Foundation (CHE 76 15652). Amino acid analyses were carried out by Mrs. Delores J. Gaut and elemental analyses by the Baron Consulting Co., Orange, CT.

Registry No. I, 17708-79-1; II, 71989-07-6; III, 71989-08-7; IV, 71989-09-8; V, 71989-10-1; VI, 71989-11-2; VII, 71989-12-3; F-Ala-OH, 35661-39-3; F-Ala-ONp, 71989-13-4; F-Asp(O-*t*-Bu)-OH, 71989-14-5; F-Asp(O-*t*-Bu)-ONp, 71989-15-6; F-Asn-OH, 71989-16-7; F-Asn-ONp, 71989-17-8; F-Glu(O-*t*-Bu)-OH, 71989-18-9; F-Glu(O-*t*-Bu)-ONp, 71989-19-0; F-Gln-OH, 71989-20-3; F-Gln-ONp, 71989-21-4; F-Gly-OH, 29022-11-5; F-Gly-ONp, 71989-22-5; F-Ile-OH, 71989-23-6; F-Ile-ONo, 71989-24-7; F-Leu-OH, 35661-60-0; F-Leu-ONp, 71989-25-8; F-Lys(BOC)-OH, 71989-26-9; F-Lys(BOC)-ONp, 71989-27-0; F-Met-OH, 71989-28-1; F-Met-ONp, 71989-29-2; F-Phe-OH, 35661-40-6; F-Phe-ONp, 71989-30-5; F-Pro-OH, 71989-31-6; F-Pro-ONp, 71989-32-7; F-Ser(*t*-Bu)-OH, 71989-33-8; F-Ser(*t*-Bu)-ONp, 71989-34-9; F-Thr(*t*-Bu)-OH, 71989-35-0; F-Thr(*t*-Bu)-ONp, 71989-36-1; F-Trp-OH, 35737-15-6; F-Trp-ONp, 71989-37-2; F-Tyr(*t*-Bu)-OH, 71989-38-3; F-Tyr(*t*-Bu)-ONp, 71989-39-4; F-Tyr(Bzl)-OH, 71989-40-7; F-Tyr(Bzl)-OPcp, 71989-41-8; F-Val-OH, 68858-20-8; F-Val-ONo, 71989-42-9; [(benzyloxy)carbonyl]-L-valine *p*-nitrophenyl ester, 10512-93-3; L-leucine, 61-90-5; *o*-*tert*-butyl-L-threonine methyl ester HCl, 71989-43-0; pentachlorophenol, 87-86-5; *p*-nitrophenol, 100-02-7; *o*-nitrophenol, 88-75-5.

Halogenation of N-Oxygenated Pyrazoles. Preparation of N-Oxygenated 4-Halopyrazole and 4,4-Dihalo-4*H*-pyrazole Derivatives

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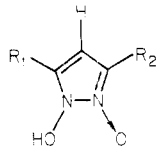
Reaction of some 1-hydroxypyrazoles and 1-hydroxypyrazole 2-oxides with iodine or with 1 equiv of *N*-chloro- or *N*-bromosuccinimide (NCS or NBS) gives high yields of the 4-halo derivatives. With 2 equiv of NBS or NCS or with *tert*-butyl hypochlorite the products are 4,4-dihalo-4*H*-pyrazole 1-oxides or 1,2-dioxides. Reaction of 3,5-diphenylpyrazole with 2 equiv of *tert*-butyl hypochlorite gives 1,4-dichloro-3,5-diphenylpyrazole, which rearranges to 4,4-dichloro-3,5-diphenyl-4*H*-pyrazole. Silver ion assisted solvolysis of the *gem*-dihalides to form 4-chloro-3*H*-pyrazole derivatives is described.

Freeman and co-workers have recently described the chlorination of 3,4,5-trisubstituted 1-hydroxypyrazoles and 1-hydroxypyrazole 2-oxides to give a series of novel 4-chloro-4*H*-pyrazole derivatives.[2] We wish to report the halogenation of some compounds of types **1** and **2**.[3] These



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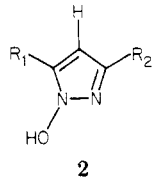


2

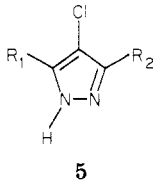
compounds undergo attack at C-4 as anticipated, but the absence of a group at that position permits aromatic substitution to occur, leading to the novel 4-halo-1-hydroxypyrazole 2-oxides and 4-halo-1-hydroxypyrazoles. Further halogenation may occur to give 4,4-dihalo-4*H*-pyrazole derivatives analogous to the 4-chloro-4*H*-pyrazoles reported by Freeman.

Results

Solutions of the 1-hydroxypyrazole 2-oxides (**1**) in aqueous ethanolic potassium carbonate reacted rapidly with 1 molar equiv of iodine–potassium iodide at room temperature, and the 4-iodo-1-hydroxypyrazole 2-oxides (**3**, X = I) precipitated upon acidification. Halogenation using *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) under similar conditions gave the corresponding **3** (X = Cl or Br). The 1-hydroxypyrazoles (**2**) could be halogenated in the same fashion to give 4-halo-1-hydroxypyrazoles (**4**). The results are summarized in Table I.

The properties of **3** are similar to those of other 1-hydroxypyrazole 2-oxides.[3,4] They exhibit limited solubility in most common solvents, give water-soluble alkali metal salts, and form complexes of their conjugate bases with transition-metal ions. The infrared and ^{1}H NMR spectra of **3** resemble those of **1**, except for the absence of the signal for the C-4 hydrogen in the NMR. The compounds **4** give broad absorptions in the infrared at 2400–2700 cm^{-1} and a highly variable signal between δ 8 and 12 in the ^{1}H NMR for the hydroxyl group.

Reduction of **3a** and **3d** with zinc in acetic acid gave the known 4-chloropyrazoles (**5**),[5] while reduction with sodium



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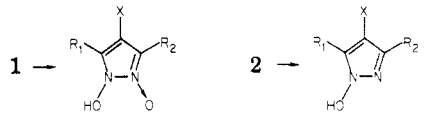
dithionite gave the 4-chloro-1-hydroxypyrazoles **4a** and **4d**. Reduction of **3** (X = Br or I) with either zinc or sodium dithionite resulted in reductive dehalogenation as well as deoxygenation. Dithionite reduction of **3h** gave a low yield of the previously unreported **2** (R_1 = R_2 = Me), but the major product of the reaction was 3,5-dimethylisoxazole, and small quantities of isoxazoles were also observed in some of the other dithionite reductions. Isoxazole formation by rearrangement of N-oxygenated azoles has been

(1) Visiting Research Professor, on leave from Hong-Ik University, Seoul, Korea.
(2) Freeman, J. P.; Janiga, E. R.; Lorenc, J. F. *J. Org. Chem.* **1977**, *42*, 3721.
(3) Hansen, J. F.; Vietti, D. E. *J. Org. Chem.* **1976**, *41*, 2871.
(4) Freeman, J. P.; Gannon, J. J. *J. Org. Chem.* **1969**, *34*, 194.
(5) Hansen, J. F.; Kim, Y. I.; Merrigan, K. A. *J. Org. Chem.*, in press.

0022-3263/80/1945-0076$01.00/0

Table I. Preparation of 4-Halo-1-hydroxypyrazole 2-Oxides (3) and 4-Halo-1-hydroxypyrazoles (4)

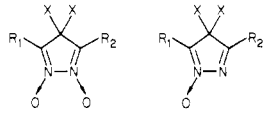


3 4

R_1	R_2	X	compd[a]	yield, %	mp, °C[b]	compd[a]	yield, %	mp, °C
Ph	Ph	Cl	3a	94	159	4a	98	190-192
Ph	Ph	Br	3b	93	157	4b	95	163-164
Ph	Ph	I	3c	88	145	4c	91	138-139
Me	Ph	Cl	3d	94	165	4d	92	161-162
Me	Ph	Br	3e	90	156	4e	92	141-142
Me	Ph	I	3f	94	137	4f	98	115-117
Me	Me	Cl				4g	85	176-178
Me	Me	Br	3h	98[c]	137	4h	84	174-175
Me	Me	I				4i	71	138-139

[a] Compounds gave satisfactory analyses for C, H, and N, except for 4c, 4f, and 4i, which were satisfactorily analyzed as the respective *O*-benzoyl derivatives, mp 152-153, 135-136, and 109-110 °C. [b] Compounds decompose sharply, but values are strongly influenced by heating rate and trace impurities; values reported are the highest observed. [c] From reduction of 6e with sodium borohydride.

Table II. Preparation of 4,4-Dihalo-4*H*-pyrazole Derivatives



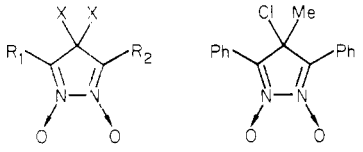
6 8

compd[a]	R_1	R_2	X	yield, %	mp, °C	IR,[b] cm^{-1}	UV-vis,[b] nm (log ε)
6a	Ph	Ph	Cl	75	163-165	1640, 1340	365 (3.94), 260 (4.32, sh), 249 (4.41)
6b	Me	Ph	Cl	87	145-147	1675, 1635, 1325	337 (3.67), 256 (4.24)
6c	Ph	Ph	Br	86	98-101	1635, 1340	380 (3.73), 255 (4.43)
6d	Me	Ph	Br	78	96-97	1665, 1625, 1325	350 (3.49), 278 (3.96, sh), 248 (4.25)
6e	Me	Me	Br	82	83-84[c]	1660, 1325	274 (3.96)
8a	Ph	Ph	Cl	92	130-131	1550	400 (3.76), 289 (4.05), 270 (4.12)
8b	Me	Ph	Cl	88	86-87	1600	354 (3.26), 285 (3.91), 240 (3.91)
8c	Me	Me	Cl	98	103-104	1515	300 (3.00, sh), 251 (3.89)

[a] Compounds gave satisfactory analyses for C, H, and N, except for 8b, which was not sufficiently stable. [b] Run in solution in $CHCl_3$. [c] Reported melting point 87-89 °C; see ref 9.

observed for phenylisatogen,[6] 3-oxo-3*H*-pyrrole 1-oxides,[7] and 3*H*-pyrazole 1,2-dioxides,[8] and the current rearrangement may proceed through a related ring opening–recyclization process.

Treatment of 3 with an additional equivalent of NBS or NCS produced the yellow 4,4-dihalo-4*H*-pyrazole 1,2-dioxides (6), which could be formed directly from 1 by



6 7

using 2 equiv of the reagent. Formation of 6 by halogenation of 3 is directly analogous to the preparation of 7 from 3,5-diphenyl-4-methyl-1-hydroxypyrazole 2-oxide reported by Freeman using *tert*-butyl hypochlorite.[2] The compounds 6 (X = Cl) could be prepared from 1 or from 3 by using 2 or 1 equiv of *tert*-butyl hypochlorite, respectively, under the conditions reported for the preparation of 7.

The 4,4-dihalo-4*H*-pyrazole 1-oxides 8 could not be prepared conveniently by using NCS or NBS. However, by using Freeman's method, the conversion of 4 (X = Cl) to 8 with *tert*-butyl hypochlorite was readily accomplished. The results and spectral characteristics of the compounds 6 and 8 are summarized in Table II.

Since 1 ($R_1 = R_2 = Me$) remains unknown, an alternate route was applied for the preparation of 6e (see Table II). Recently it was reported that this compound could be formed from the dioxime 9 of 2,4-pentanedione by treatment with sodium hypobromite.[9] Moderate yields of 6e were obtained by using this method, but superior results were realized when the reaction was modified by using *N*-bromoacetamide (NBA) in place of sodium hypobromite. The compound 6e thus prepared provided the entry to all of the 3,5-dimethylpyrazole derivatives described through the sequence summarized in eq 1.

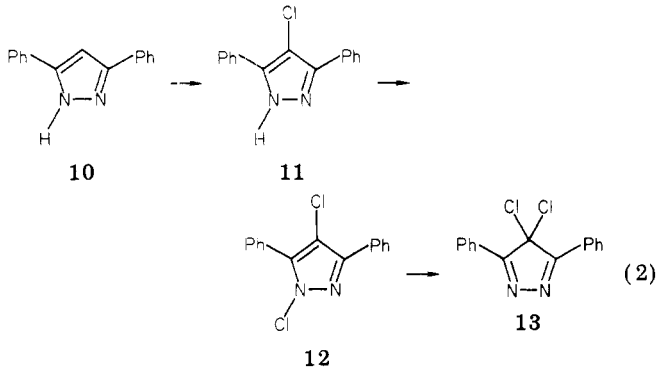
$$\underset{\mathbf{9}}{MeC(NOH)CH_2C(NOH)Me} \xrightarrow{NBA} \mathbf{6e} \xrightarrow{NaBH_4} \mathbf{3h} \xrightarrow{Na_2S_2O_4} 2\ (R_1 = R_2 = Me) \quad (1)$$

A key step in the sequence shown above was the reduction of the 4,4-dibromo-4*H*-pyrazole 1,2-dioxide 6e with sodium borohydride to the 4-bromo-1-hydroxypyrazole 2-oxide 3h. This reaction was very general for the *gem*-dihalides, permitting the reduction of 6 and 8 to the corresponding 3 and 4 in nearly quantitative yield. The re-

(6) Pinkus, J. L.; Woodyard, G. G.; Cohen, T. *J. Org. Chem.* **1965**, *30*, 1104.
(7) Jones, R. A. Y.; Sadighi, N. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2259.
(8) Freeman, J. P. *J. Org. Chem.* **1962**, *27*, 1309.
(9) Volodarskii, L. B.; Tikhonova, L. A. *Khim. Geterotsikl. Soedin.* **1977**, 248.

duction was quite vigorous in the case of **6e**, with evolution of a gas assumed to be hydrogen. The other dihalides behaved in a similar manner, except that they were reduced more slowly. No overreduction was observed, even with large excesses of sodium borohydride and prolonged reaction times.

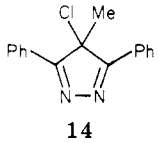
The chlorination of 3,5-diphenylpyrazole (**10**) proceeded in a stepwise fashion when *tert*-butyl hypochlorite was added gradually to an ice-cooled suspension of **10** in dichloromethane (eq 2). By use of ^{1}H NMR it was observed



10 **11** **12** **13** (2)

that the first equivalent of chlorine was introduced at C-4 to give 4-chloro-3,5-diphenylpyrazole (**11**). Introduction of the second equivalent of *tert*-butyl hypochlorite did not result in further attack at C-4 but gave a product assigned as the 1,4-dichloropyrazole **12**, which isomerized to the *gem*-dihalide **13** over a few hours in solution at 0 °C or more rapidly at higher temperatures. The novel *N*-chloropyrazole **12** could be isolated and recrystallized if heating or undue exposure to light was avoided. The white solid **12** was fairly stable when stored in the cold, but it was converted to the bright yellow **13** on standing for several hours at room temperature.

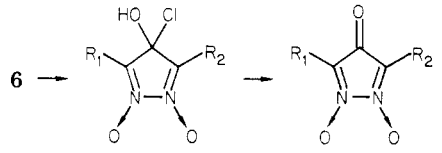
Structure **12** was assigned from its spectral properties, particularly ^{1}H NMR, which clearly showed the nonequivalence of the two phenyl substituents, with the ortho protons of one ring significantly more deshielded than the other aromatic protons. In contrast, the ^{1}H NMR spectrum of **13** shows two complex multiplets with an integration ratio of 2:3 for the two equivalent phenyl groups, the four protons in the ortho positions appearing at considerably greater chemical shift than the remaining protons. The spectral properties of **13** are otherwise similar to those of **14**.[2]



14

The N-chlorination of **11** rather than direct introduction of the second chlorine at C-4 may be the result of the electron-withdrawing inductive effect of the first chlorine, which serves to deactivate C-4 toward further electrophilic attack. Indeed, the only previously reported N-chlorination of the pyrazole ring is the formation of 1-chloro-4-nitropyrazole from 4-nitropyrazole reported by Huttel.[10] The rearrangement of **12** to **13** is similar to the reported isomerization of 1-chloro- to 3-chloro-1,2,4-triazole[11] and is reminiscent of the rearrangement of 1-nitro-,[12] 1-methoxy-,[13] and 1-(acyloxy)pyrazoles.[14]

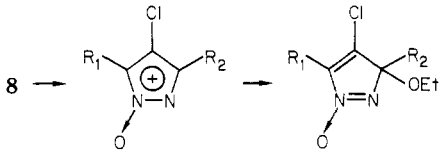
The 4,4-dihalo-4*H*-pyrazole derivatives undergo silver ion promoted solvolysis reactions which are similar to those reported by Freeman for the analogous 4-chloro-4*H*-pyrazoles.[2] The compounds **6** are converted to the known 4-oxo-4*H*-pyrazole 1,2-dioxides[15] by reaction with aqueous ethanolic silver nitrate, probably through the intermediate substitution product shown (eq 3). This transformation



(3)

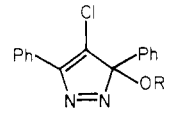
is not surprising, since the conversion of **6e** to the corresponding 4-oxo-4*H*-pyrazole 1,2-dioxide has been reported to occur upon heating in ethanol, even in the absence of silver ion.[9]

The 4,4-dichloro-4*H*-pyrazole 1-oxides (**8**) react in a different manner with ethanolic silver nitrate, undergoing ethanolysis with rearrangement to the 4-chloro-3-ethoxy-3*H*-pyrazole 1-oxides (**16**) (eq 4). The possible interme-



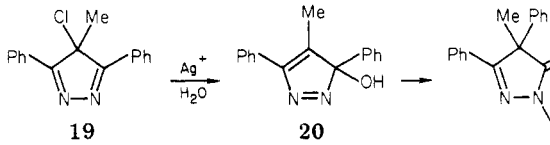
15 **16** (4)

diacy of a species such as **15** has been suggested to explain similar rearrangements in the solvolysis of 4-chloro-4*H*-pyrazole 1-oxides.[2] The same type of rearrangement also occurs in the reaction of **13** with ethanolic silver nitrate to give **17**. The alcohol **18** is formed as a byproduct in



17, R = Et
18, R = H

this reaction and is the major product when silver ion promoted hydrolysis is carried out in aqueous tetrahydrofuran. The isolation of **18** is of interest, because a structurally similar compound has been suggested, but not isolated, as a possible intermediate in the hydrolysis of **19** to give **21** (eq 5).[2] Since **18** does not exhibit any tendency



19 **20** **21** (5)

to rearrange to a pyrazolone, the intermediacy of **20** in the formation of **21** may merit further consideration.

Experimental Section

The compounds **1** were prepared as previously described[3] and were purified by recrystallization of their sodium salts from water or from ethanol–ether followed by reprecipitation with acetic acid. The compounds **2** were prepared by a modification of the method

(10) Huttel, R.; Schafer, O.; Welzel, G. *Justus Liebigs Ann. Chem.* **1956**, *598*, 186.
(11) Becker, H. G. O.; Ebisch, R. *J. Prakt. Chem.* **1972**, *314*, 923.
(12) Janssen, J. W. A. M.; Habraken, C. L.; Louw, R. *J. Org. Chem.* **1976**, *41*, 1758.
(13) Boyle, F. T.; Jones, R. A. Y. *J. Chem. Soc., Perkin Trans. 1* **1973**, 167.
(14) Freeman, J. P.; Janiga, E. *J. Org. Chem.* **1974**, *39*, 2663.
(15) Freeman, J. P.; Gannon, J. J.; Surbey, D. L. *J. Org. Chem.* **1969**, *34*, 187.

reported by reduction of 1 in refluxing ethanol–water with sodium dithionite. Infrared spectra were recorded with a Perkin-Elmer 700 or 710B spectrophotometer; ^1H NMR spectra were run in deuteriochloroform unless otherwise noted, with Me_4Si as an internal standard, by using a Perkin-Elmer R32 90-MHz spectrometer; and UV–vis spectra were run in chloroform on a Beckman Acta MVI spectrophotometer. Melting points were run in open capillary tubes with a Thomas-Hoover Uni-Melt apparatus, calibrated with standard samples. Elemental analyses were performed by Microanalysis, Inc., Wilmington, DE.

4-Iodo-1-hydroxypyrazoles and 4-Iodo-1-hydroxypyrazole 2-Oxides. A solution of 15 mmol of **1** or **2** in 50 mL of 10% aqueous K_2CO_3 and sufficient 95% ethanol to maintain a homogeneous solution was stirred at room temperature and treated over 15 min with 30 mL of 0.5 M I_2–KI solution. After an additional 15 min the solution was cooled in ice and acidified with acetic acid. The product was collected, washed with water, and dried over P_2O_5 at 0.1 torr.

Bromination or Chlorination of 1-Hydroxypyrazoles and 1-Hydroxypyrazole 2-Oxides. A solution of 15 mmol of **1** or **2** in 50 mL of 10% K_2CO_3 and sufficient 95% ethanol to maintain a homogeneous solution was stirred at 0–5 °C while 15.1 mmol of *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) was added in portions over 30 min. The resulting mixture was stirred at 0–5 °C for 30 min and was then allowed to warm to room temperature with continued stirring for 60 min. The mixture was cooled and filtered, and the filtrate was acidified with acetic acid. The products were collected, washed with water, and dried at 0.1 torr over P_2O_5.

4,4-Dihalo-4*H*-pyrazole 1,2-Dioxides (6). A solution of 15 mmol of **1** in 50 mL of 10% K_2CO_3 and 50 mL of ethanol was stirred at 15 °C while 30 mmol of NBS or NCS was added over 45 min. When addition was complete, the mixture was allowed to warm to room temperature with continued stirring for 60 min. The mixture was cooled and filtered, and the solid was washed with water and with 50% ethanol. The product, a yellow solid, was dried over P_2O_5 at 0.1 torr. The compounds were recrystallized from $CHCl_3$–hexane.

4,4-Dichloro-4*H*-pyrazole 1-Oxides (8). A mixture of 2 mmol of **2** in 10 mL of CH_2Cl_2 was stirred below 0 °C in an ice–salt bath while 4 mmol of *tert*-butyl hypochlorite[16] was added dropwise. After the mixture was stirred in the cold for 15–60 min, the solvent was evaporated under reduced pressure without heating. The residual **8** was recrystallized from CH_2Cl_2–pentane without heating.

4,4-Dibromo-3,5-dimethyl-4*H*-pyrazole 1,2-Dioxide (6e). A mixture of 22.1 g (0.16 mmol) of *N*-bromoacetamide in 200 mL of H_2O was stirred at 0 °C, and 5.20 g (0.04 mol) of 2,4-pentanedione dioxime[17] was added in portions over 45 min. The resulting red mixture was stirred at 0–5 °C for 60 min, and the solid was filtered off, washed with cold water, and dried over P_2O_5 at 0.1 torr to give 9.42 g (82%) of **6e**, which was identical with a sample prepared by the method of Volodarskii and Tikhonova.[9] **Caution**: A crude sample stored in a brown vial at room temperature detonated after a few days, shattering the cap of the vial and releasing an acrid gas. The compound decomposes slowly, even when stored in the cold in the absence of light.

Reduction of Dihalides 6, 8, and 13 with Sodium Borohydride. A solution of 0.4 g of sodium borohydride in 30 mL of ethanol–water (2:1) was stirred at 0–5 °C while 2 mmol of the *gem*-dihalide was added over 30 min. Stirring in the cold was continued for 15–180 min until the reaction was complete. The cold mixture was acidified to a Congo red end point with HCl, and the product was collected, washed with water or with ethanol–water, and dried at 0.1 torr over P_2O_5. Yields greater than 90% were obtained in each case. The products were the corresponding **3**, **4**, or **11**.

3,5-Dimethyl-1-hydroxypyrazole (2, $R_1 = R_2 =$ Me). A solution of 87 g of sodium dithionite in 200 mL of water in a 1000-mL flask equipped with a condenser for reflux was treated with 18.2 g (0.09 mol) of 4-bromo-3,5-dimethyl-1-hydroxypyrazole 2-oxide (**3h**) and heated on a steam bath. Vigorous frothing occurred after a few minutes, and the stirred mixture was heated for 15 min. The mixture was cooled to room temperature, treated with 100 mL of pentane, and allowed to stand at 5 °C overnight. The solid 1-hydroxypyrazole was filtered off and washed with pentane. The pentane layer of the filtrate was separated, and the aqueous layer was extracted with three 200-mL portions of CH_2Cl_2. The combined organic solutions were washed with saturated NaCl, and the solvent was removed by fractional distillation at atmospheric pressure. The residual liquid was distilled to give 3.42 g (40%) of 3,5-dimethylisoxazole, bp 45–46 °C (20 torr), which was identical with an authentic sample. The pot residue consisted of an additional small quantity of the 1-hydroxypyrazole. Recrystallization from water gave 0.45 g (4.2%) of 3,5-dimethyl-1-hydroxypyrazole: mp 155–156 °C; IR (Nujol mull) 2450 cm^{-1} (br d, OH); ^1H NMR δ 12.27 (s, 1 H), 5.68 (s, 1 H), 2.24 (s, 3 H), 2.09 (s, 3 H).

Anal. Calcd for $C_5H_8N_2O$: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.52; H, 7.37; N, 24.91.

4-Oxo-4*H*-pyrazole 1,2-Dioxides from 6. To a solution of 4.4 mmol of $AgNO_3$ in 25 mL of 80% ethanol was added 2 mmol of **6**. The mixture was heated on a steam bath for 30 min and filtered hot to give 3.6–3.8 mmol of silver halide. The filtrate was concentrated and cooled to give 60–85% of the 4-oxo-4*H*-pyrazole 1,2-dioxide.[15]

1,4-Dichloro-3,5-diphenylpyrazole (12). A mixture of 1.27 g (5 mmol) of 4-chloro-3,5-diphenylpyrazole **11** in 25 mL of CH_2Cl_2 was stirred at 0–5 °C and treated with 0.61 g (5.5 mmol) of *tert*-butyl hypochlorite. The mixture was stirred at 0–5 °C for 15 min after all of the solid had dissolved and was concentrated under reduced pressure without heating to 5 mL, treated with 30 mL of pentane, and cooled to −20 °C until crystallization was complete. The solid, 1.10 g (76%), had a melting point of 89–92 °C: ^1H NMR δ 8.15 (m, 2 H), 7.50–7.90 (complex, 8 H). (When the sample tube was allowed to stand at room temperature, the spectrum gradually changed to that reported for **13** below.)

4,4-Dichloro-3,5-diphenyl-4*H*-pyrazole (13). A mixture of 6.60 g (0.03 mol) of 3,5-diphenylpyrazole in 100 mL of CH_2Cl_2 was cooled in ice and treated with 8.64 g (0.08 mol) of *tert*-butyl hypochlorite. The solution was stirred overnight at room temperature and evaporated. The residual bright yellow solid was recrystallized from CH_2Cl_2–pentane to give 6.55 g (76%) of needles: mp 142–144 °C; IR (Nujol mull) 1532 cm^{-1}; ^1H NMR δ 8.41 (m, 4 H), 7.58 (m, 6 H).

Anal. Calcd for $C_{15}H_{10}N_2Cl_2$: C, 62.31; H, 3.49; N, 9.69; Cl, 24.52. Found: C, 62.11; H, 3.63; N, 9.56; Cl, 24.37.

4-Chloro-3-ethoxy-5-methyl-3-phenyl-3*H*-pyrazole 1-Oxide (16, $R_1 =$ Me; $R_2 =$ Ph). A solution of 1.55 g (9 mmol) of silver nitrate in 20 mL of 90% ethanol was stirred at room temperature while 1.10 g (4.5 mmol) of **8b** was added. The mixture was stirred for 60 min, and 0.64 g (4.5 mmol) of AgCl was filtered off. The filtrate was treated with 75 mL of H_2O and extracted with three 25-mL portions of ether. The ether extract was washed with H_2O and saturated NaCl and evaporated. The residue was extracted with boiling pentane, and the pentane solution was treated with 0.5 g of Norit A, boiled for a few minutes, and filtered. When the filtrate cooled, a solid precipitate, 0.89 g, formed. Recrystallization from 95% ethanol and then from pentane gave white flakes: mp 91–92 °C; IR (Nujol mull) 1705 (w), 1500 cm^{-1}; UV 247 nm (log ϵ 3.90); ^1H NMR δ 7.42 (m, 5 H), 3.52 (q, 2 H), 2.19 (s, 3 H), 1.28 (t, 3 H).

Anal. Calcd for $C_{12}H_{13}N_2O_2Cl$: C, 57.04; H, 5.18; N, 11.08. Found: C, 56.73; H, 5.45; N, 10.92.

4-Chloro-3,5-diphenyl-3-ethoxy-3*H*-pyrazole 1-Oxide (16, $R_1 = R_2 =$ Ph). Ethanolysis of **8a** by the above method gave the product as a white solid: mp 80–82 °C; IR (Nujol mull) 1690 (w), 1505 cm^{-1}; UV 265 nm (sh, log ϵ 3.87), 239 (4.25); ^1H NMR δ 7.3–7.85 (complex, 10 H), 3.64 (q, 2 H), 1.33 (t, 3 H).

Anal. Calcd for $C_{17}H_{15}N_2O_2Cl$: C, 64.87; H, 4.80; N, 8.89. Found: C, 64.67; H, 4.86; N, 8.73.

4-Chloro-3,5-dimethyl-3-ethoxy-3*H*-pyrazole 1-Oxide (16, $R_1 = R_2 =$ Me). Similar ethanolysis of **8c** gave the product as a white solid: mp 48–50 °C; IR (Nujol mull) 1710, 1502 cm^{-1}; UV 245 nm (log ϵ 3.89); ^1H NMR δ 3.20 (m, 2 H), 2.14 (s, 3 H), 1.58 (s, 3 H), 1.16 (t, 3 H).

Anal. Calcd for $C_7H_{11}N_2O_2Cl$: C, 44.11; H, 5.82. Found: C, 44.72; H, 5.76.

(16) Mintz, M. J.; Walling, C. "Organic Syntheses", Wiley: New York, 1973; Collect. Vol. V, p 184.
(17) Harries, C.; Haga, T. *Chem. Ber.* **1899**, *32*, 1191.

4-Chloro-3,5-diphenyl-3-ethoxy-3*H*-pyrazole (17). A mixture of 2.89 g (10 mmol) of **13** in 40 mL of ethanol (absolute) was treated with a solution of 1.7 g of silver nitrate in 1.5 mL of water and stirred at room temperature for 60 min. The AgCl was filtered off, and the filtrate was treated with 100 mL of ether, washed with four 50-mL portions of water and with 50 mL of saturated NaCl, and evaporated. The residue was treated with 50 mL of pentane and cooled, and 0.95 g of **18** was filtered off. The pentane filtrate was treated with 1 g of Norit A, heated on a steam bath, and filtered. Evaporation of the solvent gave 1.62 g of yellow oil which would not solidify on cooling and which decomposed upon attempted distillation: IR (neat) 1630 (w), 1493, 1470, 1450 cm^{-1}; UV-vis 405 nm (log ϵ 2.46), 320 (3.60), 242 (4.34); ^1H NMR δ 8.40 (m, 2 H), 7.25-7.65 (m, 8 H), 3.43 (q, 2 H), 1.31 (t, 3 H).

Anal. Calcd for $C_{17}H_{15}N_2OCl$: C, 68.34; H, 5.06; N, 9.37. Found: C, 68.69; H, 5.05; N, 9.17.

4-Chloro-3,5-diphenyl-3-hydroxy-3*H*-pyrazole (18). A solution of 2.89 g (10 mmol) of **13** in 40 mL of tetrahydrofuran was treated with a solution of 1.7 g of $AgNO_3$ in 10 mL of water and stirred at room temperature. After 75 min the AgCl was filtered off, and the filtrate was treated with 100 mL of ether. The ether solution was washed with two 50-mL portions of water and with 50 mL of saturated NaCl and evaporated under reduced pressure without heating. The pale yellow solid was recrystallized from CH_2Cl_2-pentane to give 2.58 g (95%) of **18**: mp 119-21 °C dec; IR (Nujol mull) 3230 (br d), 1630, 1490, 1455 cm^{-1}; UV-vis 385 nm (sh, log ϵ 2.54), 320 (3.56), 245 (4.30); ^1H NMR δ 8.22 (m, 2 H), 7.45 (m, 3 H), 7.35 (s, 5 H), 4.32 (br s, 1 H, exchanges with D_2O).

Anal. Calcd for $C_{15}H_{11}N_2OCl$: C, 66.55; H, 4.09; N, 10.35. Found: C, 66.33; H, 4.13; N, 10.36.

Reaction of **18** in benzene with acetyl chloride and pyridine gave the *O*-acetyl derivative, which was recrystallized as a yellow solid, mp 124-125 °C, from ether-pentane: IR (Nujol mull) 1760, 1625 (w), 1495, 1460 cm^{-1}; UV-vis 375 (sh, log ϵ 2.92), 325 (3.61), 245 (4.34); ^1H NMR δ 8.42 (m, 2 H), 7.35-7.80 (m, 8 H), 2.23 (s, 3 H).

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Registry No. **1**, $R_1 = R_2$ = Ph, 59434-82-1; **1**, R_1 = Me, R_2 = Ph, 55026-66-9; **1**, $R_1 = R_2$ = Me, 71989-58-7; **2**, $R_1 = R_2$ = Ph, 59434-85-4; **2**, R_1 = Me, R^2 = Ph, 59434-84-3; **2**, $R_1 = R_2$ = Me, 71989-59-8; **3a**, 71989-60-1; **3b**, 71989-61-2; **3c**, 71989-62-3; **3d**, 71989-63-4; **3e**, 71989-64-5; **3f**, 71989-65-6; **3h**, 71989-66-7; **4a**, 71582-22-4; **4b**, 71989-67-8; **4c**, 71989-68-9; **4d**, 71549-27-4; **4e**, 71989-69-0; **4f**, 71989-70-3; **4g**, 71989-71-4; **4h**, 71989-72-5; **4i**, 71989-73-6; **6a**, 71989-74-7; **6b**, 71989-75-8; **6c**, 71989-76-9; **6d**, 71989-77-0; **6e**, 62925-70-6; **8a**, 71989-78-1; **8b**, 71989-79-2; **8c**, 71989-80-5; **9**, 2157-56-4; **10**, 1145-01-3; **11**, 71549-28-5; **12**, 71989-81-6; **13**, 71989-82-7; **16**, R_1 = Me, R_2 = Ph, 71989-83-8; **16**, $R_1 = R_2$ = Ph, 71989-84-9; **16**, $R_1 = R_2$ = Me, 71989-85-0; **17**, 71989-86-1; **18**, 71989-87-2; **18**, *O*-acetyl derivative, 71989-88-3; 3,5-dimethylisoxazole, 300-87-8.

Substitution Reactions of Thallous Thiophenoxide and Thallous Phenylselenide with Halogen-Bearing Substrates

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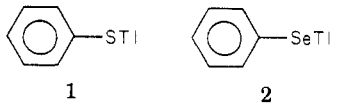
Thallous thiophenoxide (**1**) and thallous phenyl selenide (**2**) were prepared by the action of either thallous ethoxide or thallous phenoxide on thiophenol and benzeneselenol. The reagents **1** and **2** reacted readily with aroyl and acyl halides, imidoyl chlorides, α-halo ketones, α-halo esters, α-halo lactones, α-halo carboxylic acids, allyl halides, alkyl halides, chlorotrimethylsilane, chloroacetonitrile, and *N*-chlorosuccinimide to give substitution products and varying amounts of diphenyl disulfide and diphenyl diselenide. The reactions were run as heterogeneous mixtures in ether. The origin of the diphenyl disulfide and diphenyl diselenide was homolytic cleavage of the thallium-sulfur or thallium-selenium bond, on the basis of the products derived from the reactions of *N*-chlorosuccinimide with **1** and **2**.

The utility of thallium(I) salts of organic acids in synthesis was first reported by Taylor and McKillop in 1968.[1,2] They found that thallium(I) salts of β-dicarbonyl compounds were readily C-alkylated or C- or O-acylated[1] and that the thallous salts of phenols and carboxylic acids were excellent reagents for preparing phenyl esters and anhydrides, respectively, from acyl halides.[2] Since these initial papers, surprisingly little chemistry has been reported on thallium salts of other acidic groups. Recently, the reactions of thallous aliphatic sulfides with acyl halides and α-halo ketones have been noted[3] as well as an isolated example of the reaction of a heteroaromatic thallous sulfide with an acyl halide.[4] We wish to report related work on the scope and limitations of substitution reactions of various halogen-containing compounds with thallous thiophenoxide (**1**) and thallous phenyl selenide (**2**).



1 2

Results

The reagents **1** and **2** are prepared by the dropwise addition of thallous ethoxide to a solution of thiophenol or benzeneselenol, respectively, in hexane-ether. The thallous ethoxide should be clear and colorless to avoid side reactions. The thallous thiophenoxide (**1**) is isolated as a yellow solid, mp 260-265 °C (lit.[5] mp 258-260 °C), in nearly quantitative yield. Similarly, thallous phenyl sel-

(1) Taylor, E. C.; Hawks, G. H., III; McKillop, A. *J. Am. Chem. Soc.* **1968**, *90*, 2421.
(2) Taylor, E. C.; McLay, G. W.; McKillop, A. *J. Am. Chem. Soc.* **1968**, *90*, 2422.
(3) Nagao, Y.; Ochiai, M.; Kaneko, K.; Maeda, A.; Watanabe, K.; Fujita, E. *Tetrahedron Lett.* **1977**, 1345. Masamune, S.; Kamata, S; Schilling, W. *J. Am. Chem. Soc.* **1975**, *97*, 3515.
(4) Nagao, Y.; Kawabata, K.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1978**, 330.
(5) Gilman, H.; Abbott, R. K. *J. Am. Chem. Soc.* **1949**, *71*, 659.

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