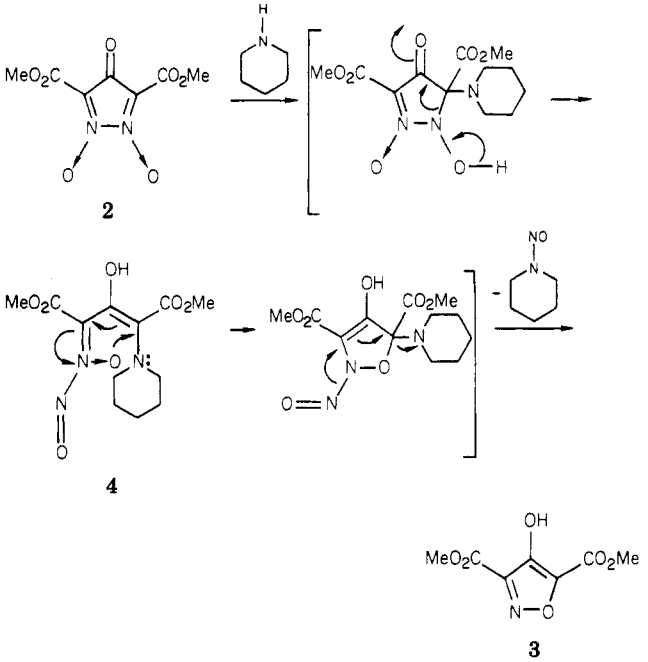
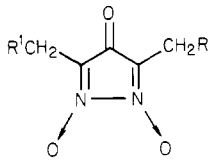
Scheme I



potentially active alkyl substituents of 2- and/or 5-alkyl-3,4-diazocyclopentadienone 3,4-dioxides (1). It was



observed that these bright yellow, orange, or red compounds were bleached in base, but no products could be characterized.

Isatogens, which contain a keto nitrone function similar to that in 1, were reported to add ethyl cyanoacetate under Knoevenagel conditions.[2] We decided to attempt a similar reaction with a derivative of 1 containing no base-sensitive alkyl groups. When ester 2[1] was treated with ethyl cyanoacetate in the presence of an equivalent of piperidine, extensive decomposition was observed but no product incorporating ethyl cyanoacetate could be found. Instead, 3,5-dicarbomethoxy-4-hydroxyisoxazole (3) was isolated in low yield. When the reaction was repeated with an excess of piperidine with no ethyl cyanoacetate present, 3 was produced in slightly greater amounts. In addition, *N*-nitrosopiperidine was isolated. Scheme I shows a mechanism to account for these results.

N-Nitroso nitrones similar to 4 have been proposed as the first intermediate in the nitrosation of oximes.[3] They were also proposed to be intermediates in the hydrolysis and thermolysis of pernitrosomesityl oxide.[4] The latter reaction, which leads to an isoxazolone oxime, is particularly similar to the present one.

It appears from the present work and other unpublished work that compounds such as 1 are too sensitive to bases to allow useful reactions to occur.

Experimental Section

2,5-Dicarbomethoxy-3,4-diazacyclopentadienone 3,4-Dioxide and Piperidine. A mixture of 1 g (4.3 mmol) of dioxide 2 and 1.0 mL of piperidine in 50 mL of ethanol was stirred at room temperature for 2 h. The mixture was concentrated to one-half its volume and was placed in a freezer ovenight. The pale yellow crystals that separated were collected on a filter: mp 140 °C dec; yield 0.25–0.3 g (20–25%). This material is the **piperidine salt of 3,5-dicarbomethoxy-4-hydroxyisoxazole.**

Calcd. for $C_{12}H_{18}N_2O_6$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.51; H, 6.59; N, 9.71. This material was identical with an authentic sample prepared from piperidine and 3,5-dicarbomethoxy-4-hydroxyisoxazole.

The salt was dissolved in chloroform, and ethereal HCl was added. Upon cooling, a white solid separated. Recrystallization from hexane–CH_2Cl_2 gave white crystals of **3,5-dicarbomethoxy-4-hydroxyisoxazole,** mp 158–158.5 (lit.[5] 157–158 °C). Its infrared spectrum was identical with an authentic sample prepared by the reaction of dimethyl acetonedicarboxylate with amyl nitrite.[5]

Chromatography of the filtrate from the original reaction misture on silica with CH_2Cl_2 as eluant yielded a yellow oil whose infrared spectrum was identical with that of an authentic sample of *N*-nitrosopiperidine.[6]

Registry No. 2,5-Dicarbomethoxy-3,4-diazacyclopentadienone 3,4-dioxide, 17952-98-6; 3,5-dicarbomethoxy-4-hydroxyisoxazole piperidine salt, 85995-80-8; 3,5-dicarbomethoxy-4-hydroxyisoxazole, 6620-30-0; piperidine, 110-89-4.

(2) Bunney, J. E.; Hooper, M. *Tetrahedron Lett.* **1966**, 3857–3860.
(3) Freeman, J. P. *Chem. Rev.* **1973**, *73*, 283–292.
(4) Freeman, J. P. *J. Org. Chem.* **1962**, *27*, 1309–1314.
(5) Klötzer, W.; Schantl, J. *Monatsh. Chem.* **1964**, *95*, 102–115.
(6) Care is required in the handling of nitrosamines because of their carcinogenicity.

A Novel Furan Synthesis. Menthofuran from 2-Bromo-4-methylcyclohexanone and (α-Formylethylidene)triphenylphosphorane

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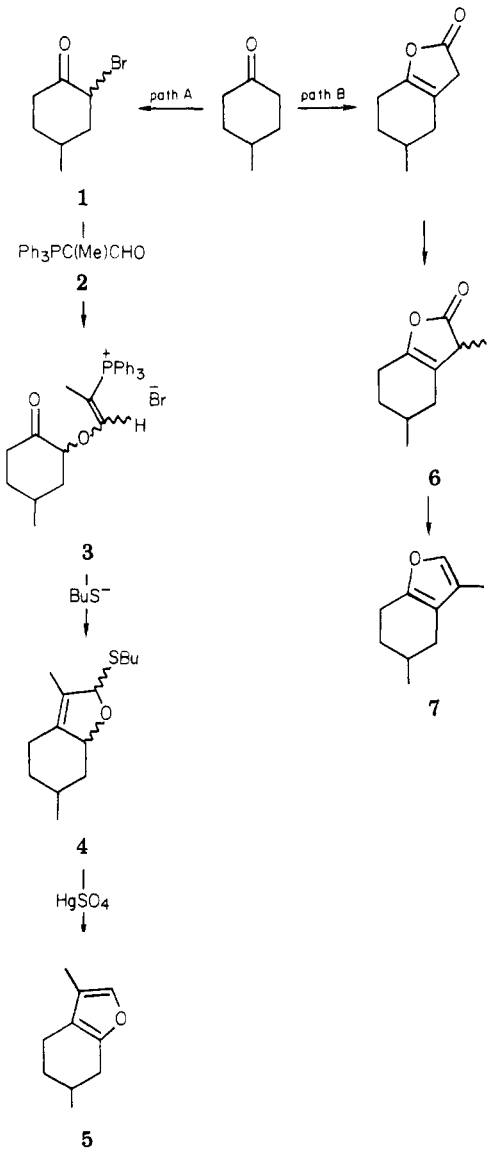
The widespread occurrence of natural products containing furan rings[1] has stimulated continued interest in the synthesis of this heterocycle with various substitution patterns.[2] The most common type of furan found naturally, exemplified by menthofuran (5) and isomenthofuran (7), has usually been prepared by reduction of a butenolide, as in 6 → 7 in path B of Scheme I.[3,4] We have previously reported a direct synthesis of furans having this substitution pattern from α-hydroxy ketones and (2-ethoxy-1-methylvinyl)triphenylphosphonium bromide,[5] but this synthesis lacked regiospecificity because acyloin isomerization could not be avoided and mixtures of isomeric fu-

(1) Devon, T. K.; Scott, A. I. "Handbook of Naturally Occurring Compounds, Terpenes"; Academic Press: New York, 1972; Vol. II.
(2) (a) Hikino, H.; Konno, C. *Heterocycles* **1976**, *4*, 817–870. (b) Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *30*, 167–238.
(3) For example, Grieco, P. A.; Pogonowski, C. S.; Burke, S. *J. Org. Chem.* **1975**, *40*, 542–543.
(4) Gariboldi, P.; Jommi, G.; Sisti, M. *J. Org. Chem.* **1982**, *47*, 1961–1962 and references therein. Gariboldi et al. described a synthesis via β-furanones that could readily be adapted to construction of furans with the substitution pattern of 5 and 7.
(5) Garst, M. E.; Spencer, T. A. *J. Org. Chem.* **1974**, *39*, 584–585.

0022-3263/83/1948-2442$01.50/0

Scheme I



rans (e.g., **5** and **7**) resulted. In this paper we report a simple synthesis of menthofuran (**5**)[6] from 4-methylcyclohexanone by a route (path A, Scheme I) that should be generally applicable to regiospecific synthesis of such furans.

We[5] and others[7] have taken advantage of the fact that (α-formylethylidene)triphenylphosphorane (**2**)[8] is readily alkylated on oxygen. In the present instance, 2-bromo-4-methylcyclohexanone (**1**)[9] was used to alkylate **2**, presumably leading to oxophosphorane **3**. This substance was not characterized but was treated with sodium *n*-butyl mercaptide in ether to afford material assumed to be **4**, which was in turn readily converted to menthofuran (**5**) by brief treatment with mercuric sulfate. The overall yield of **5** from 4-methylcyclohexanone was 49%.

Nucleophiles other than mercaptide ion (e.g., fluoride ion, tertiary amines) were tested but failed to yield furan. Use of ethoxide ion in reaction with the putative **3** afforded a mixture of **5** and **7**.

This furan synthesis requires specific preparation of an α-bromo ketone, a process conveniently accomplished via a silyl enol ether.[10] The regiochemistry of the present synthesis complements the available methodology,[3,4] which would allow conversion of 4-methylcyclohexanone to isomenthofuran (**7**).

Experimental Section

Infrared (IR) spectra were recorded on a Pye-Unicam SP-3-200 spectrophotometer. Proton nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM 390 spectrometer at 35 °C in $CDCl_3$; carbon NMR spectra were recorded on a JEOL-CFT-100 spectrometer in $CDCl_3$.

2-Bromo-4-methylcyclohexanone (1). A solution of 11.2 g (0.10 mol) of 4-methylcyclohexanone, 12.9 g (0.12 mol) of chlorotrimethylsilane,[11] 12.1 g (0.12 mol) of triethylamine (distilled from barium oxide) in 100 mL of anhydrous benzene (distilled from calcium hydride) was heated at reflux for 3 days. The benzene was evaporated and the residue was partitioned between hexane and saturated $NaHCO_3$ solution. The hexane layer was dried over $MgSO_4$ and evaporated to leave 17.2 g (92%) of 1-(silyloxy)-4-methyl-1-cyclohexene. This material was brominated by the method of Conia[10] to provide an 85% yield of the known **1**.[9]

Menthofuran (5). A solution of 0.95 g (5×10^{-3} mol) of **1** and 2.38 g (7.5×10^{-3} mol) of (α-formylethylidene)triphenylphosphorane[8] (**2**) in 25 mL of CH_2Cl_2 was heated at reflux for 24 h. Evaporation of the solvent left a viscous oil that was not characterized but which possessed new IR absorptions at 1725 and 1625 cm^{-1}. This oil was suspended in 100 mL of anhydrous ether and sequentially treated with 0.90 g (0.01 mol) of butanethiol and 0.24 g (0.01 mol) of sodium hydride. The resulting suspension was allowed to stir at room temperature for 24 h and at reflux for 24 h. The suspension was filtered and the filtrate was treated with 1.5 g (5×10^{-3} mol) of $HgSO_4$. After 1 h this suspension was filtered and concentrated to provide an oil. Elution of this oil from 20 g of Florisil with pentane afforded 0.38 g (58%) of **5** identical with an authentic sample[12] by IR, ^1H NMR, and ^{13}C NMR.[13]

Acknowledgment. This research was supported at Dartmouth by grants from the Petroleum Research Fund, administered by the American Chemical Society, and at the University of California, San Diego, by the Cancer Research Coordinating Committee.

Registry No. 1, 27579-55-1; 2, 24720-64-7; 3, 85995-54-6; 5, 494-90-6; 4-methylcyclohexanone, 589-92-4; chlorotrimethylsilane, 75-77-4; 1-(silyloxy)-4-methyl-1-cyclohexene, 38671-78-2; butanethiol, 109-79-5.

(6) For previous syntheses of menthofuran, see: (a) Trahanovsky, W. S.; Cassady, T. J.; Woods, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 6691–6695. (b) Tsuboi, S.; Shimozuma, K.; Takeda, A. *J. Org. Chem.* **1980**, *45*, 1517–1520. (c) Harirchian, B.; Magnus, P. *Synth. Commun.* **1977**, *7*, 119–123. (d) Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Chou, K. J. *J. Am. Chem. Soc.* **1977**, *99*, 4778–4782. (e) Zalkow, L. H.; Ellis, J. W. *J. Org. Chem.* **1964**, *29*, 2626–2629. (f) Zalkow, L. H.; Ellis, J. W.; Brennan, S. M. R. *Ibid.* **1963**, *28*, 1705–1707. (g) Setter, H.; Lauterbach, R. *Chem. Ber.* **1960**, *93*, 603–607. (h) Fritel, H.; Fêtizon, M. *J. Org. Chem.* **1958**, *23*, 481. (i) Fritel, H.; Baranger, P. *C. R. Acad. Sci., Ser. C* **1955**, *241*, 674–677. (j) Treibs, W.; Lucius, G.; Kögler, H.; Breslauer, H. *Justus Liebigs Ann. Chem.* **1953**, *581*, 59–65. (k) Treibs, W. *Chem. Ber.* **1937**, *70*, 85–89.

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(12) Pfaltz & Bauer, Inc., Stamford, CT.

(13) We are grateful to Ms. Janice Frazier for obtaining the ^{13}C NMR spectra.