flame-dried and charged with freshly prepared trimethylsilyl iodide[3] (32.8 g, 0.164 mol) dissolved in anhydrous ether (20 mL). At 0 °C 2-methyl-2-butene[5] (1 mL) was added followed by a dropwise addition of *N,N,N',N'*-tetramethylmethylenediamine[6] (16.8 g, 0.164 mol) in anhydrous ether (20 mL). A white precipitate formed immediately and this mixture was allowed to stir for 20 min. The precipitate was collected by vacuum filtration and washed with anhydrous ether (3 × 75 mL), air-dried, and rapidly[7] transferred to a vacuum desiccator for storage affording **1a**: yield 29.1 g, 96%; sublimed [140 °C (0.25 torr)] or recrystallized from sulfolane;[2] ^{1}H NMR (Me_4Si, Me_2SO-d_6) δ 3.6 (s, 6 H), 8.2 (s, 2 H); IR (Nujol) ν_{max} 3115, 1682 cm^{-1}.

3-[(Dimethylamino)methyl]anisole (5). Compound **5** was prepared from *m*-bromoanisole by the procedure of Poulter et al.[1d] in 86% yield: IR (neat film) ν_{max} 2780, 1600, 1145, 775 cm^{-1}; ^{1}H NMR (Me_4Si, CCl_4) δ 2.10 (s, 6 H), 3.25 (s, 2 H), 3.60 (s, 3 H), 6.50–7.20 (m, 4 H); mass spectrum *m/e* 165 (M^+).

(Aminomethyl)cyclopentene 7. The metalation of **7** was accomplished by the procedure of Smith.[9] The amine salt **1a** was added as a solid at −78 °C, and the solution was allowed to warm to room temperature and stirred for 2 h. Water was added and the solution was extracted with ether. The combined organic extracts were washed with water and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo, leaving a dark brown oil. To the crude oil stirred at room temperature was added excess methyl iodide. The solid produced was filtered by suction and washed with hexane: ^{1}H NMR (Me_4Si, $CDCl_3$) δ 5.7 (m, 1 H), 4.7 (m, 2 H), 3.7 (m, 2 H), 3.3 (s, 9 H), 2.3 (m, 2 H), 1.2 (m, 6 H).

4-(Carboethoxy)-4-[(dimethylamino)methyl]-3-isochromanone (9). A solution of 4-(carboethoxy)-3-isochromanone (**8**) (1.00 g, 4.55 mmol) in dry THF (4 mL) was added dropwise to a suspension of NaH dispersion (50%, 0.23 g, and the mixture was washed with hexane (3 × 10 mL)) at 0 °C under N_2 and stirred at 25 °C for 10 min. To this solution was added salt **1a** (930 mg, 5.00 mmol) as a solid in one portion, and the mixture was allowed to stir at 25 °C for 2 h. Following addition of water (20 mL), the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined CH_2Cl_2 extracts were washed with water (2 × 20 mL) and 10% HCl (4 × 10 mL). The acid washes were combined and extracted with Et_2O (20 mL), made basic to litmus with 10% K_2CO_3, and extracted with CH_2Cl_2 (3 × 20 mL). The CH_2Cl_2 extracts were combined, washed with water (2 × 20 mL) and brine (20 mL), dried with $MgSO_4$, and evaporated to dryness to give 0.781 g (62%) of a clear colorless viscous oil: IR (neat film) ν_{max} 2780, 1740, 1725 cm^{-1}; ^{1}H NMR (Me_4Si, $CDCl_3$) δ 1.29 (t, 3 H, *J* = 8 Hz), 2.00 (s, 6 H), 3.25 (AB q, 2 H, J_1 = 38 Hz, J_2 = 14 Hz), 4.18 (q, 2 H, *J* = 8 Hz), 5.35 (AB q, 2 H, J_1 = 30 Hz, J_2 = 16 Hz), 7.1–7.5 (m, 4 H); mass spectrum *m/e* 277 (M^+).

(Dimethylamino)methyl Phenyl Sulfide (11). To a stirred suspension of NaH (50%, 0.48 g, 9.99 mmol) in THF (20 mL) was slowly added thiophenol (1.00 g, 9.09 mmol) at room temperature under N_2. After 0.5 h, the salt **1a** was added as a solid and the resulting solution stirred overnight. Following addition of water (20 mL), the resulting mixture was extracted with ether (3 × 20 mL), and the combined organic extracts were washed successively with a saturated aqueous $NaHCO_3$ solution, water, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo, leaving a yellow oil. Bulb-to-bulb distillation at 80 °C (5 mm) yielded a clear oil (1.21 g, 80%): IR (neat film) 3030, 2940, 2860, 1580, 1440, 745, 690, 620 cm^{-1}.

1,1-Dipiperidinopropane (12a). This compound was prepared by the general method of Mannich and Davidson[11] in 85% yield: IR (neat film) ν_{max} 2935, 2860, 2800 cm^{-1}; ^{1}H NMR (Me_4Si, $CDCl_3$) δ 2.50–2.97 (m, 9 H), 1.32–1.80 (m, 17 H); mass spectrum *m/e* 210 (M^+).

1,1-Bis(di-*n*-butylamino)-2-methylpropane (12b). This compound was prepared in a 64% distilled[11] [bp 63 °C (1.5 torr)] yield: IR (neat film) ν_{max} 2955, 2920, 2860, 2795 cm^{-1}; ^{1}H NMR (Me_4Si, $CDCl_3$) δ 0.78–1.10 (m, 18 H), 1.10–1.65 (m, 6 H), 2.25–2.63 (m, 9 H); ^{13}C NMR (Me_4Si, $CDCl_3$) δ 14.16, 20.91, 29.17, 54.16; mass spectrum *m/e* 312 (M^+).

Pentamethylene(ethylidene)ammonium Iodide (13a). This compound was prepared as described above for formation of salt **1a**, in 80% yield: IR (Nujol) ν_{max} 3075, 1660 cm^{-1}; ^{1}H NMR (Me_4Si, Me_2SO-d_6) δ 1.40–2.00 (m, 13 H), 2.60–2.85 (m, 4 H), 8.6 (m, 1 H); mass spectrum *m/e* 263 (M^+).

Di-*n*-butyl(2-methylpropylidene)ammonium Iodide (13b). This compound was prepared as described above for formation of salt **12**, in 76% yield: IR (Nujol) ν_{max} 3070, 1655 cm^{-1}; ^{1}H NMR (Me_4Si, Me_2SO-d_6) δ 0.95 (t, 6 H), 1.20–1.90 (m, 15 H), 2.90–3.20 (m, 4 H), 8.85 (m, 1 H); mass spectrum *m/e* 311 (M^+).

3-Piperidinoheptane (14a). *n*-Butyllithium was added to ammonium salt **13a**, according to the procedure of Poulter et al.[1d] Chromatography of the crude adduct on silica (4:1, cyclohexane–ethyl acetate) afforded **14a** (40%): IR ($CHCl_3$) ν_{max} 2930, 2850 cm^{-1}; NMR (Me_4Si, $CDCl_3$) δ 2.5–2.9 (m, 5 H), 1.3–1.75 (m, 12 H), 0.95 (t, 6 H, *J* = 6 Hz); mass spectrum *m/e* 183 (M^+).

1-(Di-*n*-butylamino)-1-phenyl-2-methylpropane (14b). Phenyllithium was added to ammonium salt **13b**, according to the procedure of Poulter et al.[1d] Chromatography of crude adduct on silica (4:1, cyclohexane–ethyl acetate) afforded **14b** (38%): IR ($CHCl_3$) ν_{max} 2920, 2840, 1590 cm^{-1}; NMR (Me_4Si, $CDCl_3$) δ 0.95 (t, 12 H, *J* = 7 Hz), 1.4 (m, 9 H), 2.4 (t, 5 H, *J* = 16 Hz), 2.1–2.7 (m, 5 H); mass spectrum *m/e* 237 (M^+).

Acknowledgment. Support for this study was provided by the National Institutes of Health (Grant No. AM-18802) and the A. P. Sloan Foundation.

(5) The 2-methyl-2-butene was used to react with any HI that may be present from the hydrolysis of TMSI.
(6) The *N,N,N',N'*-tetramethylmethylenediamine was purchased from Aldrich and used without further purification.
(7) We found the iodide salt to be considerably less hygroscopic than the chloride salt **1b**.
(8) D. Michelot, R. Lorne, C. Hyunh, and S. Julia, *Bull. Chim. Soc. Fr.*, 1482 (1976).
(9) M. A. Guaciaro, P. M. Wovkulich, and A. B. Smith, III, *Tetrahydron Lett.*, 4661 (1978).
(10) Carbon and hydrogen elemental analyses for **1a** agreed, within experimental error, with calculated values.
(11) C. Mannich and H. Davidson, *Ber. Dtsch. Chem. Ges. B*, **69**, 2106 (1939).

Stereospecific Bromohydroperoxylation of 4,4-Dimethyl-3,5-diphenyl-4*H*-pyrazole. Synthesis and Crystal Structure of 3-Bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3*H*-pyrazole

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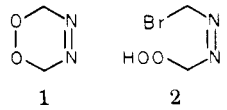
The importance of halo hydroperoxides as precursors for four[1]- and five[2]-membered-ring peroxides is well established. These hydroperoxides are conviently synthesized by the addition of electrophilic halogen to alkenes[1] or strained σ bonds[2] in the presence of concentrated (90% or greater) hydrogen peroxide. Dehydrohalogenation[1,2] to a cyclic peroxide is generally realized with base or silver salts. Our interest in the synthesis of cyclic azo peroxides[3,4] such as **1**, a model compound for an elusive intermediate



1 **2**

postulated in the chemiluminescent oxidation of luminol,[4] has led to the development of a synthetic method for bromo hydroperoxy azo compounds (e.g., **2**) that might be

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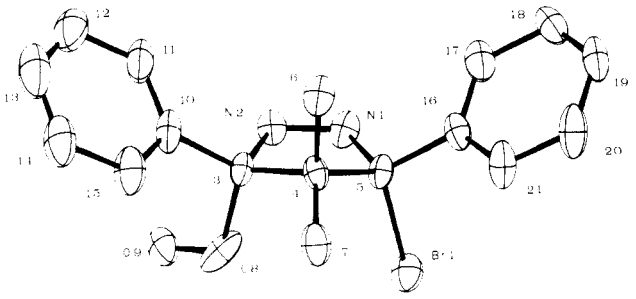
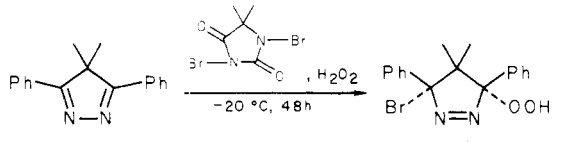


Figure 1. ORTEP drawing of 3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3*H*-pyrazole. Ellipsoids are drawn at the 50% probability level.

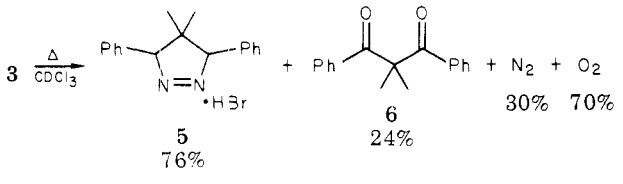
readily cyclized. We report the synthesis[5] of the first compound of this type, 3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3*H*-pyrazole (**3**).

Reaction of 4,4-dimethyl-3,5-diphenyl-4*H*-pyrazole (**4**) with 0.5 equiv of 1,3-dibromo-5,5-dimethyl-1,3-hydantoin and with excess hydrogen peroxide in ether at −20 °C for 48 h produces **3**, isolated in 75% yield. NMR analysis of



4 3

the crude reaction mixture revealed **3** and small amounts (10%) of its decomposition products (vide infra) as the sole reaction products. Characterization of **3** is provided by the following evidence: (1) the infrared spectrum displays stretching absorptions for OOH and N=N at 3250 and 1540 cm^{-1}, respectively; (2) reaction with alcoholic silver nitrate produces 96% of the theoretical amount of silver bromide; (3) thermal decomposition at 40 °C in $CDCl_3$ ($t_{1/2}$ = 10 min) produces the hydrobromide salt **5** of 4*H*-pyrazole **4** and oxygen as well as 2,2-dimethyl-1,3-diphenyl-1,3-propanedione (**6**) and nitrogen (product ratios are provided below); (4) the ^1H NMR spectrum displays two singlets for inequivalent methyl groups at δ −0.05 and at δ 1.7 and a multiplet for aromatic protons at δ 7.4–7.7.

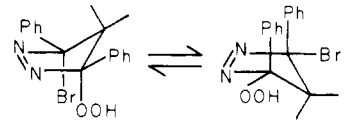


5 6
76% 24%

Complete structural proof, including verification of the cis orientation of the two aromatic rings in **3**, is provided by X-ray analysis.

Figure 1 is an ORTEP drawing[6] of 3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3*H*-pyrazole. The peroxide group and the bromine atom are arranged cis with respect to the five-membered ring. The five-membered ring adopts an envelope conformation. The N=N bond is 1.24 (1) Å, the two C–N bonds average 1.49 (1) Å, and the two C–C bonds completing the five-membered ring average 1.53 (3) Å. The O–O bond is 1.31 (1) Å, the C–O distance is 1.51 (1) Å, and the C–O–O angle is 107.5 (8)°. The 12 aromatic bonds average 1.37 (2) Å while the C–Br distance is 1.91 (1) Å.

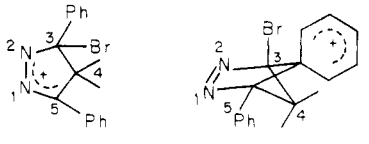
The ^1H NMR spectrum of **3**, displaying a negative chemical shift for one of the methyl groups, can be rationalized knowing the stereochemical addition of the bromo and hydroperoxy groups as cis. For the cis product, conformer **3c**, with the two aromatic rings pseudoequatorial, should be considerably more stable than 3c′. The



3c 3c′

conformational equilibrium should greatly favor **3c**, and one methyl group (over the azo moiety in **3c**) should be highly shielded attributable to the anisotropy of the azo bond.[7]

The course of the bromohydroperoxylation of 4*H*-pyrazole **4** differs dramatically from an analogous 1,4-addition reaction of chlorine with acyclic azines, for which trans addition is observed.[8] Steric interactions were postulated as controlling factors leading to the stereospecific chlorination of acyclic azines, and similar arguments can rationalize the cis bromohydroperoxylation of **4**. Initial addition of electrophilic bromine to **4** should produce ion **7**. Addition of hydrogen peroxide to **7** should



7 8

occur at C-5 from a direction opposite to the largest substituent at C-3, the aromatic ring.[9] The possibility of the existence of **7** as the phenonium ion **8**, which undergoes backside displacement by hydrogen peroxide exclusively at C-5, cannot be excluded. The net stereochemical result of either reaction pathway is to produce **3** in which the aromatic rings at C-3 and C-5 are cis.

Studies on the thermolysis of **3** and on methods for its dehydrohalogenation are in progress.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 710-B spectrophotometer. ^1H NMR spectra were recorded on a Varian T-60 NMR spectrometer with chemical shifts reported in parts per million (δ) from tetramethylsilane; ^{13}C NMR spectra were recorded on a JEOL Model JNM-FX60Q FT NMR spectrometer with chemical shifts reported in parts per million (δ) from tet-

(1) See, for example: (a) K. R. Kopecky and C. Mumford, *Can. J. Chem.*, **47**, 709 (1969); (b) N. J. Turro, P. Lechtken, N. E. Schore, G. B. Schuster, H. C. Steinmetzer, and A. Yekta, *Acc. Chem. Res.*, **7**, 97 (1974); (c) T. Wilson, *MTP Int. Rev. Sci.: Phys. Chem., Ser. Two*, **9** (1976); (d) W. Adam, *Adv. Heterocycl. Chem.*, **21**, 437 (1977); (e) P. D. Bartlett and M. E. Landis, "The 1,2-Dioxetanes", H. H. Wasserman and R. W. Murray, Eds., Academic Press, New York, 1979, p 243; (f) K. R. Kopecky, J. E. Filby, C. Mumford, P. A. Lockwood, and J. Y. Ding, *Can. J. Chem.*, **53**, 1103 (1975); (g) W. H. Richardson, F. C. Montgomery, M. B. Yelvington, and H. E. O'Neal, *J. Am. Chem. Soc.*, **96**, 7525 (1974).

(2) (a) N. A. Porter and D. W. Gilmore, *J. Am. Chem. Soc.*, **99**, 3503 (1977); (b) W. Adam, A. Birke, C. Cadiz, S. Diaz, and A. Rodriguez, *J. Org. Chem.*, **43**, 1154 (1978).

(3) (a) P. Lechtken, *Z. Naturforsch, B*, **31**, 1436 (1976); (b) M. E. Landis and D. C. Madoux, *J. Am. Chem. Soc.*, **101**, 5106 (1979).

(4) See, for example: (a) H. O Albrecht, *Z. Phys. Chem.*, **135**, 321 (1928); (b) E. H. White and D. F. Roswell, *Acc. Chem. Res.*, **3**, 54 (1970); (c) K. D. Gunderman, *Top. Curr. Chem.*, **46**, 61 (1974); (d) J. Michl, *Photochem. Photobiol.*, **25**, 141 (1977).

(5) R. L. Lindsey, M.S. Thesis, Southern Illinois University, Edwardsville, Illinois, (1979).

(6) C. K. Johnson, ORTEP, Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.

(7) (a) R. J. Crawford, A. Mishra, and R. J. Dummel, *J. Am. Chem. Soc.*, **88**, 3959 (1966); (b) K. Mackenzie in "The Chemistry of the Hydrazo, Azo, and Azoxy Groups", Part 1, S. Patai, Ed., Wiley, New York, 1975, p 345.

(8) D. S. Malament and J. M. McBride, *J. Am. Chem. Soc.*, **92**, 4586, 4593 (1970).

(9) E. L. Eliel, *Angew. Chem., Int. Ed. Engl.*, 4, 761 (1965).

ramethylsilane. Analytical gas chromatography was performed with a Dohrmann Series 15 gas chromatograph. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Combustion analyses were performed by Industrial Testing Laboratories of St. Louis. 4,4-Dimethyl-3,5-diphenyl-4*H*-pyrazole[10] and 2,2-dimethyl-1,3-diphenyl-1,3-propanedione[11] were prepared as previously described.

Reaction of 4,4-Dimethyl-3,5-diphenyl-4*H*-pyrazole with H_2O_2 and 1,3-Dibromo-5,5-dimethyl-1,3-hydantoin. Ninety percent hydrogen peroxide (6 g, 159 mmol) was added to an ice-cold slurry of 4,4-dimethyl-3,5-diphenyl-4*H*-pyrazole (1.98 g, 8.0 mmol) in anhydrous ether. The solution was warmed to room temperature, and 1,3-dibromo-5,5-dimethyl-1,3-hydantoin (1.17 g, 4.1 mmol) was added portionwise over a 20-min interval. The resulting solution was kept at −20 °C for 48 h. The solution was then washed with cold 10% aqueous sodium bicarbonate and dried over magnesium sulfate. Solvent was removed at reduced pressure at 0 °C, affording a yellow oil. Recrystallization from CH_2Cl_2–hexane (1:5) at −20 °C yielded 2.18 g (6.04 mmol, 75%) of **3** as a white solid: mp 77–80 °C dec; IR (KBr pellet) 3250 (OOH), 1540 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$), δ −0.05 (s, 3 H), 1.68 (s, 3 H), 7.2–7.8 (m, 11 H); ^{13}C NMR ($CDCl_3$) aromatics δ 138.9, 135.4, 132.1, 129.1, 128.3, 128.2, 125.7, 119.7; ^{13}C NMR ($CDCl_3$) aliphatics δ 102.4, 48.6, 25.8, 23.0, 19.9. Anal. Calcd for $C_{17}H_{17}BrN_2O_2$: C, 56.52; H, 4.74; N, 7.75. Found: C, 56.47; H, 4.78; N, 7.70.

Reaction of 3 with Ethanolic $AgNO_3$. **3** (7.6 mg, 0.021 mmol) was dissolved in 1 mL of 95% ethanol and added to 5 mL of 5% $AgNO_3$ (w/v) in ethanol. This solution was allowed to staand for 1 h in the dark. The precipitated AgBr (yellow solid) was filtered with a sintered-glass filter and dried, yielding 3.8 mg (0.02 mmol) of AgBr, 96% of the theoretical yield.

Thermolysis of 3. A solution of 0.727 g (2.02 mmol) of **3** in 25 mL of methylene chloride was heated with a water bath at 40 °C for 90 min. A ^1H NMR spectrum of the solution indicated the complete conversion of **3** into products, the hydrobromide salt **5** of pyrazole **4** and 2,2-dimethyl-1,3-diphenyl-1,3-propanedione (**6**) in the ratio of 76:24. Solvent was removed at reduced pressure, and the resulting yellow semisolid was dissolved in hot methylene chloride. Hexane was added until the hot solution became cloudy. The solution was allowed to stand at room temperature for 24 h while yellow crystals of **5** (0.4 g, 62%) precipitated. The hydrobromide salt **5** was identified by comparison of its IR and ^1H NMR spectra with those of an authentic sample prepared by the addition of HBr to **4**: IR (KBr pellet) 2350 ($^+$NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (br s, 6 H), 7.1 (variable s, 1 H), 7.6–7.9 (m, 6 H), 8.1–8.4 (m, 4 H). Removal of solvent from the recrystallization filtrant affords 0.11 g (23%) of diketone **6**, identified by comparison of its IR and ^1H NMR spectra with those of an authentic sample.[11]

Analysis of Gaseous Products from the Thermolysis of 3. **3** (0.1 g, 0.28 mmol) was dissolved in 40 mL of methylene chloride and placed in a 100-mL Erlenmeyer flask tightly stoppered with a rubber septum. The solution was cooled to −78 °C in an acetone/dry ice bath and degassed with argon for 30 min. The solution was heated with a water bath at 40 °C, and 0.5-mL samples of the gas phase were withdrawn periodically over a 45-min interval. VPC analysis for N_2 and O_2 (retention times of 5 and 2 min, respectively) content was performed on a $^1/_4$ in. × 10 ft 4A molecular sieves (20–50 mesh) column at 25 °C with argon as the carrier gas. The thermal conductivity response ratio of N_2 to O_2, as determined by analysis of air, was determined to be 1, thereby eliminating the necessity for a response correction. The ratio of O_2 to N_2 (70:30) remained constant throughout the thermal decomposition.

X-ray structure analysis: $C_{17}H_{17}O_2N_2Br$, M_r = 316.2, monoclinic, space group $P2_1/a$, a = 23.179 (6) Å, b = 6.388 (2) Å, c = 10.947 (3) Å, β = 104.00 (4)°, V = 1508.2(7) Å^3, Z = 4, d_{calcd} = 1.591 g cm^{-3}.

A crystalline sample of 3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3*H*-pyrazole was packed in dry ice and shipped by air freight to Texas Christian University. A single crystal was mounted on a Syntex $P2_1$ diffractometer and unit cell and intensity data were collected as rapidly as possible. Room-temperature unit cell dimensions were refined by a least-squares procedure utilizing 15 reflections whose angles were measured by a centering routine associated with the diffractometer. Intensity data were collected by the θ–2θ scanning technique using Cu Kα radiation (λ = 1.541 78 Å) and a graphite monochromator. Total data collection was completed within 14 h; however, the intensity of a standard reflection decreased by 40% during this period. A total of 2306 independent reflections were measured and 1608 had intensities greater than $2\sigma(I)$.

The decrease in intensity of the standard reflection was used to correct the remaining intensity data. Lorentz and polarization corrections were applied, but no absorption corrections were made. The structure was solved by the direct methods program MULTAN.[12] The nonhydrogen atoms were refined anisotropically by least-squares techniques to an R factor of 11%. The hydrogen atoms could not be located and no further refinement was made. Atomic scattering factors were taken from ref 13 and the scattering factors for bromine were corrected for the real part of the anomalous dispersion. A list of observed and calculated structure factors is available from M.E.L.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, to Westinghouse for a Westinghouse Educational Foundation grant to the Research Corporation, and to the Office of Research and Projects at Southern Illinois University at Edwardsville for support of this research. We also thank the Robert A. Welch Foundation (Grant P-074).

Registry No. **3**, 72229-10-8; **4**, 30169-45-0; **5**, 72229-11-9; **6**, 41169-42-0; hydrogen peroxide, 7722-84-1; 1,3-dibromo-5,5-dimethyl-1,3-hydantoin, 77-48-5.

Supplementary Material Available: Positional parameters for 3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3*H*-pyrazole (1 page). Ordering information is given on any current masthead page.

(10) A. B. Evnin, D. R. Arnold, L. A. Karnischky, and E. Strom, *J. Am. Chem. Soc.*, **92**, 6218 (1970).

(11) R. C. Fuson and J. T. Walfer, "Organic Syntheses", Collect. Vol. II, Wiley, New York, 1943, p 169.

(12) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).

(13) "International Tables for X-ray Crystallography", Vol. IV, Kynoch Press, Birmingham, England, 1974.

Aromatic Chlorination of *p*-Aminobenzoic Acid Derivatives. Improved Syntheses of Mono- and Dichloromethotrexate

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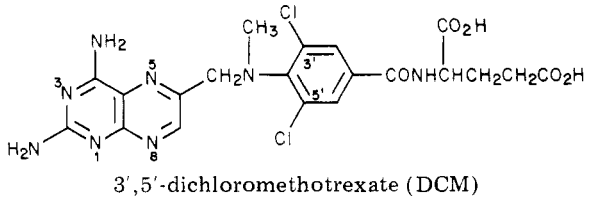
The reported syntheses of the clinically interesting[1] antitumor agent 3′,5′-dichloromethotrexate (DCM)[2] involve



3′,5′-dichloromethotrexate (DCM)

chlorination of methotrexate (MTX) with Cl_2 in formamide, dimethylformamide, or aqueous HCl with yields

(1) I. Takahashi, T. Ohnuma, and J. F. Holland, *Cancer Res.*, **39**, 1264 (1979), and references therein.

(2) *N*-[3,5-Dichloro-4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid; CAS Registry No. 528-74-5; NCI No. 29630.

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