), 1190 (CH_3), 750, 680 (phenyl).
30	$C_{42}H_{28}O_4N_{10}$	68.47	3.83	19.01	68.17	4.10	18.95	No NH, 1530 (NO_2), 1450 (phenyl), 1345 (NO_2), 890, 815, 770, 705 (phenyl).
31	$C_{42}H_{33}N_{11}$	72.92	4.81	22.27	72.88	5.50	21.61	3375 (NH), 1600 (C=N), 1580, 1525, 760, 725, 690 (phenyl).

*The infrared spectra of compounds **21**, **22**, **24**, **27**, **29**, and **31** were taken in KBr disks and are reported in cm^{-1} for the most characteristic bands (group assignments in parentheses.)
†Calculated for Cl: 19.96. Found: 19.33. Negative test obtained for Cl^-.

TABLE IV

Substituted 5-chloropyrazoles and guanidine

Substrate	Reaction solvent	Mole ratio of substrate to guanidine	Reaction temperature	Reaction time	Intermediates and products	Yield* %	Melting point (°C)	R_f†
14	ethanol	1:1.1	25°	15 min	*N,N'*-bis(3-methyl-4-nitro-5-chloro-2-pyrazolin-5-yl)-guanidine (**37**)	32* (*b*)	195–196°	—
					+			
					N-(3-methyl-4-nitro-5-pyrazolyl)-*N'*-(3-methyl-4-nitro-5-chloro-2-pyrazolin-5-yl)-guanidine (**38**)	61* (*b*)	184–185°	—
					+			
			75°	7 h	dimer of *N,N'*-bis(3-methyl-4-nitro-5-pyrazolyl)-guanidine	71* (*a*)	> 300°	—
15	ethanol – dimethyl formamide	1:1.7	40–70°	7 h	1-methyl-3-phenyl-4-benzazo-5-guanidopyrazole (**35**)	12* (*c*)	194–195°	0.37† (*d*)
					+			
			55–70°	7 h	*N,N'*-bis(1-methyl-3-phenyl-4-benzazo-5-guanylpyrazolyl)-amine (**41**)	11* (*c*)	214–216°	0.12† (*d*)
19	ethanol – dimethyl formamide	1:2.3	25–70°	6 h	1(3-nitrophenyl)-3-phenyl-4-benzazo-5-guanidopyrazole (**36**)	69* (*b*)	203–204°	0.67† (*e*)
12	ethanol	1:1.4	70°	4 h	1(4-nitrophenyl)-3-methyl-4-nitro-5-guanidopyrazole (**34**)	50* (*b*)	249–250°	0.75 (*f*)

*Recrystallization solvent: (*a*) 95% ethanol, (*b*) water, (*c*) ethanol–benzene.
†Eluent: (*d*) benzene, (*e*) ethanol – carbon tetrachloride 1:5 vol, (*f*) ethanol–chloroform 1:5 vol.

TABLE V

Chemical analysis and infrared absorption data

Compound	Formula	Calculated (%)			Found (%)			ν_{max}(Nujol)*
		C	H	N	C	H	N	
34	$C_{11}H_{11}O_4N_7$	43.28	3.63	32.12	43.68	3.67	31.73	3470, 3370 (NH), 1655 (C═N of guanidine), 1570 (phenyl), 1550 (NO_2), 1510 (phenyl), 1330 (NO_2), 845, 820 (phenyl).
35	$C_{17}H_{17}N_7 \cdot 2.5\ H_2O$	56.03	6.09	26.91	55.60	5.95	27.23	3430, 3300 (NH), 1655 (C═N of guanidine), 1580, 1500, 770, 685 (phenyl).
36	$C_{22}H_{18}O_2N_8$	61.96	4.25	26.28	61.87	4.49	26.02	3460, 3330 (NH), 1645 (C═N of guanidine), 1570 (phenyl), 1525, 1340 (NO_2), 790, 770, 730, 685 (phenyl).
37	$C_9H_{13}O_4N_9Cl_2$†	28.29	3.43	32.99	28.59	3.33	33.30	3450, 3380 (NH), 1670 (C═N of guanidine), 1500, 1345, 825 (NO_2), 760 (C—Cl).
38	$C_9H_{12}O_4N_9Cl$‡	31.27	3.50	36.46	31.55	3.61	36.25	3480, 3460, 3360 (NH), 1660 (C═N of guanidine), 1500, 1360, 820 (NO_2), 760 (C—Cl).
Dimer of **39**	$C_{18}H_{22}O_8N_{18}$	34.95	3.59	40.76	34.14§	3.99§	40.85	3400, 3330 (NH), 1665 (C═N of guanidine), 1540, 1350, 815 (NO_2).
41	$C_{34}H_{31}N_{13} \cdot 2\ H_2O$	62.09	5.36	27.68	62.38	5.48	27.27	3490, 3380, 3310 (NH), 1660 (C═N of guanidine), 1565, 1505, 770, 760, 690 (phenyl).

*Infrared spectra in cm^{-1} for the most characteristic bands (group assignments in parentheses).
†Calculated for Cl: 18.55. Found: 18.70. Negative test for Cl^-.
‡Molecular weight: Calculated: 345.7. Found (Rast method): 348. Positive test obtained for Cl; negative test obtained for Cl^-.
§Could not be purified further.

measured volume of the reaction mixture was withdrawn and the solvent evaporated under reduced pressure at 0–5° until the separation of solids occurred. The intermediates and products formed were then separated by fractional crystallization and recrystallized from an appropriate solvent. The main course of the reaction was carried on to completion, whereupon the reaction mixture was then concentrated under reduced pressure until separation of the final product was accomplished. The product, after filtration, was afterwards recrystallized from an appropriate solvent. Whenever a precipitate formed during the course of the reaction, the latter was separated by filtration and purified in the usual manner. The reaction was then repeated without the removal of the precipitate and carried on according to the method described above. The intermediates and products isolated are given in Table IV while their elemental analyses and principal infrared absorption bands are given in Table V.

1(4-Nitrophenyl)-3-methyl-4-nitro-5-nitroguanidopyrazole

1(4-Nitrophenyl)-3-methyl-4-nitro-5-guanidopyrazole (3.0 g, 0.01 mole) was added portionwise to a mixture of nitric (18.5 g, 0.20 mole, 70%) and sulfuric (51.6 g, 0.52 mole, 98%) acids between 0–5° while stirring vigorously. After all the guanidopyrazole was added, the reaction mixture was further stirred for 45 min at the above temperature and then allowed to rise slowly to 25°. The mixture was then poured over cracked ice and gradually a pale-green precipitate formed. When all the ice melted, the crude product was separated by filtration, washed with water, and dried. 1(4-Nitrophenyl)-3-methyl-4-nitro-5-nitroguanidopyrazole crystallized from ethanol (95%) in clustered rods, m.p. 193–194° (2.8 g, 77%), ν_{max}(Nujol) 3430, 3340 (NH), 3090 (OH), 1685 (NH), 1615 (C=N), 1580 (phenyl), 1530, 1335 (NO_2), 850, 845, 835 cm^{-1} (phenyl).

Anal. Calcd. for $C_{11}H_{10}O_6N_8 \cdot H_2O$: C, 35.87; H, 3.28; N, 30.42. Found: C, 35.99; H, 3.26; N, 30.41.

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