monitoring indicated all the starting phthalimide was consumed. The solid (phthalazinedione–amine complex) was filtered, washed with ethanol, and then suspended in water to which 4 mL of 50% NaOH was added. After the mixture was shaken to dissolve all the solid, the oily product was extracted with two 100-mL portions of ethyl ether and one 100-mL portion of methylene chloride. The combined organic extracts were washed with water and dried over $MgSO_4$ and the solvent was removed in vacuo to yield 2.0 g (56%) of the product. Isolated as an oil, the product was homogeneous by TLC and NMR and was used without further purification.

This procedure was used in all cases. The water-soluble amines were extracted continuously overnight with methylene chloride. For all the compounds reported in Table I, the analytical data were consistent for the assigned structures. Elemental analyses were obtained for the indicated phthalimides and appear in the Supplementary Material (see paragraph at the end of paper concerning Supplementary Material). All were homogeneous by TLC and NMR. The cinnamylamines were needed and used as the free base and were reacted immediately upon isolation. All were homogeneous by TLC and NMR. The final products formed from the amines all gave satisfactory elemental and spectral data.[9]

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Registry No. **2**, 5428-09-1; **3** (Ar = C_6H_5), 17480-07-8; **3** (Ar = *p*-BrC_6H_4), 83665-58-1; **3** (Ar = *p*-ClC_6H_4), 22621-98-3; (*E*)-**3** (Ar = *o*-ClC_6H_4), 83665-59-2; (*Z*)-**3** (Ar = *o*-ClC_6H_4), 83665-89-8; **3** (Ar = 3,4-$Cl_2C_6H_3$), 83665-60-5; **3** (Ar = *p*-$Me_2NC_6H_4$), 83665-61-6; **3** (Ar = *p*-$O_2NC_6H_4$), 83665-62-7; **3** (Ar = *p*-HOC_6H_4), 83680-96-0; **3** (Ar = 3,4-$(OCH_2O)C_6H_3$), 83681-26-9; **3** (Ar = *p*-$MeSC_6H_4$), 83665-63-8; **3** (Ar = 4-H_2N-3-$O_2NC_6H_3$), 83665-64-9; **3** (Ar = *p*-$MeOCOC_6H_4$), 83665-65-0; **3** (Ar = *p*-NCC_6H_4), 83665-66-1; **3** (Ar = *p*-$H_2NC_6H_4$), 83665-67-2; **3** (Ar = thiophene-3-yl), 83665-68-3; **3** (Ar = thiophene-2-yl), 83665-69-4; **3** (Ar = 5-$MeOC(O)C_4H_3O$), 83665-70-7; **3**·HCl (Ar = 3-pyridyl), 83665-71-8; **3** (Ar = 5-pyrimidyl), 83665-72-9; **3** (Ar = 2-amino-5-pyrimidyl), 83665-73-0; **4** (Ar = C_6H_5), 4335-60-8; **4** (Ar = *p*-BrC_6H_4), 83665-74-1; **4** (Ar = *p*-ClC_6H_4), 60691-88-5; **4** (Ar = *o*-ClC_6H_4), 83665-75-2; **4** (Ar = 3,4-$Cl_2C_6H_3$), 83665-76-3; **4** (Ar = *p*-$Me_2NC_6H_4$), 83665-77-4; **4** (Ar = *p*-$O_2NC_6H_4$), 83665-78-5; **4** (Ar = *p*-HOC_6H_4), 83665-79-6; **4** (Ar = 3,4-$(OCH_2O)C_6H_3$), 83665-80-9; **4** (Ar = *p*-$MeSC_6H_4$), 83665-81-0; **4** (Ar = 4-H_2N-3-$O_2NC_6H_3$), 83665-82-1; **4** (Ar = *p*-$MeOCOC_6H_4$), 83665-83-2; **4** (Ar = *p*-NCC_6H_4), 83680-97-1; **4** (Ar = *p*-$H_2NC_6H_4$), 83665-84-3; **4** (Ar = thiophen-3-yl), 83681-27-0; **4** (Ar = thiophen-2-yl), 83665-85-4; **4** (Ar = 5-$MeOC(O)C_4H_3O$), 83665-86-5; **4** (Ar = 3-pyridyl), 83665-87-6; **4** (Ar = 5-pyrimidyl), 83665-88-7; **4** (Ar = 2-amino-5-pyrimidyl), 83681-28-1; C_6H_5I, 591-50-4; *p*-BrC_6H_4I, 589-87-7; *p*-ClC_6H_4I, 637-87-6; *o*-ClC_6H_4I, 615-41-8; 3,4-$Cl_2C_6H_3I$, 20555-91-3; *p*-$Me_2NC_6H_4Br$, 586-77-6; *p*-$O_2NC_6H_4I$, 636-98-6; *p*-HOC_6H_4Br, 106-41-2; *p*-$MeSC_6H_4Br$, 104-95-0; 4-H_2N-3-$O_2NC_6H_3Br$, 875-51-4; *p*-$MeOCOC_6H_4Br$, 619-42-1; *p*-NCC_6H_4Br, 623-00-7; *p*-$H_2NC_6H_4Br$, 106-40-1; 3,4-$(OCH_2O)C_6H_3Br$, 2635-13-4; 3-bromothiophene, 872-31-1; 2-bromothiophene, 1003-09-4; 5-$MeOC(O)C_4H_3O$ bromide, 2527-99-3; 3-pyridyl iodide, 1120-90-7; 5-pyrimidyl bromide, 4595-59-9; 2-amino-5-pyrimidyl bromide, 7752-82-1.

Supplementary Material Available: Full NMR and selected elemental data for the compounds in Table I (6 pages). Ordering information is given on any current masthead page.

(9) The biological results of the final products have been presented; see "Abstracts of Papers", G. W. Adelstein, N. J. Malek, A. E. Moorman, D. G. Colton, and B. S. Pitzele, 183rd National Meeting of the American Chemical Society, Las Vegas, NV, Mar 28-Apr 2, 1982, American Chemical Society, Washington, DC, 1982, Abstr MEDI 61. The paper will be submitted to *J. of Med. Chem.*

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Reaction of Maleic Hydrazide with Diazomethane

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During derivatization studies on the growth regulator maleic hydrazide (for gas chromatography purposes), methylation with diazomethane was investigated. Maleic hydrazide behaves as a monobasic acid[1] and is thought to exist as structure 1A,[2] i.e., 6-hydroxy-3(2*H*)-pyridazinone, as opposed to structure 1B, i.e., 1,2-dihydro-3,6-pyridazinedione. Since diazomethane normally forms methyl ethers with weakly acidic hydroxy compounds such as enols, it was anticipated that the 6-hydroxy group would be preferentially methylated.

However, treatment of maleic hydrazide with an ethereal solution of diazomethane yielded significant amounts of three different compounds. Characterization of these compounds and subsequent studies indicated that the initial reaction gave both oxygen and nitrogen methylation with a substantial preponderance of the latter.

Results and Discussion

The major product (45%) from reaction of ethereal diazomethane with maleic hydrazide was readily identified by comparison of its properties with a known sample as 2-methyl-6-methoxy-3(2*H*)-pyridazinone (**3**).[3] Identification of a second reaction product (16%) as 6-methoxy-3(2*H*)-pyridazinone (**2**) was suggested by its nuclear magnetic resonance (NMR) and mass spectral (MS) data. Confirmation of this supposition followed treatment of the compound with diazomethane. Although only a small percentage (approximately 12%) was converted, the new product proved identical in all respects with the 2-methyl-6-methoxy analogue **3**.

The third (9%) and most interesting product from the reaction of maleic hydrazide with diazomethane exhibited extreme sensitivity (i.e., nanogram quantities) to gas chromatographic electron capture detection. This high sensitivity suggested the presence of strongly conjugated electrophores,[4] a situation that could exist only if the enedione system remained intact. MS data for the compound exhibited a molecular ion at m/e 82 above that for maleic hydrazide. The NMR spectra indicated the presence of three distinct methyl groups and one aromatic hydrogen. These properties suggested structure **8** (5,6-dihydro-1,5,6-trimethyl-1*H*-pyrazolo[3,4-*d*]pyridazine-4,7-dione) for the compound. The formation of **8** may be rationalized by assuming initial N-methylation of the 1 and 2 positions, followed by cycloaddition of diazomethane[5] across the 4,5 double bond (Scheme I). The pyrazoline intermediate **6** if thermally unstable could undergo intramolecular rearrangement and oxidation.[6] N-Methylation of the resultant pyrazole **7** would complete the sequence.

To help elucidate the reaction pathway for compound **8**, quantities of the presumed intermediates 2-methyl-6-hydroxy-3(2*H*)-pyridazinone (**4**)[2] and 1,2-dihydro-1,2-dimethyl-3,6-pyridazinedione (**5**) were prepared.[3] Treatment of compound **5** with diazomethane afforded **8** in good yields. Reaction of compound **4** with diazomethane also

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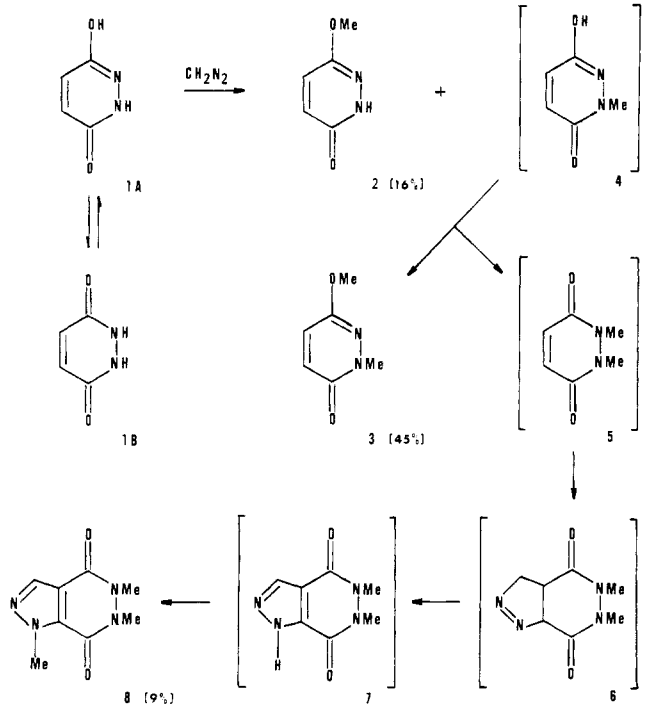
Scheme I



furnished substantial quantities of 8 and a trace of 5. However, the major product isolated proved to be the 2-methyl-6-methoxy derivative 3.

Some inferences from the foregoing experimental observations can be summarized as follows.

(a) In comparison to the N-methylated compound 4 the methoxy precursor 2 reacts very slowly with diazomethane. This suggests that initial nitrogen methylation is the preferred pathway to the 2-methyl-6-methoxy derivative 3.

(b) It appears that the *N*-pyrazolo derivative 8 is formed solely by reaction of diazomethane with the *N,N*-dimethyl intermediate 5. If so, the amount of 8 produced on reaction of the *N*-methyl derivative 4 with diazomethane can be taken as a measure of the intermediate *N,N*-dimethyl compound 5 involved. Thus, on the basis of product analysis, the preferred second stage of the reaction between maleic hydrazide and diazomethane proceeds by oxygen methylation. A possible explanation for this observation is that if as postulated for these types of reactions[7] a proton is transferred from compound 4 to diazomethane, reaction of methyldiazonium ion with nitrogen in the resultant pyridazinone anion may now be more sterically hindered by the presence of an adjacent *N*-methyl group.

Experimental Section

Melting points are uncorrected and were determined on a Kofler hotstage microscope. NMR spectra were recorded on a Varian T-60 NMR spectrometer with Me_4Si as an internal standard. Infrared (IR) spectra were determined by using a Beckman IR-20A spectrophotometer. Mass spectra were determined on a Perkin-Elmer Hitachi mass spectrometer. A Tracor 222 gas chromatograph equipped with an electron-capture ^{63}Ni detector (with linearizer) and a nitrogen-specific detector were utilized for gas chromatography determinations. Thin-layer chromatograms (TLC) were run on glass plates coated with silica gel GF. Separated components were detected by UV fluorescence and iodine vapor.

Reaction of Maleic Hydrazide (1) with Diazomethane. A suspension of maleic hydrazide (1; 500 mg, 4.46 mmol) in diethyl ether (100 mL) was treated with an approximate fivefold excess of alcohol-free diazomethane[8] in diethyl ether. The mixture was stirred overnight at room temperature in the dark. The ether was then removed under vacuum and the residue purified by preparative TLC (ethyl acetate). Crystallization of the major component (R_f 0.53) from hexane gave 2-methyl-6-methoxy-3-(2*H*)-pyridazinone (3):284 mg (2.03 mmol); mp 64–65 °C (lit.[3] mp 64–66 °C); IR (Nujol) 1690, 1610 cm^{-1}; NMR ($CDCl_3$) δ 6.89 (2 H, s, CH=CH), 3.83 (3 H, s, OCH_3), 3.65 (3 H, s, NCH_3); MS, *m/e* 140. Crystallization of a second component (R_f 0.44) from ethyl acetate gave 6-methoxy-3(2*H*)-pyridazinone (2):91 mg (0.72 mmol); mp 162–164 °C; IR (Nujol) 3175, 1690, 1610 cm^{-1}; NMR ($CDCl_3$) δ 8.88 (1 H, s, NH), 6.95 (2 H, s, CH=CH), 3.82 (3 H, s, OCH_3); MS, *m/e* 126. Crystallization of a third component (R_f 0.27) from ethyl acetate afforded 1,2-dihydro-5,6-dihydro-1,5,6-trimethyl-1*H*-pyrazolo[3,4-*d*]pyridazine-4,7-dione (8): 76 mg (0.39 mmol); mp 182–184 °C; IR (Nujol) 1660, 1550 cm^{-1}; NMR ($CDCl_3$) δ 8.06 (1 H, s, aromatic, N=CH), 4.30 (3 H, s, aromatic, NCH_3) 3.68 (3 H, s, $C(O)NCH_3$) 3.64 (3 H, s, $C(O)NCH_3$); MS, *m/e* 194. Repetition of the above reaction on compound 2 (35 mg) yielded compound 3 (4.6 mg) and starting material.

Reaction of 1,2-Dihydro-1,2-dimethyl-3,6-pyridazinedione (5) with Diazomethane. 1,2-Dihydro-1,2-dimethyl-3,6-pyridazinedione (5) was prepared from the reaction of maleic hydrazide (1) and dimethyl sulfate as described:[3] mp 136–137 °C (lit.[3] mp 135–136 °C); IR (Nujol) 1645, 1590 cm^{-1}; NMR ($CDCl_3$) δ 6.92 (2 H, s, CH=CH), 3.68 (6 H, s, $C(O)NCH_3$); MS, *m/e* 140. It (70 mg, 0.5 mmol) was treated with an excess of ethereal diazomethane as described for maleic hydrazide. Preparative TLC clean-up furnished a compound (43 mg, 0.22 mmol) which had a melting point, mixture melting point, IR, and NMR identical with those of 8.

Reaction of 2-Methyl-6-hydroxy-3(2*H*)-pyridazinone (4) with Diazomethane. 2-Methyl-6-hydroxy-3(2*H*)-pyridazinone (4) was prepared from the reaction of maleic hydrazide (1) with dimethyl sulfate and dilute sodium hydroxide as described:[3] mp 210–212 °C (lit.[3] mp 210–211 °C); IR (Nujol) 1680, 1610, 1525 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ -10.95 (1 H, s, C=COH), 6.91 (2 H, s, CH=CH), 3.60 (3 H, s, NCH_3); MS, *m/e* 126. The compound (4; 100 mg, 0.79 mmol) was treated with an excess of ethereal diazomethane as described for maleic hydrazide. Preparative TLC furnished two major products. The first (45 mg, 0.33 mmol) had a melting point, mixture melting point, IR, and NMR identical with those of compound 3. The second compound (29 mg 0.15 mmol) had a melting point, mixture melting point, IR, and NMR identical with those of compound 8. Gas chromatographic analysis of the reaction mixture also indicated trace amounts (<2%) of compound 5.

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Registry No. 1, 123-33-1; 2, 1703-10-2; 3, 7154-81-6; 4, 5436-01-1; 5, 7685-97-4; 8, 83633-47-0; diazomethane, 334-88-3.

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Synthesis of (±)-*O*-Methylcryptaustoline Iodide

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Dibenzopyrrocoline derivatives obtruded into early laboratory attempts by Robinson[1] and Schöpf[2] to demonstrate the practicality of the biogenetic hypothesis for

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