Synthesis and Some Reactions of 4*H*-Pyrazole Derivatives[1]

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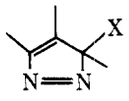
Chlorination of 1-hydroxypyrazoles and 1-hydroxypyrazole 2-oxides with *tert*-butyl hypochlorite produced 4-chloro-4*H*-pyrazole 1-oxides (**3**) and 1,2-dioxides (**4**), respectively, in good yields. Silver-assisted acetolysis and hydrolysis of **4** yielded the corresponding acetates and carbinols, but similar reactions with **3** led in acetic acid to 3-acetoxy-3*H*-pyrazole 1-oxides (**8**) and in water to decomposition of the heterocycle to acetylenes and carboxylic acids. Silver-assisted hydrolysis of a 4-chloro-4*H*-pyrazole (**15**) led to rearrangement to a 4,4-disubstituted 5-pyrazolone **16**.

Most of the reported chemistry of the nonaromatic isomers of the pyrazoles, the 3*H*- and 4*H*-pyrazoles (**1** and **2**, respectively), involves their rearrangement to the aromatic



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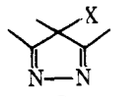

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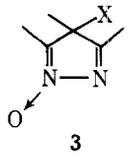
form (the van Alphen-Hüttel rearrangement[2]). We have now synthesized 4*H*-pyrazole 1-oxides and 1,2-dioxides containing functional groups which allow a study of substitution reactions in the pyrazole ring under conditions in which aromatization rearrangements are precluded.

Synthesis

Halogenation of 1-hydroxy-3,4,5-trisubstituted pyrazoles[3] and of their 2-oxides[3] produced the 4-halo derivatives corresponding to structures **3** and **4**, X = Cl (Table I). *tert*-Butyl



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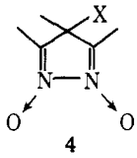

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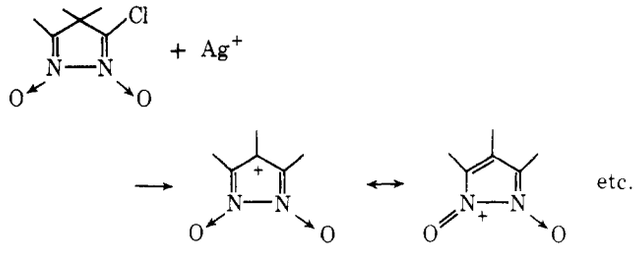
hypochlorite or gaseous chlorine worked equally well with the 1-hydroxy 2-oxides, but the 3,5-alkyl-substituted 1-hydroxypyrazoles suffered some side-chain halogenation when chlorine was used. No halogenation at any other ring position was observed. It had been reported previously that bromination of 3,4,5-trisubstituted pyrazoles gave unstable 4-bromo-4*H*-pyrazoles.[4,5] We have been able to obtain a pure crystalline 4-chloro-4*H*-pyrazole (**2**, X = Cl) but only from the 3,5-diphenyl derivatives. 3,5-Alkyl groups were chlorinated preferentially by both chlorine and *tert*-butyl hypochlorite. The *N*-oxygen substituent thus makes electrophilic substitution in the ring easier as might have been anticipated.

Lead tetraacetate oxidation of the 1-hydroxypyrazole 2-oxides yielded 4-acetoxy-4*H*-pyrazole dioxides (**4**, X = O_2CCH_3) but the yields from this reaction were uniformly low.

Some additional[6] 4-nitro-4*H*-pyrazole dioxides (**4**, X = NO_2) were prepared but they were too unstable to obtain pure samples.

Reactions

The 4-chloro-4H-pyrazole dioxides (**4**, X = Cl) reacted in a straightforward manner with both silver acetate in acetic acid and with silver nitrate in aqueous dioxane to produce the 4-acetoxy (**4**, X = CH_3CO_2) and 4-hydroxy (**4**, X = OH) derivatives. The mechanism of these reactions is not known but it is tempting to suggest that a cationic intermediate **5** is involved. Eschenmoser and co-workers[7] have shown that acyclic α-chloronitrones rapidly yield dienoid cations upon treatment with silver ion. While ion **5** might be considered



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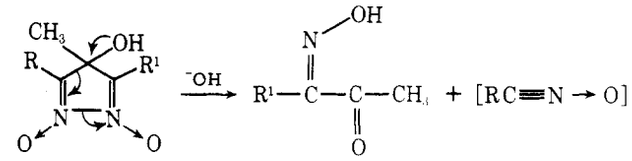
antiaromatic (4π electron monocycle), the effect of the two-electron-releasing oxygen atoms probably is dominant.

It was hoped that hydrolysis of the 4-acetoxy-4*H*-pyrazoles would provide a convenient source of the 4-carbinols, but the hydrolysis proved to be more complex than anticipated and synthetically useless. In large part the failure of this method was due to the instability of the carbinols in base. When carbinol **6a** was heated with aqueous methanolic potassium hydroxide, it was converted to 1-phenyl-1-oximinoacetone (**7a**) and diphenylfuroxan. Similarly, 2,3-butanedione monoxime (**7b**) was obtained from 4-hydroxy-3,4,5-trimethyl-4*H*-py-



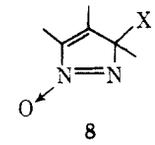
6a, R = R' = C_6H_5
b, R = R' = CH_3
c, R = CH_3, R' = C_6H_5

7a, R' = C_6H_5
b, R' = CH_3

razole 1,2-dioxide (**6b**), while the unsymmetrical carbinol **6c** gave a mixture of the two possible monoximes. The decomposition mode is pictured below; presumably the furoxan resulted from dimerization of benzonitrile oxide.

These monoximes were also obtained along with the carbinols from the acetate hydrolyses but in poor yield. The best route to the carbinols involves hydrolysis of the chlorides described above.

The 4-chloro-4*H*-pyrazole monoxides (**3**, X = Cl) reacted completely differently. Treatment of these compounds with silver acetate in acetic acid produced principally the 3-acetoxy-3*H*-pyrazoles (**8**, X = CH_3CO_2) accompanied in some instances by the expected derivative **3**, X = CH_3CO_2. Al-



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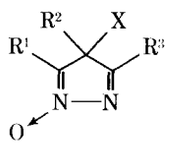
though it has been determined[8] that the 3-acetates (**8**, X = CH_3CO_2) can be thermally isomerized to the 4-acetates (**3**, X = CH_3CO_2), it is likely that the 4-acetates were direct products of the substitution reaction since the temperatures employed

Table I. 4*H*-Pyrazole Derivatives



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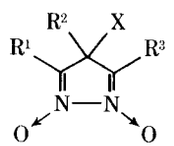

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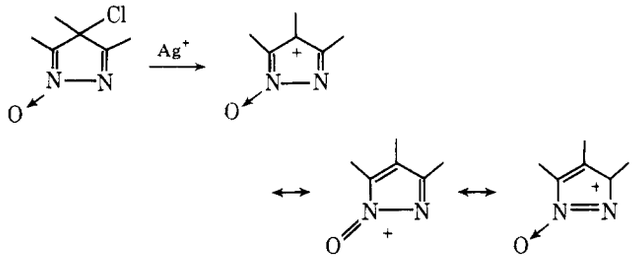
Compd	Registry no.	R^1	R^2	R^3	X	Yield	Mp, °C[d]	Procedure[e]	IR, cm^{-1} [a]	NMR, δ [b]
3a	61355-02-0	C_6H_5	CH_3	C_6H_5	Cl	97	113–115	A	1595, 1550	2.16 (s, CH_3)
3b	63689-82-7	CH_3	CH_3	CH_3	Cl	70	Oil[c]	A		
3c	63689-83-8	CH_3	CH_3	C_6H_5	Cl	77	62–64	A	1600, 1560	1.90 (s, $R^1 = CH_3$), 2.20 (s, $R^2 = CH_3$)
3d	63689-84-9	C_6H_5	CH_3	C_6H_5	CH_3CO_2	7	189–191	C	1755, 1610, 1565, 1540	1.93, 2.03 (s, CH_3)
3e	63689-85-0	CH_3	CH_3	C_6H_5	CH_3CO_2	4	Oil	C	1760, 1640, 1610	1.40, 2.10, 2.22 (s, CH_3)
3f	63689-86-1	C_6H_5	CH_3	C_6H_5	OH	20	243–244	Exptl section	3500, 1570	1.83 (s, CH_3), 6.90 (OH)
4a	61355-03-1	C_6H_5	CH_3	C_6H_5	Cl	86	143–145	A	1635	2.23 (s, CH_3)
4b	63689-87-2	CH_3	CH_3	CH_3	Cl	88	103–105	A	1660	1.85 (s, 4-CH_3), 2.25 (s, 3,5-CH_3)
4c	63689-88-3	CH_3	CH_3	C_6H_5	Cl	92	116–119	A	1665, 1615	2.03 (s, 4-CH_3), 2.34 (s, 3-CH_2)
4d	63689-89-4	CH_3	CH_3	$CH(CH_3)_2$	Cl	74	120–121	B	1665, 1660	1.35, 1.42, 2.97 [$CH(CH_3)_2$], 2.20 (s, 3-CH_3), 1.83 (s, 4-CH_3)
4e	61355-09-7	CH_3	C_6H_5	C_6H_5	Cl	90	127–128	B	1680, 1635	2.06 (s, CH_3)
4f	61355-07-5	CH_3	$C_6H_5CH_2$	C_6H_5	Cl	74	126–127	A	1695, 1640	2.40 (s, CH_3), 3.74 (AB quartet, CH_2)
4g	63689-90-7	Cl_3C	CH_3	Cl_3C	Cl	57	195–197	B	1500	2.25 (s, CH_3)
4h	63689-91-8	CH_3	CH_3	CH_3	CH_3CO_2	67	165–167	D	1755, 1670	1.58 (s, 4-CH_3), 2.10 (s, 3,5-CH_3, acetate CH_3)
4i	63689-92-9	CH_3	CH_3	$CH(CH_3)_2$	CH_3CO_2	70	155–156	Ref 3	1755, 1670, 1665	1.23, 1.33, 2.84 [$CH(CH_3)_2$], 1.60 (s, 4-CH_3), 2.02, 2.07 (s, 3-CH_3, acetate CH_3)
4j	63689-93-0	CH_3	CH_3	C_6H_5	CH_3CO_2	31	151–153	Ref 3	1750, 1670, 1615	1.80 (s, 4-CH_3), 2.08, 2.14 (s, 3-CH_3, acetate CH_3)
4k	63689-94-1	C_6H_5	CH_3	C_6H_5	CH_3CO_2	57	250–252	C	1750, 1635	2.03, 2.08 (s, 4-CH_3, acetate CH_3)
4l	63689-95-2	CH_3	C_6H_5	C_6H_5	CH_3CO_2	81	159–160	C	1750, 1680, 1640	1.93 (s, 3-CH_3), 2.15 (s, acetate CH_3)
4m	63689-96-3	CH_3	$C_6H_5CH_2$	C_6H_5	CH_3CO_2	76	155–156	C	1750, 1680, 1635	2.14 (s, 3-CH_3 and acetate CH_3), 3.51 (AB quartet, CH_2)
4n	63689-97-4	CH_3	CH_3	CH_3	OH	77	198–200	E	3300, 1665	1.50 (s, 4-CH_3), 2.05 (s, 3,5-CH_3), 6.10 (OH)
4o	17953-15-0	C_6H_5	CH_3	C_6H_5	OH	42	214–215	E	3300, 1625	1.78 (s, 4-CH_3), 5.28 (OH)
4p	63689-98-5	CH_3	CH_3	C_6H_5	OH	55	212–214	E	3320, 1670, 1630	1.75 (s, 4-CH_3), 2.10 (s, 3-CH_3), 7.20 (OH)
4q	63689-99-6	CH_3	CH_3	CH_3	NO_2	57	106–108	Ref 6	1680, 1560	
4r	17953-13-8	C_6H_5	CH_3	C_6H_5	NO_2	86	115	Ref 6	1640, 1545	2.35 (s, 4-CH_3)
4s	17953-14-9	CH_3	CH_3	C_6H_5	NO_2	94	107	Ref 6	1680, 1640, 1545	

[a] Measured in KBr disks. [b] Measured in $CDCl_3$ or CCl_4 at 60 mHz. [c] Used without further purification. [d] The chloro derivatives were crystallized from hexane or hexane–CH_2Cl_2. The acetates and carbinols were crystallized from methanol. [e] The procedures may be found in the Experimental Section.

(~10 °C) were much lower than those required for isomerization (100 °C).

The 3-acetoxy compounds again may arise from a cation **9**, which now is unsymmetrical and in which the electrophilic character is shared by positions 3 and 4. Analogous 3-methoxy derivatives (8, X = OCH_3)[9] were obtained when the reactions



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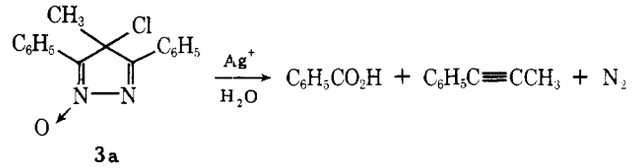
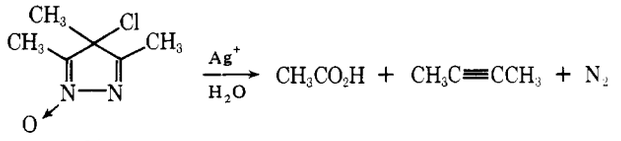
were carried out with silver nitrate in methanol, a result also suggestive of an ionic intermediate. However, it is also possible that the 3-derivatives are formed by an electrophilically assisted S_N2'-like reaction in which no cation is involved.

Reaction of the 4-chloro monoxides **3a** and **3b** with aqueous silver nitrate was more complex since it was accompanied by

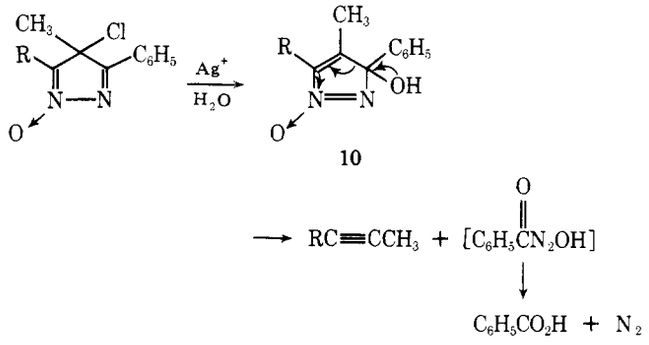


3a

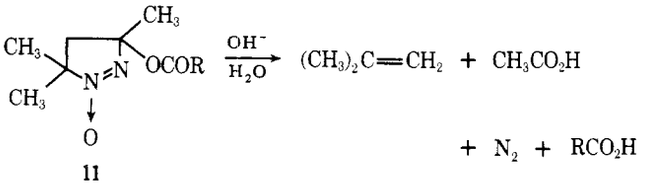


3b

complete destruction of the heterocycle. The products were acetylenes, carboxylic acids, and nitrogen. If water attacks the 3 position as do methanol and acetate ion, the intermediate carbinol **10** must unravel to the products observed:



This decomposition reaction is reminiscent of that of 3-acyloxy-Δ^1-pyrazoline 1-oxides (**11**) which produced alkenes, acids, and nitrogen upon hydrolysis.[10]



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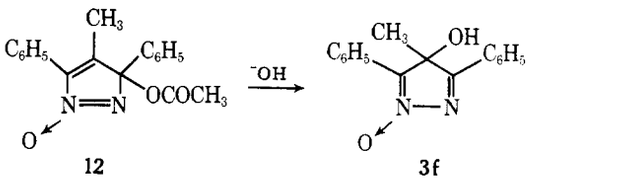
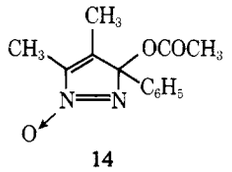
The hydrolysis of the 3-acetoxy-3*H*-pyrazole 1-oxides produced acetylenes and acids also. These hydrolyses were not completely straightforward, however, since some (20%) 4-hydroxy-4-methyl-3,5-diphenyl-4*H*-pyrazole 1-oxide (**3f**) was obtained from the hydrolysis of acetate **12**. Also hydrolysis of acetate **14**[3] produced 1-phenylpropyne rather than the



12 **3f**



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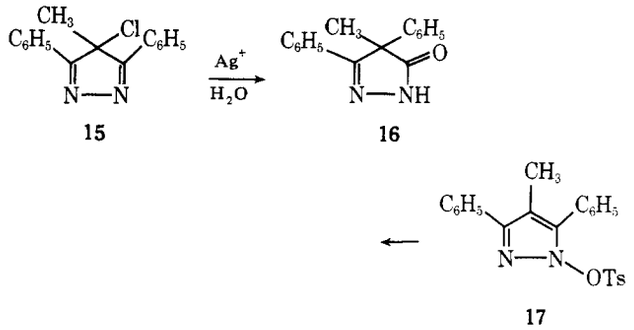
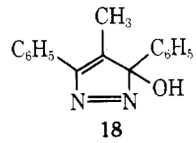
expected 2-butyne. It is not too surprising that nucleophilic attack occurs in the ring as well as at the acetate carbonyl group.

For comparison purposes hydrolysis of the parent 4-chloro-4*H*-pyrazoles was examined. Silver ion induced hydrolysis of the 4-chloro-4*H*-pyrazole (**15**) produced pyrazolone **16** in 78% yield. This same pyrazolone had been obtained[8] by hydrolysis of tosylate **17**. Since Closs and Heyn[4] had observed



15 **16** **17**

that reaction of a 4-bromo-4*H*-pyrazole with methanol yielded a 3-methoxy-3*H*-pyrazole, and in analogy to the silver ion assisted hydrolysis of the mono-*N*-oxides described above, it is reasonable to assume that carbinol **18** is an intermediate in these reactions.[11] The rearrangement of **18** to pyrazolone



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16 is analogous to that of 4-hydroxy-4*H*-pyrazoles to 2-pyrazolin-4-ones reported[13] recently although the present one occurs at much milder temperatures.[14]

It is interesting to contrast the rearrangement of these 3-hydroxy-3*H*-pyrazoles (assumed structure) to the fragmentations observed with 3-hydroxy-1-pyrazolines which lose nitrogen when treated with either acid (with the formation of unsaturated ketones) or base (with the formation of saturated but often rearranged ketones.)[15] It is not obvious why the presence of the conjugated olefinic bond so drastically changes the chemistry of the α-hydroxy azo functionality.

Experimental Section

Preparation of 4-Chloro-3,4,5-trisubstituted 4*H*-Pyrazole 1,2-Dioxides (4) (Table I). Procedure A. *tert*-Butyl hypochlorite (10% mol excess) was added to a stirred suspension of 1–5 mmol of the 1-hydroxy-3,4,5-trisubstituted pyrazole 2-oxide[3] in 20–50 mL of CH_2Cl_2 at 0 °C. The mixture was held at 0 °C for 30 min, allowed to warm to room temperature, and evaporated to dryness under reduced pressure. The oily solid residue was dissolved in 10 mL of CH_2Cl_2 and hexane was added to turbidity. Upon cooling a solid separated. It was collected and dried in a desiccator.

Procedure B. Chlorine gas was bubbled gently through a suspension of 1–5 mmol of the 1-hydroxy-3,4,5-trisubstituted pyrazole

2-oxide[3] in 50 mL of CH_2Cl_2 at 0 °C. Dissolved gases were removed with solvent by evaporation and the residue was crystallized as in procedure A.

4-Acetoxy-3,4,5-trisubstituted Pyrazole 1,2-Dioxides (Table I). Procedure C. A solution of 1–5 mmol of the 4-chloro-4*H*-pyrazole 1,2-dioxide in 10–25 mL of glacial acetic acid was treated with an equivalent of silver acetate at 25 °C. After stirring for 30 min the mixture was filtered and diluted with 150 mL of ice water. The solid which separated was collected by filtration and recrystallized from methanol or ether.

Procedure D. An equivalent of lead tetraacetate was added to a suspension of 10 mmol of 1-hydroxy-3,4,5-trisubstituted pyrazole 2-oxide[3] in 20–40 mL of CH_2Cl_2 at 0 °C. The mixture was stirred at 0 °C for 1 h and at 25 °C for 12 h. After it was filtered, the solution was washed with 10% Na_2CO_3 and saturated NaCl and dried. The solvent was evaporated and the oily residue was induced to crystallize by stirring in cold ether.

4-Hydroxy-3,4,5-trisubstituted Pyrazole 2-Oxides (Table I). Procedure E. A solution containing 3 mmol of $AgNO_3$ in 10 mL of H_2O was added to 3 mmol of the 4-chloro-4*H*-pyrazole 1,2-dioxide in 15 mL of dioxane; the resulting mixture was stirred at 25 °C for 15 min and filtered. The filtrate was diluted with H_2O and extracted with CH_2Cl_2. The organic extracts were dried and concentrated and the residue was chromatographed on silica. The desired carbinols were eluted with ethyl acetate. The aryl-substituted pyrazole dioxides produced small amounts of 2,5-disubstituted 3,4-diazacyclopentadienone 3,4-dioxides[6] also.

Alkaline Decompositon of 3,5-Diphenyl-4-hydroxy-4-methyl-4*H*-pyrazole 1,2-Dioxide (4o) (Table I). To a solution of 0.564 g (2 mmol) of **4o** in 20 mL of CH_3OH was added 5 mL of 0.4 M KOH solution and the mixture was heated under reflux for 2 h. The cooled mixture was concentrated, extracted with ether, and worked up in the usual way. The concentrate was crystallized from CCl_4 to yield 0.25 g (75%) of 1-phenyl-1,2-propanedione 1-oxime (**7a**), mp 162–163 °C (lit.[16] mp 164–165 °C). The mother liquor from this crystallization was concentrated and chromatographed on silica. Elution with $CHCl_3$ gave 0.12 g (23%) of diphenylfuroxan, mp 113–115 °C (lit.[17] mp 114 °C).

The same procedure with carbinol **4n** produced 60% of 2,3-butanedione monoxime, mp 74–75 °C (lit.[18] mp 74.5 °C).

Chlorination of 1-Hydroxy-3,4,5-trisubstituted Pyrazoles. A slurry of the hydroxypyrazole[3] (3–10 mmol) in 50–100 mL of CH_2Cl_2 was treated with slightly less than an equivalent of *tert*-butyl hypochlorite at 0 °C. After stirring for 15 min, the mixture was concentrated and the residue was crystallized from hexane. (See Table I).

Silver-Assisted Acetolysis of 4-Chloro-4*H*-pyrazole 1-Oxides. These reactions were conducted in the same way as that described for the dioxides (procedure C) except that the mother liquor from the methanol recrystallization was concentrated and subjected to column chromatography with elution with benzene–ether mixtures.

Silver-Assisted Hydrolysis of 4-Chloro-4*H*-pyrazole 1-Oxides. Procedure E was followed except that the crude residue from the washing was chromatographed on silica. From 2.57 g of **3a** (Table I) there was obtained 0.54 g (52%) of 1-phenylpropyne by elution with hexane, bp 180–184 °C (lit.[19] bp 182–183 °C), and benzoic acid (0.72 g, 65%), eluted with ether.

A crude sample of 3,4,5-trimethyl-4-chloro-4*H*-pyrazole 1-oxide, prepared by procedure A, in 20 mL of dioxane was treated at −15 °C with aqueous $AgNO_3$. The reaction flask was connected to a trap held at −78 °C and the mixture was stirred for 2 h at room temperature. The contents of the cold trap were analyzed by infrared and NMR spectroscopy and identified as 2-butyne.

Alkaline Hydrolysis of 3,5-Diphenyl-4-methyl-3-acetoxy-3*H*-pyrazole 1-Oxide (12). A mixture of 0.62 g (2 mmol) of **12**[3] in 25 mL of dioxane and 0.3 g of KOH in 10 mL of water was heated under reflux for an hour, cooled, neutralized, and extracted with ether. The organic residue was chromatographed on silica and eluted with chloroform. There was obtained 47.2 mg (25%) of 1-phenylpropyne, 0.1 g (19%) of **3f** (Table I), and 35 mg (27%) of benzoic acid.

3,5-Diphenyl-4-chloro-4-methyl-4*H*-pyrazole (15). A solution of 2.44 g (0.01 mol) of 3,5-diphenyl-4-methylpyrazole[20] in 50 mL of CH_2Cl_2 was treated with 1.2 g (0.011 mol) of *tert*-butyl hypochlorite at 5 °C. After a few minutes the mixture turned bright yellow. After 15 min the mixture was concentrated to ~ 20 mL, diluted with 40 mL of hexane, and chilled. The bright yellow solid was collected and dried: mp 112–114 °C dec; IR (KBr) 1515 cm^{-1}; NMR (CCl_4) δ 1.99 (s, CH_3).

Anal. Calcd for $C_{16}H_{13}ClN_2$: C, 71.51; H, 4.88; Cl, 13.19; N, 10.42. Found: C, 71.38; H, 4.91; Cl, 13.11; N, 10.60.

Hydrolysis of 3,5-Diphenyl-4-chloro-4-methyl-4*H*-pyrazole. A solution of 0.1 g (0.4 mmol) of **15** in 20 mL of dioxane was treated at room temperature with an equivalent of $AgNO_3$ in 7 mL of H_2O. After stirring for 15 min, the mixture was filtered, diluted with water, and extracted with CH_2Cl_2. The dried extracts were concentrated and chromatographed on silica gel. Elution with benzene yielded 72 mg of 3,4-diphenyl-4-methyl-5-pyrazolone (**16**), mp 183–184 °C, identical in all respects with authentic material.[8]

Registry No.—**12,** 17953-47-8; **15,** 61355-01-9; 1-hydxoxy-3,5-diphenyl-4-methylpyrazole 2-oxide, 17953-33-2; 1-hydroxy-3,4,5-trimethylpyrazole 2-oxide, 17953-31-0; 1-hydroxy-4,5-dimethyl-3-phenylpyrazole 2-oxide, 15674-34-7; 1-hydroxy-4,5-dimethyl-5-isopropylpyrazol 2-oxide, 63690-00-6; 1-hydroxy-3,4-diphenyl-5-methylpyrazole 2-oxide, 63690-01-7; 1-hydroxy-5-methyl-4-benzyl-3-phenylpyrazole 2-oxide, 63690-02-8; 1-hydroxy-3,5-trichloromethyl-4-methylpyrazole 2-oxide, 63690-03-9; 3,5-diphenyl-4-methylpyrazole, 17953-46-7.

References and Notes

(1) This research was supported in part by a grant from the National Cancer Institute, National Institutes of Health, CA 10742.
(2) For leading references to these reactions, see R. K. Bramley, R. Grigg, G. Guilford, and P. Milner, *Tetrahedron,* **29,** 4159 (1973).
(3) J. P. Freeman and J. J. Gannon, *J. Org. Chem.,* **34,** 194 (1969).
(4) G. L. Closs and H. Heyn, *Tetrahedron,* **22,** 463 (1966).
(5) P. Bouchet, J. Elguero, R. Jacquier, and F. Forissier, *C. R. Hebd. Seances Acad. Sci., Ser. C,* **269,** 570 (1969).
(6) J. P. Freeman, J. J. Gannon, and D. L. Surbey, *J. Org. Chem.,* **34,** 187 (1969).
(7) U. M. Kemper, T. K. Das Gupta, K. Blatt, P. Gygax, D. Felix, and A. Eschenmoser, *Helv. Chim, Acta,* **55,** 2187 (1972).
(8) J. P. Freeman and E. Janiga, *J. Org. Chem.,* **39,** 2663 (1974). That the 4-acetoxy derivative was the principal or only product of this substitution as reported herein is in error.
(9) F. T. Boyle and R. A. Y. Jones, *J. Chem. Soc., Perkin Trans. 1,* 167 (1973).
(10) J. P. Freeman, *Tetrahedron Lett.,* 749 (1961).
(11) A different mechanism based upon proposals for the conversion of 3-hydroxyindoles to oxindoles[12] was suggested previously[8] but seems less likely now.
(12) P. G. Gassman, G. A. Campbell, and G. Mehta, *Tetrahedron,* **28,** 2749 (1972).
(13) J. E. Baldwin, O. W. Lever, Jr., and N. R. Tzodikov, *J. Org. Chem.,* **41,** 2874 (1976).
(14) It is possible that the present rearrangement is of the 1,2-semipinacolic or semibenzilic acid type rather than a thermal 1,5-sigmatropic rearrangement, but no experiments to distinguish these possibilities have been carried out.
(15) J. P. Freeman and C. P. Rathjen, *J. Org. Chem.,* **37,** 1686 (1972).
(16) H. Rheinboldt and O. Schmitz-Dumont, *Justus Liebigs Ann. Chem.,* **444,** 113 (1925).
(17) N. E. Boyer, G. Snyder, H. R. Gutowsky, and H. R. Snyder, *J. Am. Chem. Soc.,* **77,** 4238 (1955).
(18) S. Mitchell and J. Cameron, *J. Chem. Soc.,* 1964 (1938).
(19) A. Wohl and K. Jaschinowski, *Ber.,* **61,** 1452 (1928).
(20) M. Lapp, F. Dallacker, and S. Munner, *Justus Liebigs Ann. Chem.,* **618,** 110 (1958).