ence between a methiodide and a corresponding protonated system is an axial methyl substituent then an axial methyl β-substituent parameter at C-2,6 can be derived. In the 4-piperidones an average downfield shift of 7.1 ppm is derived while in the piperidines the corresponding value is 8.1 ppm. The $CH_3NCH_{3\,C\text{-}\alpha}{}^+$ parameter given in Table III for the piperidines (10.5 ppm) was derived from the data on the methiodides of 1,2-dimethyl- (VIII) and 1,2,6-trimethylpiperidine (IX) and consequently comprises an effect from the *N*-methyl-axial substituent (8.1 ppm) and the C-2′ methyl effect for the hydrochlorides (2.2 ppm). The sum of these values (10.3 ppm) is remarkably close to the composite value (10.5 ppm) as given in Table III. Similarly, in the piperidones the corresponding value (4.6 ppm) comprises the axial β-substituent effect (7.1 ppm) and the "charge effect" at C-2,6 (−3.1 ppm) providing the sum 4.0 ppm, also in close agreement with the composite value. These summations add further justification to the parameterization procedure suggested by the results of the present work. The effects of methiodation at the C-3,5 and C-4 sites follow similar trends to the hydrochlorides, though their magnitudes are greater. Further effects are also apparent at the substituent methyl carbons. The *N*-methyl carbons are found downfield 11.2 and 2.1 ppm, on the average, compared with the *N*-methyl carbon in the neutral molecule, while the shift at C-2′ in the 2-methyl-4-piperidones is shifted upfield an average of 4.6 ppm on methiodation. This latter shift is presumably steric in origin (see ref 35). A similar shift effect at C-3′ in the hydrochlorides (0.8 ppm) of the 3-methyl-4-piperidones VI and VII is also observed in the methiodides (0.9 ppm) and is also attributed to the steric effects.

The methiodides of substituted 4-piperidones are generally hydrolyzed in aqueous solution.[9,10] The carbon-13 shifts of the resulting geminal diols are given in Table I and although the upfield shift (approximately 100 ppm) at C-4 is clearly indicative of the change from a carbonyl to a geminal diol center no trends are clear for the other ring carbons.

Conclusions

The substituent additivity parameters summarized in Table III, in addition to the considerations outlined in the Discussion section, should provide a useful basis for the analysis of structure and conformation in more complex molecules. In subsequent studies, to be published, we have used these parameters with some success in order to determine conformations in a series of synthetic analgesics.[36]

Registry No.—IV, 1445-73-4; IV HCl, 34737-83-2; IV CH_3I, 34737-84-3; V, 13669-32-4; V HCl, 34737-86-5; V CH_3I, 34737-87-6; VIa, 4629-80-5; VIa HCl, 4629-76-9; VIa CH_3I, 34737-88-7; VIb, 34737-89-8; VIb HCl, 26822-34-4; VIb CH_3I, 34737-91-2; VII, 20281-02-1; VII HCl, 29849-51-2; VII CH_3I, 34737-92-3; VIIIa, 109-05-7; VIIIb, 671-36-3; VIIIb HCl, 5072-43-5; VIIIb CH_3I, 34737-95-6; IXa, 504-03-0; IXb, 669-81-8; IXb HCl, 5072-29-7; IXb CH_3I, 34737-99-0.

Acknowledgments.—This work was supported in part by the National Research Council of Canada, Grant A6416. We thank the referee for some helpful comments and Mr. Glen Bigam for spectrometer maintenance.

[36] *E.g.*, A. J. Jones, A. F. Casy, and K. M. J. McErlane, *Tetrahedron Lett.*, 1727 (1972).

Synthesis and Mass Spectra of Some 2-Carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-4(1*H*)-quinazolinones

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A synthesis of 2-carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-4(1*H*)-quinazolinones is described and the major electron impact fragmentation pathways of this series are discussed.

We have recently noted that enamines **1**, prepared by condensation of anthranilamides and dimethyl acetylenedicarboxylate, are versatile precursors of several classes of heterocyclics.[2] Treatment of **1** with NaOMe in xylene produces a new class of benzodiazepinediones **4**, which are labile in alcohol. The reaction of **1** with NaOMe in MeOH leads directly to maleimides **2** and quinazolinones **3**, which can also be obtained in the same ratio in a separate experiment as the ring contraction products of the benzodiazepinediones, thus pointing toward **4** as a possible intermediate.

The isolation of pure quinazolinones by this technique is tedious, since careful fractional separation from the maleimide coproducts is necessary, and only three quinazolinones (**3a**–**c**) were prepared by this route. With an *N*-methyl group on either the amide or amino nitrogen of the anthranilamide, steric hindrance apparently prevents formation of a benzodiazepinedione intermediate and only quinazolinone (**3d** or **3e**) (not admixed with maleimide) results in base-catalyzed cyclization of the corresponding adduct.

We have now found that the quinazolinones **3** can be obtained uncontaminated by benzodiazepine or maleimide coproducts, by simple thermolysis of the enamino adducts **1**. The quinazolinones obtained displayed two saturated ester carbonyls in their ir spectra between 1725 and 1750 cm^{-1} and a characteristic CH_2 resonance

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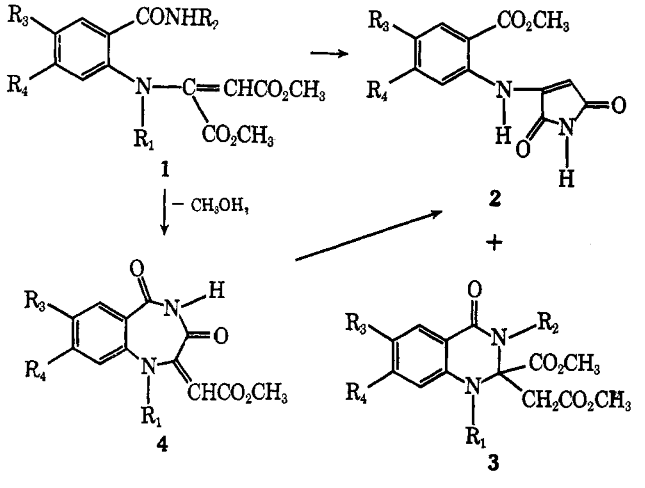
[2] N. D. Heindel, V. B. Fish, and T. F. Lemke, *J. Org. Chem.*, **33**, 3997 (1968).

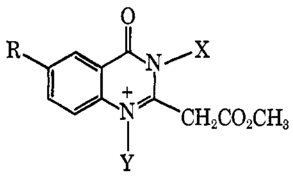


	R_1	R_2	R_3	R_4
a	H	H	H	H
b	H	H	Cl	H
c	H	CH_3	H	H
d	CH_3	H	H	H
e	CH_3	CH_3	H	H
f	H	C_6H_5	Cl	H
g	CH_3	H	Cl	H
h	H	CH_3	Cl	H
i	H	H	OCH_3	Cl
j	H	H	F	H

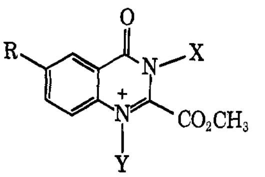
in the nmr at δ 3.18 ± 0.10 ppm. The mass spectral fragmentation patterns for several of the quinazolinones were tabulated (Table I) for the purpose of assigning fundamental pathways. Very few electron impact studies have been performed on this heterocyclic class.[3]

The molecular ions were observed for all the quinazolinones at very low abundancies (less than 0.1% of the base peak) except for the dimethyl compound **3e**, which has a parent ion of 2.7 relative intensity.

The nature of the substituents at C-2 in all the quinazolinones was clearly demonstrated by the appearance of the generally abundant ions, a and b, resulting from



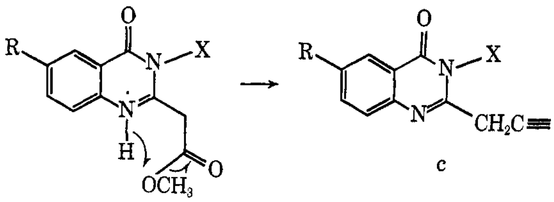
a



b

a "type A_1" cleavage[4] of carbomethoxy ($\cdot CO_2Me$, 59 mass units) and carbomethoxymethyl ($\cdot CH_2CO_2Me$, 73 mass units), respectively, from the molecular ion.

Another general feature of the cracking patterns was the loss of methanol (mass 32) from the a species. The process is envisioned as proceeding through a concerted, cyclic intermediate leading to species c.



c

TABLE I

MASS SPECTRA OF 2-CARBOMETHYL-2-CARBOMETHOXYMETHYL-3-R_1-2,3-DIHYDRO-6-R_2-4(*H*)-QUINAZOLINONES[a]

Compd	Molecular ion, *m/e*	*m/e* (rel abundance)
3a	278	219 (100), 205 (25), 187 (29), 173 (4.4), 160 (24), 159 (96), 146 (10), 145 (31), 132 (12), 130 (15), 129 (12), 120 (8.8), 119 (13), 91 (14), 90 (7.0), 89 (14)
3b	312	253 (14), 238 (75), 221 (1.0), 193 (7.6), 180 (100), 179 (27), 178 (32), 160 (12), 153 (50), 124 (42), 74 (35)
3c	292	233 (100), 219 (14), 201 (15), 173 (35), 159 (15), 146 (15), 132 (20), 104 (7.7)
3d	292	233 (100), 219 (23), 202 (7.9), 201 (49), 174 (8.8), 159 (8.8), 134 (10), 132 (7.9), 105 (16), 104 (16), 78 (10), 77 (18)
3e	306	306 (2.7), 248 (15), 247 (100), 233 (12), 215 (5.4), 188 (5.4), 160 (15), 145 (8.0), 114 (15), 73 (14)
3f	388	329 (53), 328 (100), 315 (14), 297 (21), 269 (57), 255 (9), 234 (8), 180 (8), 153 (9), 132 (54), 125 (7), 124 (10), 117 (10), 91 (9), 77 (40)
3g	326	326 (2.5), 267 (100), 253 (11), 235 (33), 208 (5.0), 193 (6.3), 168 (11), 166 (4.4), 139 (9.4), 138 (9.4), 111 (6.3), 77 (8.8), 75 (7.5)

[a] Values of ion abundancies (relative to base peak) of less than 1% and of ions containing the minor isotope of chlorine are omitted from the table.

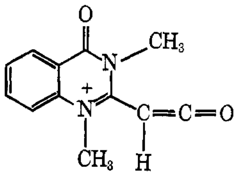
That the overall transition to these P − 91 ions did in fact encompass a distinct 32 mass loss was indicated by the presence of the appropriate metastable ions (Table II).

TABLE II

METASTABLE IONS

Compd	m^*	Transition	Calcd
3a	159.5	219 → 187	159.7
	135.4	187 → 159	135.2
	104.5	159 → 129	104.7
3b	130.0	180 → 152	130.1
3c	173.5	233 → 201	173.4
3d	173.5	233 → 201	173.4
3e	187.5	247 → 215	187.1
3g	207	267 → 235	206.8

This same pathway was not available to the dimethyl derivative **3e**, and thus an alternative route to the *m/e* 215 ion appears to be the loss of methanol totally from the side chain, leading to species d.



d

The P − 91 species (c or d) further fragmented with losses of either CO (mass 28) or ketene (mass 42). The product of the first loss is the result of losing the side

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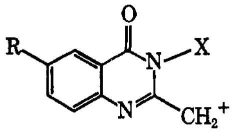
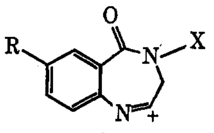
(3) G. Spiteller, *Advan. Heterocycl. Chem.*, **7**, 343 (1966).

(4) K. Biemann, "Mass Spectrometry: Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962, pp 76–77.

chain carbonyl function to form e or its ring-expanded version f.

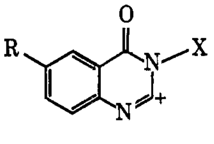

e

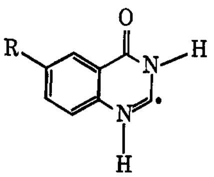

f

This transition was verified by the occurrence of a metastable peak for **3a** at 135.4 (Table II). This process did not occur for any of the quinazolinones with a methyl group at N-1.

Support for the intermediacy of a ring-expanded species was evidenced in at least one case by the facile loss of CH_2NH_2 (mass 30) from **3a** (metastable ion at 104.5), plausible only for species f.

Formation of ion g was observed for all the quinazolinones. This ion could arise by a McLafferty rearrangement of a or by loss of ketene from c.

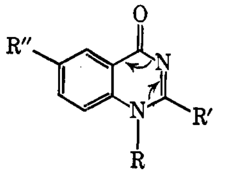

g

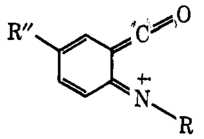

h

In the cases of **3a,b** this species could also have arisen from the loss of a hydrogen from h, which was produced by consecutive losses of $\cdot CO_2Me$ and $\cdot CH_2CO_2Me$ from the molecular ion.

Other prominent features of the high-mass portion of the spectra were the large abundances of the *m/e* 238 ion for **3b** and the *m/e* 328 ion for **3f** arising from McLafferty rearrangements with concomitant losses of CH_3CO_2Me and HCO_2Me, respectively, from the molecular ions.

Some of the compounds showed a tendency to undergo a retro Diels–Alder cleavage (type D)[5] in the same manner reported by Budzikiewicz, *et al.*,[6] for a series of quinazolinones in which the preferred cleavage of atoms 2 and 3 led to species i.




i

Important fragmentations of this type were observed for **3a** and **3f**, leading to ions *m/e* 119 (p − 159) and 153 (p − 236), respectively.

The contribution of this fragmentation pattern (**3b**) (*m/e* 153, p − 159) was uncertain due to the ease at which another process occurred, verified by the presence of a metastable ion at *m/e* 130 and due to the loss of HCN (mass 27) from the base peak.

Experimental Section

Melting points were determined between glass slide covers on a Fisher-Johns block and are reported uncorrected. Nmr spectra were determined on a Varian A-60 spectrometer using TMS as an internal standard.

Mass spectra were run on a Hitachi Perkin-Elmer RMU-6E high-resolution instrument equipped with a double-focusing sector and a direct solids inlet system. All of the compounds were analyzed by placing approximately 1 mg of the sample into a 1-mm i.d. quartz tube which was introduced into the ion source of the spectrometer by a vacuum interlock. It was necessary to elevate the temperature of the direct inlet system to 80° in order to achieve ionization at 80 eV. At this temperature, a quite singular mass spectrum was obtained for each of the compounds. High mass calibration of the spectra was accomplished by the use of tungsten hexacarbonyl as an internal standard.

Microanalyses were performed by the late Dr. V. B. Fish of these laboratories and by Dr. G. I. Robertson of Florham Park, N. J.

Anthranilamides.—These materials, with exceptions as noted, were prepared by nucleophilic ring opening of isatoic anhydrides with amines and have been described in the literature.[2,7,8]

Preparation of Dimethyl Acetylenedicarboxylate Adducts of Anthranilamides.—Reaction of equimolar amounts of the anthranilamide and dimethyl acetylenedicarboxylate in refluxing MeOH (0.1 mol/100 ml of solvent) produced the desired adducts. This procedure has been previously described for **1a–c**[2] and for **1i–j**[8] and was applied herein to the preparation of **1d–h**. The adduct **1e**, prepared from 2-(*N*-methylamino)-*N*-methyl benzamide, was a viscous oil and was utilized directly in synthesis of the quinazolinone.

1d was prepared in 71% yield by reaction of 2-(*N*-methylamino)benzamide and dimethyl acetylenedicarboxylate. Light yellow crystals, mp 161.5–163° (from benzene), were obtained.

Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.52; H, 5.51; N, 9.58. Found: C, 57.81; H, 5.77; N, 9.74.

1f, prepared by condensation of 2-amino-5-chlorobenzanilide and the alkyne ester, was obtained in 71% yield, mp 143–145° (from MeOH).

Anal. Calcd for $C_{19}H_{17}ClN_2O_5$: C, 58.69; H, 4.41; N, 7.20. Found: C, 58.65; H, 4.21; N, 7.40.

1g was obtained by reaction of 2-(*N*-methylamino)-5-chlorobenzamide with dimethyl acetylenedicarboxylate in 80% yield. The analytical sample, mp 171.5–172.5°, was isolated by recrystallization from MeOH.

Anal. Calcd for $C_{14}H_{15}ClN_2O_5$: C, 51.46; H, 4.63; N, 8.57. Found: C, 51.72; H, 4.48; N, 8.43.

1h, prepared in 75% yield by condensation of 2-amino-5-chloro-*N*-methylbenzamide and dimethyl acetylenedicarboxylate, melted at 163–165° after two recrystallizations from MeOH.

Anal. Calcd for $C_{14}H_{15}ClN_2O_5$: C, 51.46; H, 4.63; N, 8.57. Found: C, 51.51; H, 4.60; N, 8.28.

1e was obtained as a viscous oil by condensation of 2-(*N*-methylamino)-*N*-methylbenzamide[9] with acetylenedicarboxylate by the previously described method.[2,8] This oil was converted to the quinazolinone **3e** by redissolving in MeOH containing 0.1 g of NaOMe, then refluxing for 24 hr, concentrating, and diluting with water. The crude product precipitate (63%) was recrystallized from 95:5 cyclohexane–benzene to yield the analytical material, mp 85–86.5°.

Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.72; H, 5.81; N, 9.24.

Thermal Cyclizations to Quinazolinones.—The other quinazolinones reported herein were prepared by fusion of the anthranilamide adducts at 15–30° above their melting points. A sample procedure, illustrated by the synthesis of **3f**, follows.

6-Chloro-2-carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-3-phenyl-4-(1*H*)-quinazolinone (3f).—A 1.94-g (5.0 mmol) sample of **1f** was heated in an open tube at 165–175° for 2 hr. The cooled residue was then triturated with a mixture of equal parts of benzene and cyclohexane and filtered. The collected crystals (1.53 g, 79%) were washed with cyclohexane and re-

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[5] F. W. McLafferty, "Mass Spectrometry of Organic Ions," Academic Press, New York, N. Y., 1963, p 423.

[6] S. C. Pakrashi, J. Bhattacharyya, L. F. Johnson, and H. Budzikiewicz, *Tetrahedron*, **19**, 1011 (1963).

[7] N. D. Heindel, W. P. Fives, T. F. Lemke, and R. A. Carrano, *J. Pharm. Sci.*, **60**, 703 (1971).

[8] N. D. Heindel, W. P. Fives, T. F. Lemke, J. E. Rowe, H. W. Snady, and R. A. Carrano, *J. Med. Chem.*, **14**, 1233 (1971).

[9] H. Yale, *J. Heterocycl. Chem.*, **8**, 193 (1971).

crystallized from methanol to yield the pure quinazolinone **3f**: mp 198–200°; ir (Nujol mull) 3260 (NH), 1752 and 1738 (ester CO), and 1638 cm^{-1} (amide CO); nmr (DMSO-d_6) δ 7.93 (s, 1, NH, exchanges with D_2O), 7.58–7.26 (m, 7, ArH), 6.85 (d, 1, J_0 = 8.5 Hz, ArH_8), 3.64 (s, 3, OCH_3), 3.19 (s, 3, OCH_3), and 3.13 ppm (s, 2, CH_2CO).

Anal. Calcd for $C_{19}H_{17}ClN_2O_5$: C, 58.69; H, 4.41; N, 7.20. Found: C, 58.94; H, 4.20; N, 7.19.

2-Carbomethoxy-2-carbomethoxymethyl-6-chloro-2,3-dihydro-1-methyl-4(1*H*)-quinazolinone (3g).—Pyrolysis of **1g** provided an 88% yield of **3g**, which was recrystallized from benzene, mp 180–182°.

Anal. Calcd for $C_{14}H_{15}ClN_2O_5$: C, 51.46; H, 4.63; N, 8.57. Found: C, 51.64; H, 4.55; N, 8.67.

2-Carbomethoxy-2-carbomethoxymethyl-6-chloro-2,3-dihydro-3-methyl-4(1*H*)-quinazolinone (3h).—A 94% yield of **3h** was obtained from **1h**. Recrystallization from 1:1:1 MeOH–benzene–cyclohexane provided the analytical sample, mp 147.5–149°.

Anal. Calcd for $C_{14}H_{15}ClN_2O_5$: C, 51.46; H, 4.62; N, 8.57. Found: C, 51.53; H, 4.47; N, 8.67.

2-Carbomethoxy-2-carbomethoxymethyl-6-methoxy-7-chloro-2,3-dihydro-4(1*H*)-quinazolinone (3i).—**3i** was obtained by pyrolysis of **1i**. Four recrystallizations from MeOH gave the purified product (36%),[10] mp 169.5–171.5°.

Anal. Calcd for $C_{14}H_{15}ClN_2O_6$: C, 49.06; H, 4.41; N, 8.17. Found: C, 49.36; H, 4.58; N, 8.07.

2-Carbomethoxy-2-carbomethoxymethyl-6-fluoro-2,3-dihydro-4(1*H*)-quinazolinone (3j).—This compound was prepared in 36%[10] yield from **1j**, mp 178–180° (after recrystallization from MeOH).

Anal. Calcd for $C_{13}H_{13}FN_2O_5$: C, 52.70: H, 4.42; N, 9.45. Found: C, 52.92; H, 4.48; N, 9.42.

2-Carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-1-methyl-4(1*H*)-quinazolinone (3d).—**3d** was prepared by dissolving 3.0 g (0.01 mol) of **1d** in 50 ml of xylene containing 0.1 g of NaOMe and heating to reflux for 3.5 hr. Chilling precipitated 1.32 g of unreacted **1d**. Dilution of the filtrate with petroleum ether (bp 30–60°) gave 1.18 g of product. Two recrystallizations from MeOH yielded 1.02 g (34% conversion) of pure **3d**,[10] mp 118–120°.

Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.52; H, 5.51; N, 9.58. Found: C, 57.73; H, 5.41; N, 9.53.

Registry No.—**1d**, 34804-41-6; **1e**, 34804-42-7; **1f**, 34804-43-8; **1g**, 34804-44-9; **1h**, 34804-45-0; **3a**, 17244-35-8; **3b**, 17244-36-9; **3c**, 17244-40-5; **3d**, 34804-49-4; **3e**, 34804-50-7; **3f**, 34804-51-8; **3g**, 34803-90-2; **3h**, 34803-91-3; **3i**, 34803-92-4; **3j**, 34803-93-5.

Acknowledgment.—We gratefully acknowledge the financial support of the doctoral research of Thomas F. Lemke by Atlas Chemical Industries.

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[10] The low yields of these compounds are partially a result of the increased solubility in the recrystallization solvents. No attempt was made to optimize the yields.

Synthesis of Trimethylhydroquinone from Aliphatic Precursors

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Received January 25, 1972

Condensation of a properly substituted α,β-unsaturated aldehyde or ketone with an appropriate aliphatic ketone leads to a trimethyl-2-cyclohexen-1-one structure. These molecules are readily aromatized to the corresponding phenols in high purity with Pd/C under mild conditions. A novel indirect electrolytic oxidation involving Fremy's radical[2] yielded trimethyl-*p*-benzoquinone (**9**) which in turn was reduced to trimethylhydroquinone (**1**). The latter is an important intermediate in the synthesis of vitamin E.

Various methyl-substituted phenols and particularly trimethylphenols are prepared from phenol *via* methylation processes. Although these processes can be controlled so that a particular mono- or polymethylated phenol can be obtained as the major product, mixtures are invariably obtained. Such mixtures require separation by methods which can be tedious especially if phenols of high purity are required.

We now wish to describe a general method for obtaining a number of specifically substituted trimethylphenols in pure form. Since only standard laboratory techniques are involved, the overall scheme should lend itself to the preparation of a variety of ^{14}C ring- and/or chain-labeled phenols, *p*-quinones, and the hydroquinones derived thereform.

Our main objective was to find a practical synthesis for 2,3,5- and/or 2,3,6-trimethylphenol based on readily available aliphatic starting materials. Both of these phenols represent important intermediates in the production of trimethylhydroquinone and thus of vitamin E.

The basic concept comprised the construction of a suitably substituted trimethylcyclohexenone carbon skeleton which, in a second step, could be aromatized to the corresponding trimethylphenol (Scheme I).[3]

Chapurlat and Dreux[4] described the condensation of 3-penten-2-one with 2-butanone to yield 3,5,6-trimethyl-2-cyclohexen-1-one (**2**). We found that the same product was obtained from the more readily accessible 4-chloro-2-pentanone[5] and 2-butanone. A different substitution pattern was obtained in the cyclohexenone ring when methyl vinyl ketone was condensed with 3-pentanone under strongly alkaline conditions. The uv absorption at λ_{max}^{EtOH} 239 nm was compatible with the 2,3,6-trimethyl-2-cyclohexen-1-one[6] structure, **4**.

The reaction we studied most carefully was the condensation of crotonaldehyde with 3-pentanone in the presence of KOH.[7] Under optimal conditions a 77% yield (uv analysis) of **6** as a mixture of cis and trans isomers (nmr) was obtained.

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[1] To whom correspondence should be addressed.

[2] P. A. Wehrli and F. Pigott, *Inorg. Chem.*, **9**, 2614 (1970).

[3] No stereochemistry is indicated in **2**, **6**, and **7**.

[4] R. Chapurlat and J. Dreux, *C. R. Acad. Sci.*, **253**, 2361 (1961): bp for **2**, 85–86° (4.5 mm).

[5] A. Wohl and R. Maag, *Chem. Ber.*, **43**, 3280 (1910); 4-chloro-2-pentanone is undoubtedly an intermediate in their preparation of 3-penten-2-one.

[6] T. Ichikawa, H. Owatari, and T. Kato, *Bull. Chem. Soc. Jap.*, **41**, 1228 (1968): bp for **4**, 92–96° (16 mm); bp for **6**, 92–100° (24 mm).

[7] After this work was completed, we became aware of a Dutch Patent abstract (6,903,484, Sept 10, 1969): bp for **6**, 74–76° (12 mm).