^{1}H NMR ($CDCl_3$) δ 2.4 (3 H, s), 3.3–4.3 (7 H, m), 7.35 and 7.8 (4 H, 2d, J = 8 Hz); $[\alpha]^{25}_D$ −9.3° (c 4.99, CH_3OH).

(*R*)-Glycidol (6).[13] To an ice-cooled solution of **3** (120.5 g, 0.49 mol) in methanol (200 mL) and ether (100 mL) was added sodium pellets (10.7 g, 0.45 mol) in three portions over approximately 1 h. Stirring was continued with ice cooling for 1 h. The reaction mixture was concentrated at 30 °C, and the residue was taken up in ether. After filtration, the solvent was removed at 30 °C (25 mm), and the residue was treated with chloroform and reconcentrated to remove the last traces of methanol. An additional chloroform treatment as above gave (*R*)-glycidol (**6**; 33.5 g, 93%), which was used without purification in subsequent steps.

A small sample of **6** was obtained by distillation (bp 70 °C, 15 mm) prior to thermal decomposition of crude **6** to give material having the following properties: ^{1}H NMR ($CDCl_3$) δ 3.95 (1 H, d of d, J = 12 and 2 Hz), 3.55 (1 H, d of d, J = 12 and 5 Hz), 3.15 (1 H, m), 2.75 (2 H, m); $[\alpha]^{24}_D$ 16.5° (c 5.88, $CHCl_3$).

(*S*)-3-Mesyloxy-1,2-epoxypropane (7). To an ice-cooled solution of **6** (5.0 g, 0.068 mol) and triethylamine (8.1 g, 0.080 mol) in toluene (100 mL) was added, over 15 min, methanesulfonyl chloride (8.0 g, 0.070 mol) in toluene (25 mL). Stirring was continued with cooling for 1 h. The solution was filtered and concentrated to give an 80–85% yield of the crude product; this material could be used without further purification. Distillation gave **7** (61%): bp 92–95 °C (0.1 mm); $[\alpha]^{22}_D$ 23.7° (c 5.16, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 4.5 (1 H, d of d, J = 12 and 3 Hz), 4.1 (1 H, d of d, J = 12 and 6 Hz), 3.3 (1 H, m), 3.1 (3 H, s), 2.8 (2 H, m).

Anal. Calcd for $C_4H_8O_4S$: C, 31.57; H, 5.30. Found: C, 31.99; H, 5.37.

(*R*)-Epichlorohydrin [(*R*)-5]. Concentrated HCl (20 mL) was added to **7** (5.0 g, 0.033 mol) over 15–20 min. After stirring for an additional 30 min, the water was removed through the addition and subsequent evaporation of ethanol. Finally, residual ethanol was removed at room temperature and 0.1 mm to give **8** (5.4 g, 85%): ^{1}H NMR ($CDCl_3$) δ 4.35 (2 H, d), 4.1 (1 H, m), 3.65 (2 H, d), 3.1 (3 H, s), 2.9 (1 H, broad s); $[\alpha]^{22}_D$ 7.1° (c 5.78, CH_3OH).

To **8** (5.4 g, 0.029 mol) in dry ethylene glycol (20 mL) was added a solution of sodium ethylene glycolate [from sodium pellets (0.8 g, 0.034 mol)] in dry ethylene glycol (20 mL). After stirring for 15 min, (*R*)-epichlorohydrin (**5**) (2.2 g, 86%) was distilled from the reaction mixture at room temperature and 0.2 mm and trapped in dry ice/acetone: ^{1}H NMR ($CDCl_3$) δ 3.6 (2 H, d), 3.2 (1 H, m), 2.8 (2 H, m); $[\alpha]^{22}_D$ −33.0° (c 4.22, CH_3OH).

A small sample was further purified by preparative GC on an HP 5710 A instrument using a 6 ft 5% OV-17 column with an oven temperature of 60 °C to give (*R*)-**5**, $[\alpha]^{23}_D$ −34.3° (c 1.50, CH_3OH).[18]

Anal. Calcd for C_3H_5ClO: C, 38.94; H, 5.45. Found: C, 38.74; H, 5.51.

The chiral purity was determined at concentrations of 0.5–1.0% (w/v) in $CDCl_3$ using chiral Eu(hfbc)$_3$, 97 ± 2% (*R*)-**5**.[18]

(*S*)-Epichlorohydrin [(*S*)-5]. To triphenylphosphine (13.2 g, 0.05 mol) in CCl_4 (20 mL) and DMF (50 mL) was added **3** (12.3 g, 0.05 mol) in DMF (50 mL) all at once. After the addition was complete, the temperature increased to 50 °C over 15 min. The mixture was then allowed to stir for 3 h. The residual solvents were removed (50 °C, 2 mm), and the residue was taken up in H_2O and extracted with CH_2Cl_2. The organic phase was washed again with H_2O, dried (Na_2SO_4), and concentrated. Residual solvents were removed at 25 °C and 0.2 mm over 18 h.

To this residue, composed of triphenylphosphine oxide and (*S*)-**4**, in dry ethylene glycol (50 mL) was added a solution of sodium ethylene glycolate [from sodium pellets (1.25 g, 0.054 mol)] in dry ethylene glycol (50 mL). After stirring for 15 min, (*S*)-epichlorohydrin (**5**) was distilled from the reaction mixture at room temperature and 0.2 mm and trapped in dry ice/acetone. The ^{1}H NMR spectrum indicated that traces of CH_2Cl_2 and H_2O were present, $[\alpha]^{20}_D$ 28.1° (c 2.47, CH_3OH).

A small sample was purified by preparative GC to yield pure (*S*)-**5**, $[\alpha]^{23}_D$ 33.0° (c 1.126, CH_3OH).[18]

Anal. Calcd for C_3H_5ClO: C, 38.94; H, 5.45. Found: C, 38.82; H, 5.81.

The chiral purity was determined at concentrations of 0.5–1.0% (w/v) in $CDCl_3$ using chiral Eu(hfbc)$_3$, 99 ± 1% (*S*)-**5**.[18]

Acknowledgments. The authors are grateful to Drs. Ralph Hirschmann and E. L. Engelhardt for their interest and encouragement throughout this work and to Drs. G. S. Ponticello, A. K. Willard, and J. R. Huff for many helpful discussions. Technical assistance was provided by Dr. W. C. Randall, Mr. K. B. Streeter, and Ms. J. M. Stranick for analytical determinations and by Mr. A. Augenblick for GC analyses.

Registry No.—**1**, 1707-77-3; **2**, 22323-82-6; **3**, 41274-09-3; **4**, 67800-61-7; (*R*)-**5**, 51594-55-9; (*S*)-**5**, 67843-74-7; **6**, 57044-25-4; **7**, 67800-62-8; **8**, 67800-63-9; (*R*)-3-tosyloxypropanediol acetonide, 23788-74-1.

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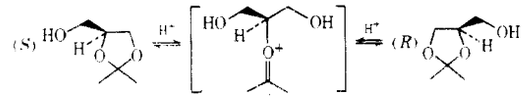
(12) Although earlier workers[11] used crude alcohol **2**, we felt that a purification at this point in the synthesis would be desirable. Crude **2** derived from $NaIO_4$ cleavage and $NaBH_4$ reduction followed by quenching with acetic acid exhibited a good optical rotation, but distillation of this material gave racemic product (**2**). A reasonable mechanism by which a trace acidic impurity (presumably derived from $NaIO_4$) could cause the racemization of (*S*)-**2** is indicated below.



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(14) R. H. Schlessinger and G. S. Ponticello, *Tetrahedron Lett.*, 4361 (1969). Since crude **4** was used in the preparation of (*S*)-**5**, the use of excess CCl_4 without DMF led to the isolation of (*S*)-**5** contaminated with varying amounts of CCl_4. The use of DMF allowed for the removal of most of the contaminating CCl_4 at an earlier stage.
(15) The isolation of **7** and **8** as racemic mixtures has been reported: N. Nakabayashi, E. Masuhara, and Y. Iwakura, *Bull. Chem. Soc Jpn.*, **39**, 413 (1966).
(16) The NMR spectrum of the crude (*R*)-glycidol (**6**) indicated that it was ≥95% pure.
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(18) Trace impurities in each chiral sample complicated their analyses with Eu(hfbc)$_3$. Therefore, aliquots of both (*R*)-**5** and (*S*)-**5** were purified by preparative gas chromatography as indicated in the Experimental Section. The minor inconsistency between optical rotation and chiral shift NMR data may be due to trace impurities, which cannot be detected in the NMR spectra, in either (*R*)-**5** or (*S*)-**5**, or both.
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A Novel Naphthyridinone Synthesis via Enamine Cyclization

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In a recent paper,[1] we described the use of dimethylformamide dimethyl acetal (DMF acetal) in the synthesis of 4-

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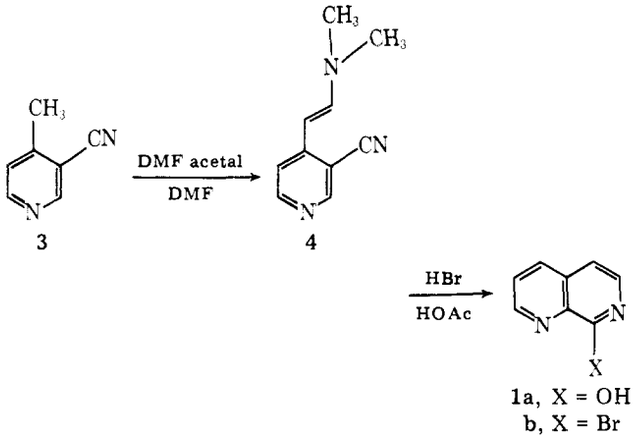
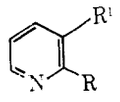
Scheme I



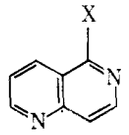
and/or 5-substituted 2-bromonicotinic acid derivatives via enamine cyclization. We now wish to report on an extension of that work as applied to the synthesis of naphthyridinones. Previously reported methods for the preparation of such systems, i.e., 1-hydroxy-2,7-naphthyridine (**1a**)[2] and 5-hydroxy-1,6-naphthridine (**2a**),[3,4] are severely limited by low overall yields (≤5%).

Our initial approach to the synthesis of the naphthyridinone **1a** is outlined in Scheme I. Reaction of 4-methylnicotinonitrile (**3**)[5] with DMF acetal in refluxing DMF provided the enamine **4** in good yield. The trans geometry of **4** was confirmed by its ^{1}H NMR spectrum: δ 5.23 (d, 1 H, J = 13 Hz) and 7.03 (d, 1 H, J = 13 Hz). Cyclization of **4** with 30% HBr–HOAc afforded the naphthyridinone **1a** in an overall 41% yield. In contrast to the results obtained in the pyridine series,[1] where the 2-bromo derivative was the exclusive product, only the naphthyridinone **1a** was isolated; none of the corresponding 1-bromo-2,7-naphthyridine (**1b**) was detected.

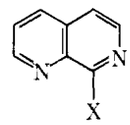
The naphthyridinone **2a** was prepared by a similar sequence in an overall 47% yield. In this example, the enamine **6** on treatment with HBr–HOAc yielded 5-bromo-1,6-naphthyridine (**2b**) in 16% yield, in addition to **2a.** It should also be mentioned that we could not successfully prepare the required intermediate, 2-methyl-3-cyanopyridine,[6] by the reported method of Rozsa and Borivoje.[7] Instead, **5** was synthesized by the procedure of Baumgarten and Dornow[6] using β-ethoxyacrolein diethyl acetal[8] and β-aminocrotononitrile.



5, R = CH_3; R^1 = CN
6, R = $-CH{=}CHN(CH_3)_2$; R^1 = CN
8, R = CN; R^1 = CH_3
9, R = CN; R^1 = $-CH{=}CHN(CH_3)_2$



2a, X = OH
b, X = Br



7a, X = OH
b, X = Br

Although 8-hydroxy-1,7-naphthyridine (**7a**) may be prepared in excellent yield by a modified Skraup procedure,[9] the possibility of preparing **7a** by an enamine cyclization was also investigated. The enamine **9**, required for this synthesis, was obtained in 56% yield from the reaction of 2-cyano-3-methylpyridine (**8**)[10] and DMF acetal. However, the conditions required for the preparation of **9** were somewhat more drastic than those used in the previous examples cited. Treatment of **9** with 30% HBr–AcOH gave naphthyridine **7a** in only a 5% overall yield. In this case, the corresponding bromo derivative **7b** was not obtained.

Both analytical and spectral data were utilized to characterize the compounds described in this note. In addition to the enamine **4**, the trans conformations of the intermediate enamines **6** and **9** were also indicated by ^{1}H NMR spectra. The presence or absence of the corresponding bromonaphthyridines, in each reaction, was determined by mass spectral and NMR analyses.

In summary, the reaction of DMF acetal with methylcyanopyridines, followed by acid cyclization of the resulting enamines, provides a facile naphthyridone synthesis.

Experimental Section

NMR spectra were determined in the indicated solvent on a Varian T-60 using tetramethylsilane as internal standard for proton spectra. Splitting patterns are designated as s, singlet; bs, broad singlet; d, doublet; dd, double doublet; and m, multiplet. Coupling constants are expressed in hertz (Hz). Mass spectra were taken on an AE1 MS 902 high-resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 500 mA. The samples were processed by a DS 50 Data Acquisition System. The low-resolution spectra were run at an ionizing voltage of 70 eV and an ionizing current of 100 mA. Melting points were determined on a Thomas-Hoover apparatus, in open capillary tubes, and are uncorrected. The enamines were distilled through a short-path distillation apparatus and boiling points are uncorrected. Concentration of solutions was accomplished using a Büchi rotary evaporator under water aspirator pressure (15–20 mm). The organic solutions were dried over Na_2SO_4.

Preparation of *N,N*-Dimethyl-2-(3-cyano-4-pyridyl)ethenamine (4). A solution of **3** (13.8 g, 0.12 mol), DMF (100 mL), and DMF acetal (14.0 g, 0.12 mol) was heated at reflux under N_2. After 16 h, the reaction mixture was concentrated at atmospheric pressure until the internal temperature reached 150 °C. The mixture was then cooled, poured into H_2O (1 L), and extracted with C_6H_6 (6 × 200 mL). The combined organic extracts were washed with H_2O (2 × 200 mL), dried, filtered, and evaporated to dryness. The residue was distilled at 150–160 °C (0.2 mm) to yield 12.6 g (63%) of **4**. An analytical sample was prepared by crystallization from C_6H_6–C_6H_{14}: mp 88–90 °C; ^{1}H NMR ($CDCl_3$) δ 2.95 (6 H, s), 5.2 (1 H, d, J = 13 Hz), 7.17 (1 H, d, J = 5 Hz), 7.37 (1 H, d, J = 13 Hz), 8.23 (1 H, d, J = 5 Hz), and 8.47 (1 H, s); MS m/e (M^+) 173 ($M^+ - 15$), 158, and ($M^+ - 42$) 131.

Anal. Calcd for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.43; H, 6.56; N, 24.66.

Preparation of *N,N*-Dimethyl-2-(3-cyano-2-pyridyl)ethenamine (6). The enamine **6** was prepared in a manner similar to **4** from **5** (9.0 g, 0.076 mol), DMF acetal (11.0 g, 0.092 mol), and DMF (50 mL) to yield 10.8 g (82%) of **6**: bp 133–135 °C; mp 49–50 °C after sublimation at 50 °C (0.03 mm); ^{1}H NMR ($CDCl_3$) δ 2.93 (6 H, s), 5.43 (1 H, d, J = 13 Hz), 6.80 (1 H, dd, J = 4,8 Hz), 7.67 (1 H, dd, J = 2, 8 Hz), 7.87 (1 H, d, J = 13 Hz), and 8.4 (1 H, dd, J = 2, 4 Hz); MS m/e (M^+) 173 ($M^+ - 15$), 158, and ($M^+ - 42$) 131.

Anal. Calcd for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.33; H, 6.22; N, 24.38.

Preparation of *N,N*-Dimethyl-2-(2-cyano-3-pyridyl)ethenamine (9). A solution of **8** (20.0 g, 0.17 mol), DMF (200 mL), and DMF acetal (30 mL, 0.25 mol) was heated at 120 °C with stirring under N_2 for 5 days. Additional acetal was periodically added in 5-mL aliquots (total 45 mL, 0.38 mol). The solution was then evaporated to dryness to give a crude oil which solidified on standing. The solid was crystallized from ligroin to yield 16.5 g (56%) of **9**. An analytical sample was prepared by recrystallization from ligroin: mp 71.5–72 °C; ^{1}H, NMR ($CDCl_3$) δ 2.92 (6 H, s), 5.27 (1 H, d, J = 13 Hz), 6.96 (1 H, d, J = 13 Hz), 7.32 (1 H, dd, J = 4, 8 Hz), 7.60 (1 H, dd, J = 2, 8 Hz), 8.08 (1 H, dd, J = 2, 4 Hz); MS m/e (M^+) 173 ($M^+ - 15$), 158, and ($M^+ - 42$) 131.

Anal. Calcd for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.55; H, 6.56; N, 24.42.

Preparation of 5-Hydroxy-1,6-naphthyridine (2a). A solution of 30% HBr in AcOH (200 mL) was added dropwise with mechanical stirring at 40 °C to a solution of **6** (10.8 g, 0.062 mol) in AcOH (100 mL). After the addition, the thick slurry was stirred at 55 °C for 2 h. The mixture was then evaporated to dryness and the residue treated with ice and saturated aqueous Na_2CO_3. The aqueous layer was filtered and the filtrate extracted with Et_2O. The aqueous layer was placed in a continuous extractor with $CHCl_3$ to yield 7.0 g of crude **2a.**

Sublimation at 160–180 °C (0.1 mm) yielded 5.1 g (56%) of **2a**. An analytical sample was prepared by crystallization from CH_3OH: mp 243–244.5 °C (lit.[3,4] mp 236–238 °C); ^1H NMR (Me_2SO-d_6) δ 6.67 (1 H, d, J = 8 Hz), 7.47 (1 H, d, J = 8 Hz), 7.53 (1 H, dd, J = 4, 8 Hz), 8.53 (1 H, dd, J = 2, 8 Hz), 8.93 (1 H, dd, J = 2, 4 Hz), and 11.67 (1 H, bs, exchange).

Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 66.08; H, 4.43; N, 19.16.

The ether layer from above was dried, filtered, and evaporated to dryness. The residue was covered with C_6H_{14} and filtered to yield 2.4 g of crude **2b**. Sublimation at 70–80 °C (0.1 mm) gave 1.9 g (15%) of **2b**: mp 112–13 °C; ^1H NMR ($CDCl_3$) δ 7.63 (2 H, m), 8.5 (2 H, m), and 9.06 (1 H, dd, J = 2, 4 Hz). MS calcd for $C_8H_5BrN_2$: 207.9637. Found: 207.9635.

Preparation of 1-Hydroxy-2,7-naphthyridine (1a). Compound **1a** was prepared in a manner similar to **2a** from **4** (3.0 g, 0.017 mol), 30% HBr–HOAc (60 mL), and HOAc (30 mL) to yield 1.58 g (64%) of **1a**, sublimation 170–180 °C (0.1 mm). An analytical sample was prepared by crystallization from isopropyl alcohol: mp 260–62 °C (lit.[2] mp 255–62 °C); ^1H NMR (Me_2SO-d_6) δ 6.53 (1 H, d, J = 6 Hz), 7.43 (1 H, d, J = 6 Hz), 7.53 (1 H, d, J = 6 Hz), 8.67 (1 H, d, J = 6 Hz), 9.3 (1 H, s), and 10.83 (1 H, bs, exchange).

Anal. Calcd for $C_8H_6N_2O$: C, 65.74; H, 4.14; N, 19.17. Found: C, 65.49; H, 4.51; N, 18.78.

Preparation of 8-Hydroxy-1,7-naphthyridine (7a). Compound **7a** was prepared in a manner similar to **2a** from **9** (14.2 g, 0.082 mol), 30% HBr–HOAc (150 mL), and HOAc (75 mL) to yield 0.6 g (5%) of **7a**, sublimation 180–200 °C (0.1 mm). An analytical sample was prepared by crystallization from CH_3OH: mp 236–39 °C (lit.[8] 236–39 °C); ^1H NMR (Me_2SO-d_6) δ 6.50 (1 H, d, J = 6 Hz), 7.27 (1 H, d, J = 6 Hz), 7.67 (1 H, dd, J = 4, 8 Hz), 8.13 (1 H, dd, J = 2, 8 Hz), 8.60 (1 H, dd, J = 2, 4 Hz), and 11.5 (1 H, bs, exchange).

Anal. Calcd for $C_8H_6N_2O$: C, 65.74; H, 4.14; N, 19.17. Found: C, 66.13; H, 4.47; N, 19.39.

Acknowledgments. The authors are grateful to Drs. Ralph Hirschmann and E. L. Engelhardt for their interest and encouragement throughout this work. Technical assistance was provided by Mr. K. B. Streeter and J. Stranick for analytical determination, Ms. J. S. Murphy for ^1H NMR spectra, and Mr. R. E. Rhodes for mass spectra.

Registry No.—**1a**, 67988-50-5; **2a**, 23616-31-1; **3**, 5444-01-9; **4**, 67988-51-6; **5**, 1721-23-9; **6**, 67988-52-7; **7a**, 67967-11-7; **8**, 20970-75-6; **9**, 67988-53-8.

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(10) Gratefully obtained from W. Halczenko of this laboratory.

Preparation and Photochemistry of Methyl 3,3,4-Triphenyl-3*H*-pyrazole-5-carboxylate

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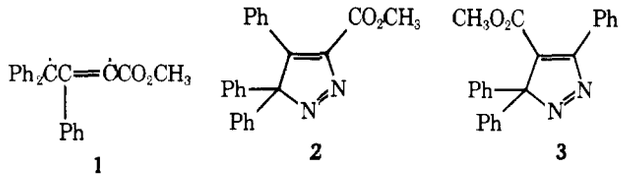
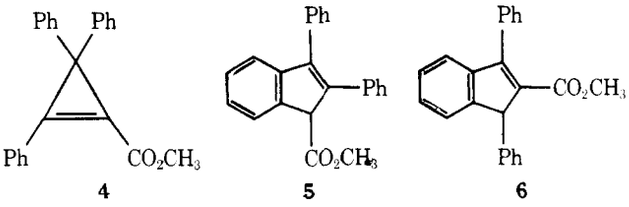
In order to study the reactivity of diradical **1**, we sought to generate it from the title compound **2**. Although van Alphen[1] had reported the synthesis of **2** from methyl 3-phenyl-2-propynoate and diphenyldiazomethane (DPDM), Hüttel and co-workers[2] later assigned structure **3** to the only



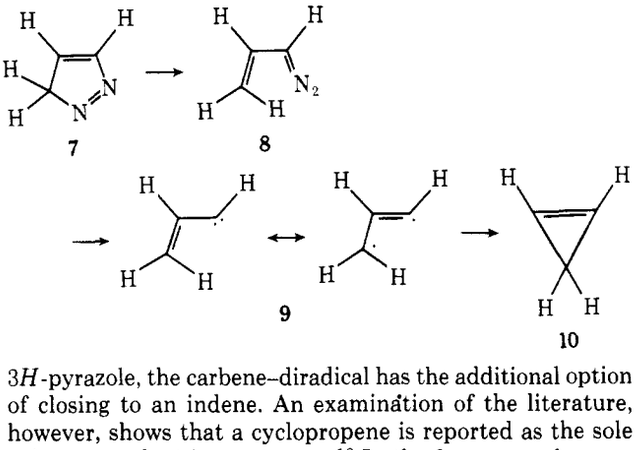
product isolated from this reaction. Their assignment was based on the observation that **3** underwent thermal rearrangement to a product that was then hydrolyzed and decarboxylated to the known 1,3,5-triphenyl-1*H*-pyrazole.[3]

We have now isolated both **2** and **3**, in a ratio of about 1:2, from the reaction of DPDM with methyl 3-phenyl-2-propynoate[4] and have unambiguously assigned their structures as follows. When a solution of **2** in benzene was irradiated through Pyrex for a short time, **4** and **5** were formed in a ratio



of about 1.2:1. Their properties matched those of authentic samples prepared by other routes.[5,6] When a solution of **3** was irradiated under these same conditions, **4** and **6** were formed in a ratio of about 1.3:1. An authentic sample of **6** was prepared from the corresponding acid, a known compound.[7] There was no change in **4** when it was irradiated under these conditions.

In general, the irradiation of a 3*H*-pyrazole (**7**) leads successively to the isomeric vinyl diazo compound **8**, to the vinyl carbene **9** after nitrogen loss, and finally to cyclopropene (**10**).[8,9] When a phenyl group is attached to position 3 of the



3*H*-pyrazole, the carbene–diradical has the additional option of closing to an indene. An examination of the literature, however, shows that a cyclopropene is reported as the sole primary product in most cases.[10] In the few cases where an indene is reported,[11] the irradiation was conducted under conditions known to isomerize cyclopropenes to indenes. The one exception[12] to this generalization is discussed below.

The simultaneous formation of cyclopropene and indene in the present case can be rationalized as a substituent effect on the multiplicity of **9**. A theoretical treatment[13] predicts that **8** leads initially to singlet carbene **9**, which may react or decay to triplet carbene **9** (14 kcal lower), which will then yield product. The relative energies of singlet and triplet **9** are apparently markedly affected by substituents; **11**, for example, shows an ESR signal, but **12** does not.[9] It may be that indene and cyclopropene come from different spin states of **9**: cyclopropene from the singlet and indene from the triplet. Al-

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