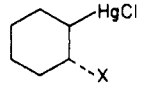
6-*t*-Bu, 90; 2-Me, mixture of 4 and 6-*t*-Bu, 90; 4-Ph, 2-*t*-Bu, 60; 3-Ph, 6-*t*-Bu, 60; 2-Ph, 2.2:1 mixture 6-*t*-Bu and 4-*t*-Bu, 69; 2-Cl, 1.3:1 mixture of 6-*t*-Bu and 4-*t*-Bu, 85; 3-MeO_2C, 6-*t*-Bu, 74; 3-MeNHCO, 6-*t*-Bu, 87; 4-methylquinoline, 2-*tert*-butyl-4-methylquinoline, 93; benzothiazole, 2-*tert*-butylbenzothiazole, 70. Reactions were not observed with 4-benzyl-, 4-acetyl-, 4-cyano-, 4-(dimethylamino)-, 2-methoxy-, or 2- or 3-fluoropyridines or with acridine, thiophene, furan, pyrrole, *N*-benzylpyrrole, or imidazole.

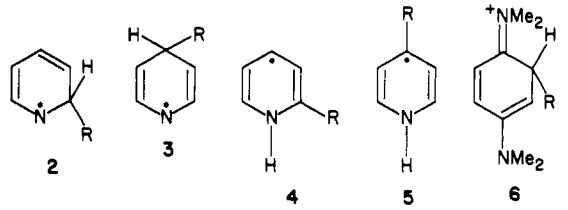
Olefin mercuration products such as **1** reacted with photostimulation to produce the expected mixtures or alkylated pyridines, e.g., X = $NHCOCH_3$, 69%, o/p = 2.3.



1, X = $NHCOCH_3$; OCH_3; OH

The olefin mercuration product need not be isolated and a one-pot reaction can be achieved by first reacting an olefin with $Hg(O_2CCF_3)_2$ in MeOH[11] followed by the addition of excess pyridine and sunlamp irradiation to initiate the chain process. Table II summarizes typical yields.

The initial attack of R· upon pyridine leads to the azacyclohexadienyl radicals **2** and **3**. These may lose H^+ to



pyridine to form the radical anion ($R\pi^{-}$· in Scheme II) or undergo isomerization (presumably via reaction with PyH^+ and Py) to yield the easily oxidized radicals **4** and **5** ($R\pi H$ in Scheme II). There is a consistent trend in the ortho/para ratios (*n*-Bu· = 1.9; *i*-Pr = 3.1; 2-norbornyl = 4.1; *t*-Bu = 6.0), indicating that radicals which are better electron donors yield a higher fraction of the ortho substitution product. In the case of TMPDA, the initially formed adduct can undergo electron transfer without hydrogen migration to form **6** which may aromatize in a subsequent step. Reaction of TMPDA failed with R = *t*-Bu but occurred readily with R = cyclohexyl or benzyl to give only the monoalkylated products.[12]

Typical Procedures. *exo*-2-Norbornylmercury chloride (3 g) in 10 mL of pyridine at 30–35 °C was deoxygenated by a helium stream and irradiated by a 275-W sunlamp ~20 cm from the Pyrex tube. Mercury metal precipitated from the solution after an induction period of 5–10 min. After 24 h, the pyridine solution was added to 10 mL 0.1 M KOH, and extracted with Et_2O, and the ether solution was washed twice with 10 mL of H_2O. The dried ether solution was evaporated and Kugelrohr distilled to give 1.40 g (90%) of a 4.1:1 mixture (by GLC) of 2- and 4-*exo*-2-norbornylpyridines, bp 125–145 °C (0.1 torr). The 2- and 4-alkylpyridines are readily distinguished by GCMS since the 2-alkyl derivatives have a pronounced $M^+ - H$ peak while 4-alkyl derivatives give mainly M^+.[13]

Cyclohexene (1.64 g) was added to a stirred solution of 6.36 g of $Hg(OAc)_2$ in 20 mL of MeOH. After 10 min, 8 mL of C_5H_5N was added and the solution irradiated 40 h with the sunlamp to yield 3.0 g of Hg and 2.1 g of a mixture of *o*- and *p*-(2-methoxycyclohexyl)pyridine, bp 95–115 °C (2 torr). A more rapid reaction and higher yield was observed using $Hg(O_2CCF_3)_2$.

TMPDA (1.09 g, 6.6 mmol) and 2.15 g of $PhCH_2HgCl$ (6.5 mmol) in 40 mL Me_2SO were irradiated by sunlamp for 40 h. Workup provided 1.19 g (70%) of the benzyl derivative, bp 125–145 °C (0.01 torr).

(11) Brown, H. C.; Rei, M.-H. *J. Am. Chem. Soc.* **1969**, *91*, 5646.

(12) Reaction of 5-hexenylmercury chloride with 1 equiv of TMPDA formed a mixture of 5-hexenyl- and cyclopentylcarbinyl products. Although reaction of $PhCH_2HgCl$ with C_5H_5N forms mainly $PhCH_2CH_2Ph$ from the reaction $PhCH_2\cdot + PhCH_2HgCl \rightarrow PhCH_2CH_2Ph + HgCl$,[2] with the more reactive TMPDA (1 equiv), the benzylated product (80%) and $PhCH_2CH_2Ph$ (7%) were formed (GC yields). Toward $PhCH_2\cdot$, TMPDA was 6 times as reactive as $Me_2C{=}NO_2^-$, giving a reactivity series toward $PhCH_2\cdot$ of $Me_2C{=}NO_2^-$(1) > TMPDA(0.16) > $PhCH_2HgCl$(<0.01) > C_5H_5N(<10^{-4}).

(13) McDonald, F. R.; Widecora, A.; Cook, G. L. *Appl. Spectrosc.* **1968**, *22*, 325, 329.

Glen A. Russell,* Deliang Guo, Rajive K. Khanna

Department of Chemistry
Iowa State University
Ames, Iowa 50011

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Thermal, Four-Carbon + Three-Carbon Cycloaddition Reaction of Cyclopropenone Ketals. Total Synthesis of Deacetamidocolchiceine: Formal Total Synthesis of Colchicine

Summary: A total synthesis of deacetamidocolchiceine, constituting a formal total synthesis of colchicine, is described and is based on the implementation of a thermal, four-carbon + three-carbon cycloaddition of α-pyrone **4** with the cyclopropenone ketal **3** in a process proceeding by way of the reversible, thermal generation of a three-carbon 1,3-dipole best represented as a nucleophilic and delocalized singlet vinylcarbene.

Sir: Colchicine (**1**), a potent mitotic inhibitor exhibiting a characteristic and specific binding with tubulin which prevents microtubule assembly and spindle formation, has been the subject of extensive synthetic,[2] biosynthetic,[3] and biochemical investigations.[3] Most recent efforts have focused on defining the complete spectrum of colchicine's

(1) (a) Searle Scholar Recipient, 1981–1985. National Institutes of Health research career development award recipient, 1983–1988 (CA 00898/01134). Alfred P. Sloan research fellow, 1985–1989. Correspondence regarding this work should be addressed to this author at the following address: Department of Chemistry, Purdue University, West Lafayette, IN 47907. (b) National Institutes of Health predoctoral fellow, 1981–1984 (GM 07775).

(2) Structure determination: (a) Dewar, M. J. S. *Nature (London)* **1945**, *155*, 141. Total synthesis: (b) Schreiber, J.; Leimgruber, W.; Pesaro, M.; Schudel, P.; Threlfall, T.; Eschenmoser, A. *Helv. Chim. Acta* **1961**, *44*, 540. (c) van Tamelen, E. E.; Spencer, F. A.; Allen, O. S.; Orvis, R. L. *Tetrahedron* **1961**, *14*, 8. (d) Sunagawa, G.; Nakamura, T.; Nakazawa, J. *Chem. Pharm. Bull.* **1962**, *10*, 291. Nakamura, T. *Ibid.* **1962**, *10*, 299. (e) Scott, A. I.; McCapra, F.; Buchanan, R. L.; Day, A. C.; Young, D. W. *Tetrahedron* **1965**, *21*, 3605. Scott, A. I.; McCapra, E.; Nabney, J.; Young, D. W.; Day, A. C.; Baker, A. J.; Davidson, T. A. *J. Am. Chem. Soc.* **1963**, *85*, 3040. (f) Woodward, R. B. *Harvey Lect.* **1963**, 31. (g) Martel, J.; Toromanoff, E.; Huynh, C. *J. Org. Chem.* **1965**, *30*, 1752. (h) Matsui, M.; Yamashita, K.; Mori, K.; Kaneko, S. *Agric. Biol. Chem.* **1967**, *31*, 675. Kaneko, S.; Matsui, M. *Ibid.* **1968**, *32*, 995. (i) Kato, M.; Kido, F.; Wu, M. D.; Yoshikoshi, A. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1516. (j) Kotani, E.; Miyazak, F.; Tobinaga, S. *J. Chem. Soc., Chem. Commun.* **1974**, 300. Tobinaga, S. *Bioorg. Chem.* **1975**, *4*, 110. (k) Evans, D. A.; Hart, D. J.; Koelsch, P. M. *J. Am. Chem. Soc.* **1978**, *100*, 4593. Evans, D. A.; Tanis, S. P.; Hart, D. J. *Ibid.* **1981**, *103*, 5813. (l) For resolution methods in the conversion of deacetamidocolchiceine (**2b**) to colchicine with resolution of deacetylcolchiceine; see: Corrodi, H.; Hardegger, E. *Helv. Chim. Acta* **1957**, *40*, 193.

(3) For a recent review, see: Capraro, H.-G. "Alkaloids"; Academic Press: Orlando, Florida, 1984; Vol. 23, pp 1–70.

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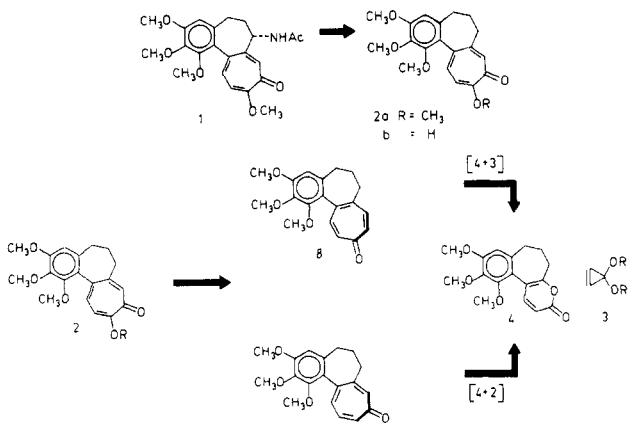
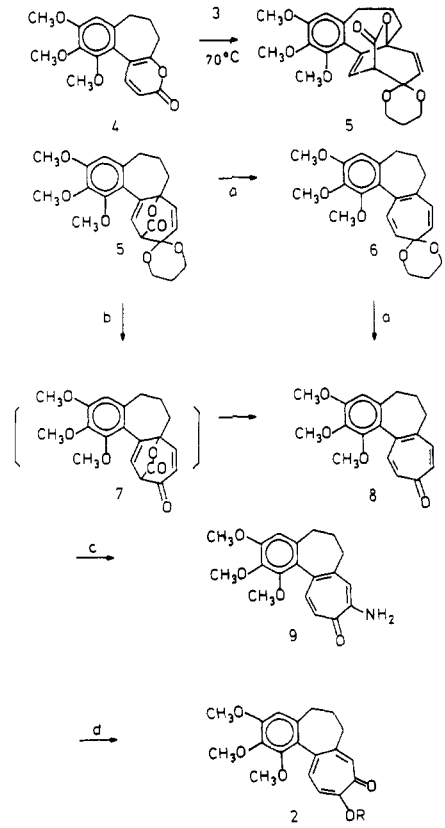
Scheme I



biological properties and the underlying mechanism of cytotoxic and antimitotic action, as well as the complete exploration of the structural features that affect potency, tubulin binding, and toxicity.[3] Despite the interest in such studies, most investigations are limited to those employing colchicine, or derivatives readily prepared from naturally occurring colchicine, because of the relative difficulty expected to be encountered in the total synthesis of structurally related tropolones.[3]

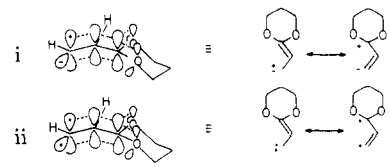
Herein, we detail a simple, total synthesis of deacetamidocolchiceine (**2b**), constituting a formal total synthesis of colchicine (**1**), which can be expected to be amenable to the preparation of structurally related compounds. The approach (Scheme I) is based on the successful implementation of a thermal, four-carbon + three-carbon cycloaddition of cyclopropenone ketal **3**[4] with Eschenmoser's α-pyrone **4**[2b] in a process proceeding by way of the reversible, thermal generation of a three-carbon 1,3-dipole

Scheme II[a]



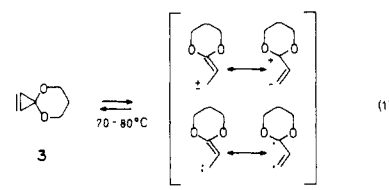
[a] For the conversion of **4** to **5**: benzene, 0.25 M, 2–3 equiv of **3**, 21–36 h, 60–73%. (a) 210 °C, neat 2–3 min; SiO_2 chromatography or HOAc-THF-H_2O, 25 °C, 5 min, 60%. (b) HOAc-THF-H_2O (6:5:2), 100 °C, 3.5 h, 70%. (c) 5–10 equiv of NH_2NH_2, EtOH, 0 °C (1 h) and 25 °C (5 h), 53% **9**.[9] (d) 2 N KOH-EtOH (1:1), 100 °C, 21 h, 90–100% (**2b**, R = H). CH_2N_2, CH_3OH-THF (**2a**, R = CH_3 and deacetamidoisocolchicine).

(4) (a) Boger, D. L.; Brotherton, C. E.; Takusagawa, F., unpublished observations. (b) Boger, D. L.; Brotherton, C. E. *Tetrahedron*, in press. For descriptions of the thermal reactions of cyclopropenone ketals with electron-deficient olefins, see: (c) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1984**, *104*, 805. Boger, D. L.; Brotherton, C. E. *Tetrahedron Lett.* **1984**, *25*, 5611. For a description of the thermal reactions of cyclopropenone ketals with carbon–heteroatom double bonds, see: (d) Boger, D. L.; Brotherton, C. E.; Georg, G. I. *Tetraherdron Lett.* **1984**, *25*, 5615. (e) For the preparation of cyclopropenone ketal **3**, see: Butler, G. B.; Herring, K. H.; Lewis, P. L.; Sharpe, V. V.; Veazey, R. L. *J. Org. Chem.* **1977**, *42*, 679. Boger, D. L.; Brotherton, C. E.; Georg, G. I. *Org. Synth.*, submitted for publication. For additional studies, see: Albert, R. M.; Butler, G. B. *J. Org. Chem.* **1977**, *42*, 674. Baucom, K. B.; Butler, G. B. *Ibid.* **1972**, *37*, 1730. Breslow, R.; Oda, M. *J. Am. Chem. Soc.* **1972**, *94*, 4787. Breslow, R.; Oda, M.; Percoraro, J. *Tetrahedron Lett.* **1972**, 4415, 4419. The ease of thermal generation of the vinylcarbene (70–80 °C, benzene) from cyclopropenone ketal **3** and its nucleophilic character are consistent with past observations in which stabilization of an empty p orbital provides the necessary stabilization for observable ground-state singlet carbenes, cf. i. The observed chemical behavior of the vinyl-



carbene generated thermally from **3** is consistent with stepwise addition–cyclization reactions that might be expected to be characteristic of a partially delocalized triplet vinylcarbene, cf. ii. However, the instances of 2π insertions, $[{}_{\pi}2_s + {}_{\omega}2_s]$ cycloadditions, with an observable endo effect,[4c] and the $[{}_{\pi}4_s + {}_{\pi}2_s]$ cycloaddition detailed herein are an expectant characteristic of a delocalized singlet vinylcarbene. The reversible generation of the vinylcarbene is implicated by the past observations that the principal products observed in the generation of vinylcarbenes are, in fact, cyclopropenes and the apparent efficiency with which i/ii is intermolecularly trapped. For a discussion of these and related topics, see: Jones, M., Moss, R. A., Eds. "Carbenes"; Wiley-Interscience: New York, 1973; Vol. 1, pp 51–53, 280–283, 337–339.

best represented as a nucleophilic and delocalized singlet vinylcarbene[4] (eq 1). The approach is complementary to

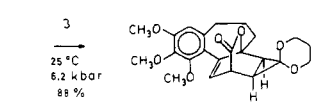


(1)

a second, potential route to **2** which is based on the room temperature inverse electron demand Diels–Alder, four-carbon + two-carbon, reaction of cyclopropenone ketal **3**[4b] with the same α-pyrone **4** (Scheme I).[5]

Treatment of the α-pyrone **4** with the cyclopropenone ketal **3** (2–3 equiv, 75 °C, 21–36 h, benzene) afforded the

(5) (a) In related efforts, treatment of α-pyrone **4** with cyclopropenone ketal **3** under pressure-promoted Diels–Alder conditions (6.2 kbar, 25 °C, 4 days) provides the stable, exo [4 + 2] cycloadduct (88%) as shown below. A full discussion of these and related efforts on the inverse electron demand Diels–Alder reaction[4b] of **3** will be described in a full account of these studies. (b) A trace of the [4 + 2] cycloaddition product shown below (less than 5%) can be isolated from the thermal reaction (70–80 °C) of **4** with **3**.



expected bicyclolactone **5** (60–73%) as the only significant reaction product[5b] and thus represents an effective trap of the apparent, transient delocalized singlet vinylcarbene (Scheme II). The structure of the [3 + 4] cycloadduct **5** was clear from its spectroscopic properties[6] and was confirmed by conversion to deacetamidocolchiceine (**2b**) (Scheme II). Expectant efforts to promote decarboxylation of **5** to afford the cycloheptatrienone ketal **6** were successful, although the decarboxylation reaction required selected conditions for isolation and confirmation of the cycloheptatrienone ketal **6**.[7] Hydrolysis of **6**, which occurred upon attempted chromatographic purification of **6** or with mild aqueous acid treatment, provided **8**. More conveniently, warm aqueous acid treatment of **5**, which proceeds with initial ketal hydrolysis and is followed by a subsequent thermal decarboxylation,[8] provided tropone **8** in an excellent, direct conversion (70%). The intermediacy of the bicyclolactone **7** was demonstrated by its isolation[8] and subsequent thermal conversion to tropone **8**.

Introduction of the additional ring C hydroxyl required for the conversion of tropone **8** to **2a/b** was accomplished, as anticipated, by way of the deacetamidoisocolchiceinamide (**9**) by using existing protocols.[9,2d] Treatment of **8** with hydrazine afforded deacetamidoisocolchiceinamide (**9**),[9] which upon basic hydrolysis provided deacetamidocholchiceine (**2b**). Diazomethane methylation of **2b** provided deacetamidocolchicine (**2a**) and deacetamidoisocolchicine as previously described.[2b]

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Supplementary Material Available: Characterization and spectral information on **4–9** and **2b** are provided (4 pages). Ordering information is given on any current masthead page.

(6) Complete spectral information for **5** is provided in the supplementary material.

(7) Efforts to promote the thermal decarboxylation of **5** in solution (120 °C, toluene, 15 h, recovered **5**; 150–160 °C, mesitylene, recovered **5** and unidentified products; 200 °C, triisopropylbenzene, 1.5 h, unidentified products) were unsuccessful. Warming a solid sample of **5** at 210 °C (neat, 2–3 min) provided clean conversion of **5** to **6**.

(8) Treatment of **5** with mild aqueous acid [5% aqueous H_2SO_4–dioxane (1:1), 25 °C, 15 h] provided a mixture of recovered **5** (ca. 90%) and **7** (ca. 10%) with no detectable **8** (ca. 0%). Spectral characterization for **7** (^{1}H NMR) and **8** (full characterization) are provided in the supplementary material. Thermolysis of **7** (toluene, 110 °C, 1.5 h) provided complete conversion to tropone **8**. For related observations, see ref 4a.

(9) The reaction of tropone **8** with hydrazine under a variety of conditions afforded a 3:2 mixture of the 9-aminotropone **9** (deacetamidoisocolchiceinamide) and 11-aminotropone which were readily separated by chromatography and independently characterized. Deacetamidoisoamidoisocolchiceinamide (**9**) was identical in all respects with the properties reported for authentic material[2b] and upon hydrolysis provided deacetamidocolchiceine (**2b**) also identical in all respects with the properties reported for authentic material.[2b] Independent hydrolysis of the isomeric 11-aminotropone provided the corresponding 11-hydroxytropone (tropolone) displaying properties identical in all respects with that described for authentic material.[2b] In the Eschenmoser total synthesis of colchicine, on which most subsequent efforts have been based, this 11-hydroxytropone was converted to deacetamidoisocolchiceinamide (**9**) and subsequent hydrolysis provided deacetamidocolchiceine (**2b**).[2b]

Dale L. Boger,*[1a] Christine E. Brotherton[1b]

Department of Medicinal Chemistry
University of Kansas
Lawrence, Kansas 66045-2500

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A Novel Synthetic Route to Heterocyclic Quinones

Summary: A new synthetic route to heterocyclic quinones is presented. This involves the addition of nucleophiles to the quinone methides generated from azidoquinones. The resulting azidohydroquinones proceed to aminoquinones which, in turn, lead to heterocyclic quinones via condensation of the amino substituent with proximal electrophilic sites.

Sir: Reported here are illustrative examples of transformations arising from an unusual and potentially general route to a large variety of heterocyclic quinones. As formally outlined in Scheme I, the method combines a number of reactions which alone have received little attention. Together, they constitute one mechanistic sequence which rationalizes the formation of the observed products and provides predictive insight to a variety of synthetic targets. The generalized sequence of steps include (1) equilibration of an appropriately substituted azidoquinone, **1**, to the quinone methide, **2**, and its in situ trapping (Michael addition) to give the unstable azidohydroquinone, **3**,[1] (2) spontaneous disproportionation of the azidohydroquinone to the aminoquinone,[2] **4**, and (3) in some cases subsequent ring closure or rearrangements induced by nucleophilic attack of the resulting amino group on a proximate electrophilic site.

The following represent illustrative examples of the above reaction sequence. Refluxing an aqueous THF solution of the azidoquinone **5** for 1.5 h resulted in the formation of the aminoquinone **6a** (79%) (Scheme II). When the reflux time was extended to 5 h the ring closed indoloquinone **7a** was isolated in 74% yield. In an analogous fashion, **6b** (77%) was obtained when **5** was decomposed in methanol. However, **7b** was not obtained by extending the reflux time (15 h) but was formed upon reduction of **6b** ($Na_2S_2O_4$) followed by subsequent air oxidation of the hydroquinone. Decomposition of **5** in acetic acid (90 °C) gave **7c** (65%). The structures of these products are based upon their spectral and analytical properties, and these data can be obtained as supplementary material. Structural data for **6a** and **7a** are provided here as representative examples. **6a**: mp 179–180 °C; IR (KBr, cm^{-1}) 3460 (s), 3400 (s), 3300, (s), 1740 (s), 1720 (s), 1680 (m); ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 6 H), 4.46 (s, 1 H), 6.32 (br s, 2 H), 7.60–7.77 (m, 2 H), 8.03–8.11 (m, 2 H); MS (CI, M + 1), 320. Anal. Found: C, 56.46; H, 3.95. **7a**: mp 207–210 °C dec; IR (KBr, cm^{-1}) 3390 (m), 3250 (s), 1765 (s), 1730 (s), 1688 (m), 1680 (m); ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3 H), 4.48 (br s, 1 H), 7.73–7.86 (m, 3 H), 8.10–8.14 (m, 2 H); MS (M^+), calcd for $C_{14}H_9NO_6$ 287.04299, found 287.04269.

A number of unusual transformations were observed when the azidoquinones were treated with enolates of acidic ketones. For example, when **9** was slowly added to a THF solution of dimedone containing a catalytic amount of sodium hydride, **10** was isolated in 68% yield (Scheme III). Surprisingly, when the related azidoquinone **11** was subjected to the above reaction conditions, a different reaction pathway was followed. Here a 64% yield of the indoloquinone **12** was realized. Characteristic spectral data for **12** are as follows: mp 231–233 °C dec; IR (Nujol, cm^{-1}) 3220 (w), 1764 (m), 1750 (w), 1680 (m); ^{1}H NMR ($CDCl_3$) δ 1.8 (t, J = 7 Hz, 3 H), 1.23 (s, 3 H), 1.35 (s, 3 H), 2.28

(1) Equilibration of an azidoquinone to a quinonemethide has not previously been reported. However, precedent for such a transformation within the quinone field is well-known. See, for example: Smith, L. I.; Kaiser, E. W. *J. Am. Chem. Soc.* **1940**, *62*, 138. Jurd, L. *Aust. J. Chem.* **1978**, *31*, 347.

(2) Moore, H. W.; Shelden, H. R. *J. Org. Chem.* **1968**, *33*, 4019.

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