the EtOH and then lyophilized to afford **7** as a solid (2.66 g, 93%): mp 117–119 °C; IR (KBr) 3370, 2110, 1090, 1065 cm^{-1}; ^{13}C NMR (D_2O) δ 61.0, 62.7, 63.8, 67.9, 69.9, 98.3.

Anal. Calcd for $C_6H_{11}N_3O_5$: C, 35.12; H, 5.40; N, 20.48. Found: C, 35.21; H, 5.27; N, 20.60.

2(*R*),5(*R*)-Bis(hydroxymethyl)-3(*R*),4(*R*)-dihydroxypyrrolidine (3). A solution of 5-azidofructose **7** (2.05 g, 10 mmol) in 100 mL of EtOH containing a catalytic amount of 10% Pd/C was treated with H_2 at ~25 psi. When H_2 uptake ceased, the mixture was filtered through Celite and the volatiles were removed under reduced pressure affording 1.63 g (100%) of **3** as a colorless solid: mp 115–117 °C; ^{13}C NMR (D_2O) δ 61.8, 62.2, 78.1; $[\alpha]_D$ + 55.8° (*c* 1.0, H_2O) [lit.[4] $[\alpha]_D$ +56.4° (*c* 7.0, H_2O)].

Anal. Calcd for $C_6H_{13}NO_4$: C, 44.17; H, 8.03; N, 8.58. Found: C, 44.09; H, 8.03; N, 8.40.

Glycosidase Inhibition Studies. Invertase (EC 3.2.1.26), α-glucosidase (EC 3.2.1.20), β-glucosidase (EC 3.2.1.21), *p*-nitrophenyl α-D-glucopyranosides and *p*-nitrophenyl β-D-glucopyranosides were obtained from Sigma Chemical Co. Hydrolysis of sucrose was monitored by the rate of glucose production as assayed by NAD reduction during enzymatic oxidation of glucose 6-phosphate to 6-phosphogluconate. Hydrolysis of *p*-nitrophenyl glucosides was monitored by absorbance at 405 nm after appropriate dilution of the hydrolysate with 0.1 M $NaHCO_3$. The buffer system for all pHs tested was 25 mM citrate, 25 mM *N*-(2-hydroxyethyl)piperazine-*N'*-2-ethanesulfonic acid, and 25 mM 2-morpholinoethane sulfonic acid and all reactions were run at 30 °C.

Registry No. **3**, 59920-31-9; **4**, 53821-66-2; **5**, 94801-00-0; **6**, 94801-01-1; **7**, 94801-02-2; α-glucosidase, 9001-42-7; β-glucosidase, 9001-22-3; invertase, 9001-57-4; *p*-nitrophenyl α-D-glucopyranoside, 3767-28-0; *p*-nitrophenyl β-D-glucopyranoside, 2492-87-7; sucrose, 57-50-1; glucose, 50-99-7.

Synthesis of 4-Substituted Cycloheptatrienones by Oxidative Cheletropic Elimination of Nitrosobenzene from 6-Substituted 8-Phenyl-8-azabicyclo[3.2.1]octa-3,6-dien-1-ones

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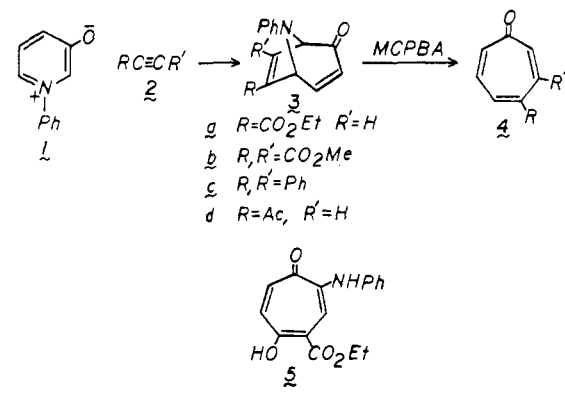
Three recent model studies for natural product synthesis have made use of cycloheptatrienone.[2-4] Actual application of these models will require efficient preparations of substituted cycloheptatrienones. We have reported a preparation of 3- and of 4-carbethoxycycloheptatrienone in which we mentioned our attempts to remove "*N*-phenyl" from 6,*N*-diphenyl-8-azabicyclo[3.2.1]octa-3,6-dien-1-one (**3d**).[5] In this note, we describe a solution to this cheletropic elimination that yields 4-substituted cycloheptatrienones in two steps.

Katritzky, Dennis, and co-workers[6] have attempted to synthesize cycloheptatrienones starting with cycloadducts

Scheme I



obtained from the reactions of electron-deficient olefins with 3-hydroxypyridinium betaines. During Hofmann elimination, an oxidation occurred to give 2-aminocycloheptatrienones despite numerous attempts to prevent this oxidation. Our plan was to react 1-phenyl-3-hydroxypyridinium betaines with acetylenes. The resulting cycloadducts would be oxidized to amine *N*-oxides that then would be pyrolyzed to provide the desired cycloheptatrienones and nitrosobenzene.[7]

These two steps were realized with the following limitations. Betaine **1** was reacted with acetylenes **2a–d** to provide cycloadducts **3a–d**. No cycloadducts were obtained with diphenylacetylene or 1-hexyne (Scheme I). Treatment of **3a–c** with *m*-chloroperbenzoic acid provided cycloheptatrienones **4a–c** respectively. No intermediate *N*-oxides could be isolated. Two equivalents of *m*-chloroperbenzoic acid were necessary for complete reaction of the cycloadduct. A mixture of nitrosobenzene and nitrobenzene also was formed. Oxidation of **3d** provided trace amounts (<5%) of a mixture of products.[8]

Side product **5** was obtained from the oxidation of cycloadduct **3a**. Meisenheimer rearrangement of the *N*-oxide followed by cleavage of the N–O bond would provide **5**. Compound **5** exhibited a carbonyl stretch at 1668 cm^{-1} in the infrared spectrum for the ester group, which is similar to that for ethyl salicylate. The lack of a large hydroxyl stretch at 3300 cm^{-1} indicates strong intramolecular hydrogen bonding. The rest of the spectral data is consistent with structure **5**.

This cheletropic loss of nitrosobenzene from **3a–c** appears to be among the more facile examples of this reaction. Although aziridine *N*-oxides[9] and aromatic 1,4-imine N-oxides[10] fragment under comparable conditions, the former reaction relieves ring strain and the latter generates an aromatic system. The 8-azabicyclo[3.2.1]octa-3,6-dien-1-one is not strained, and the product lacks substantial resonance stabilization. We have noted that 4-carbethoxycycloheptatrienone and nitrosobenzene do not react with each other under these conditions.

We have developed a two-step synthesis of 4-substituted cycloheptatrienones. This route is limited by the cyclo-

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(2) Rigby, J. H. *Tetrahedron Lett.* **1982**, *23*, 1863–1867.
(3) Garst, M. F.; Roberts, V. A. Prussin C. *J. Org. Chem.* **1982**, *47*, 3969–3970.
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(5) Garst, M. E.; Roberts, V. A. *J. Org. Chem.* **1982**, *47*, 2188–2190.
(6) Dennis, N.; Katritzky, A. R.; Parton, S. K.; Nomura, Y.; Takahasli, Y.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans 1* **1976**, 2289–2296.
(7) For an alternative solution, see: Chapman, O. L.; Bugner, D. E.; Pacific Conference on Chemistry and Spectroscopy, 1981, Abstract No. 180.
(8) The major compound was bright red and formed during workup. We have been unable to purify or isolate anything from this mixture. The NMR spectrum of this material showed no methyl ketone. No **3d** remained at the end of the reaction, and nitrosobenzene was formed. Therefore, cycloheptatrienone **4d** probably was formed during the reaction but was either further oxidized or decomposed during workup.
(9) Baldwin, J. E.; Bhatnagar, A. K.; Choi, S. C.; Shortridge, T. J. *J. Am. Chem. Soc.* **1971**, *93*, 4083–4084. Heine, H. W.; Meyers, J. D.; Peltzer, E. T. *Angew. Chem., Int. Ed. Engl.* **1970**, *8*, 374.
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addition of betaine 1 with electron-deficient acetylenes[6] and by the stability of the final cycloheptatrienone to the mild oxidation conditions and subsequent workup.

Experimental Section

General Procedures. Infrared spectra were recorded as thin films on a Beckman IR 18-AX spectrophotometer; bands yielding structural information are reported in reciprocal centimeters (cm^{-1}), using polystyrene calibration. Nuclear magnetic resonance spectra were recorded on a Varian EM 390 spectrometer at 35 °C in deuteriochloroform, and peak positions are reported in parts per million (ppm) from tetramethylsilane (Me_4Si) internal standard, using multiplet (m), quartet (q), triplet (t), doublet (d), or singlet (s). Proton-decoupled ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian CFT-20 spectrometer. These peak positions are reported in ppm, using Me_4Si as an internal standard. Mass spectra were obtained from a Finnigan 4021 instrument at 70 eV. The percentage of the base peak is given in parentheses.

A Varian 3700 gas chromatograph with FID detector outfitted with 6 ft × $^1/_4$ in. glass column containing 3% SE-30 or 3% Dexil on 100/120 Gas Chrom Q was used for GC analysis.

Column chromatography was executed at medium pressure (50–100 psi) on E. Merck silica gel 60, particle size 0.040–0.063 mm.

6-Carbethoxy-8-phenyl-8-azabicyclo[3.2.1]octa-3,6-dien-2-one (3a). The method of Katritzky[6] was modified as follows. Triethylamine (2.50 g, 0.025 mol) was added to a solution of 3-hydroxy-1-phenylpyridinium chloride (5.00 g, 0.025 mol) in 75 mL of dry acetonitrile. The resulting precipitate of triethylamine hydrochloride was filtered and the solvent of the filtrate was removed under reduced pressure. Benzene (75 mL) was added to the hygroscopic residue under nitrogen. Ethyl propiolate (3.50 g, 0.036 mol) was added and the resulting solution refluxed for 8 h. The resulting reaction mixture was filtered through a pad on Florisil with ethyl acetate. Evaporation of the solvent followed by chromatography of the residue on Florisil with ethyl acetate–hexanes (1:4) yielded adduct **3a**. Recrystallization from absolute ethanol provided 2.30 g (35%) of **3a**: mp 109–111 °C; IR 3060, 2980, 1725, 1697, 1600, 1250 cm^{-1}; NMR δ 1.3 (t, 3 H, J = 8 Hz), 4.3 (q, 2 H, J = 8 Hz), 4.3 (m, 1 H), 5.2 (d, 1 H, J = 4 Hz), 5.5 (dd, 1 H, J = 10, 2 Hz), 6.7–6.9 (m, 2 H), 7.0–7.4 (m, 5 H).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.35; H, 5.61; N, 5.20. Found: C, 71.26; H, 5.73; N, 5.21.

6,7-Dicarbomethoxy-8-phenyl-8-azabicyclo[3.2.1]octa-3,6-dien-2-one (3b). The above procedure was followed with 2.00 g (0.010 mol) of 3-hydroxy-1-phenylpyridinium chloride, 1.00 g of triethylamine, and 2.84 g (0.20 mol, 2 equiv) of dimethyl acetylenedicarboxylate. The mixture was refluxed for 70 min. Chromatography as above followed by recrystallization gave 29% of **3b**: mp 155–157 °C; IR 3060, 2860, 1725, 1700, 1600, 1495, 1435, 1250 cm^{-1}; NMR δ 3.9 (5, 6 H), 5.2 (m, 2 H), 5.6 (dd, 1 H, J = 10, 2 Hz), 6.7–7.0 (m, 3 H), 7.2–7.5 (m, 3 H).

Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.15; H, 4.82; N, 4.47. Found: C, 65.15; H, 4.92; N, 4.30.

6,8-Diphenyl-8-azabicyclo[3.2.1]octa-3,6-dien-2-one (3c). The procedure of Katritzky[6] was used to prepare this compound.

6-Acetyl-8-phenyl-8-azabicyclo[3.2.1]octa-3,6-dien-2-one (3d). The above procedure was followed with 2.00 g (0.010 mol) of 3-hydroxy-1-phenylpyridinium chloride, 1.00 g of triethylamine, and 1.38 g (0.020 mol) of 3-butyn-2-one. The mixture was refluxed for 6 h. Chromatography provided 1.50 g (60% yield) of **3d**: mp 156–159 °C; IR 3050, 1692, 1670, 1600, 1495 cm^{-1}; NMR δ 2.1 (5, 3 H), 5.0 (m, 1 H), 5.2 (m, 1 H), 5.4 (dd, 1 H, J = 10, 1 Hz), 6.6–7.3 (m, 7 H).

Synthesis of Cycloheptatrienones 4a–c.[11] Cycloadduct **3a** (0.27 g, 1.0 mmol) was dissolved in 10 mL of methylene chloridene under nitrogen. A solution of *m*-chloroperbenzoic acid (0.40 g, 2.0 mmol) in 2 mL of methylene chloride was added dropwise over 5 min. The resulting solution was stirred at room temperature for 1 h. The organic layer was washed rapidly with two ice-cold 5-mL portions of 5% sodium carbonate and 5 mL of brine. The organic layer was dried over $MgSO_4$ and the solvent evaporated. Chromatography on silica gel with ethyl acetate–hexanes, 4:1, removed nitrobenzene and nitrosobenzene. Further elution with ethyl acetate–hexanes (1:1) provided the substituted cycloheptatrienones.

Cycloheptatrienone 4a (61%):[5] Eluted before **4a** with ethyl acetate–hexane (1:1) was a bright red compound **5** (13%): IR 3330, (w) 3040, 2990, 1668, 1620, 1600, 1560, 1515, 1285, 1225 cm^{-1}; NMR δ 1.33 (t, 3 H, J = 6 Hz, 4.37 (q, 2 H, J = 6 Hz), 7.1–7.5 (m, 8 H), 7.9 (br s, 1 H), 8.15 (s, 1 H); ^{13}C NMR 176.7, 171.4, 161.8, 143.7, 139.3, 136.0, 132.3, 129.3, 124.1, 122.0, 111.5, 109.6, 62.7, 13.8; mass spectrum, m/z 285 (M^+, 32), 239 (85), 210 (100), 182 (32), 154 (36), 129 (22), 105 (11), 104 (11), 77 (70).

Cycloheptatrienone 4b (63%): UV (EtOH) 233, 321 nm; IR 3040, 3010, 2960, 2850, 1730, 1640, 1595, 1438, 1270 cm^{-1}; NMR δ 3.80 (s, 3 H), 3.85 (s, 3 H), 6.9–7.3 (m, 3 H), 7.60 (dd, 1 H, J = 7, 3 Hz).

Cycloheptatrienone 4c (55%): UV (EtOH) 222 nm (ε 13000), 303.5 (5000); IR 3040, 1665, 1620, 1560, 1480, 1220 cm^{-1}; NMR δ 6.5–7.5 (m); mass spectrum, m/z 182 (M^+, 47), 155 (25), 154 (100), 153 (62), 152 (52), 128 (13), 127 (11), 121 (22), 77 (39).

No evidence of compounds analogous to **5** was seen in the oxidations of **3b** or **3c**.

Registry No. **3a**, 94957-17-2; **3b**, 94957-18-3; **3c**, 94957-19-4; **3d**, 94957-20-7; **4a**, 80865-79-8; **4b**, 94957-21-8; **4c**, 94957-22-9; **5**, 94957-23-0; 3-hydroxy-1-phenylpyridinium chloride, 15941-41-0; dimethyl acetylenedicarboxylate, 762-42-5; 3-butyn-2-one, 1423-60-5; ethyl propiolate, 623-47-2; 1,2-diphenylethyne, 501-65-5.

(11) Our previous attempts failed for one or more of the following reasons. These cycloheptatrienones decompose in chloroform or on alumina. The *m*-chlorobenzoic acid is difficult to remove by chromatography. We did not anticipate the observed NMR chemical shifts. The moderate yields of **a–c** are due too partial decomposition during workup.

Synthesis with HOCl. Conversion of Pulegone and Isopulegol to Menthofuran. Preparation of 3,6-Dimethyl-2,6-cycloheptadien-1-one from Phorone

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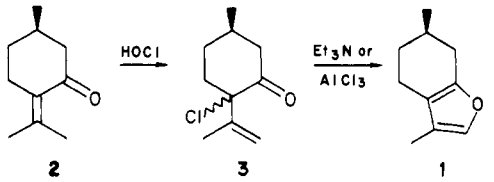
Herein we illustrate the utility of the reaction of HOCl with olefins[1] and conjugated ketones[2] by the synthesis of the isomeric chloroisopulegones from (−)-isopulegol (**4**) and (+)-pulegone (**2**), followed by their facile conversion to (+)-menthofuran (**1**).[3]

Treatment of (+)-pulegone (**2**) with 1 equiv of HOCl[2] afforded 4-chloroisopulegone (**3**) as a mixture of stereo-



2 **3** **1**

isomers[4] in 75% isolated yield. Dehydrochlorination of **3** was affected by refluxing with triethylamine and afforded

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(4) The NMR analysis indicates a 3:2 mixture of stereoisomers.

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