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REACTIONS OF ACYCLIC ENEDIONES WITH MENTHOFURAN

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Abstract—Menthofuran has been treated with several enones and conjugated enediones in acidic ethanolic media. Substitutive addition was the predominant mode of reaction with enones, while condensation at an aldehyde carbonyl of an enedione occurred faster than substitutive addition, which was itself faster than condensation at a ketone carbonyl. The stereochemical orientation about the C=C double bond in the enones seemed of little import.

THE acid-catalyzed condensation of furans with saturated carbonyl compounds to produce difurylmethane structures (**1**) is well documented.[2,3] The general mode of acid-catalyzed reaction of furans with unsaturated ketones, aldehydes, or esters appears to be less certain. Most systems react by a 1,4 "substitutive addition" mechanism,[4–6] yet a few examples of Diels–Alder addition have also been reported.[7] With menthofuran (**2**) as the furan system, Yur'ev[4] has reported exclusive substitutive addition with both acrolein (**3a**) and crotonaldehyde (**3b**), the 1:1 adducts being obtained in 58 and 34% yield, respectively. Since these yields were somewhat lower than those reported[5] using 2-methylfuran (**4**), and since 2-methylfuran formed a 1:1 adduct with α,β-unsaturated ketones in 50–60% yield, we felt it necessary to treat menthofuran (**2**) with methyl vinyl ketone (**3c**) under the acid-catalyzed conditions in an

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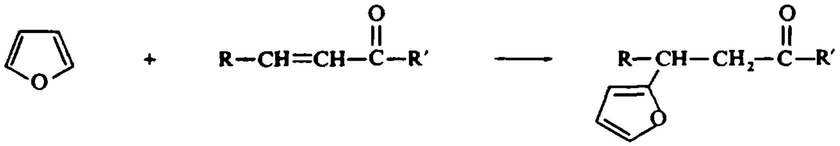

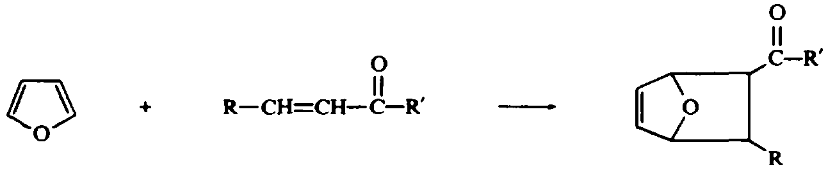

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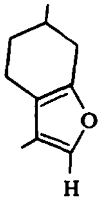

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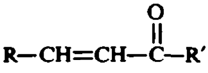

$$R{-}CH{=}CH{-}\overset{O}{\overset{\|}{C}}{-}R'$$

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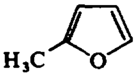
a: R = H, R′ = H
b: R = CH$_3$, R′ = H
c: R = H, R′ = CH$_3$



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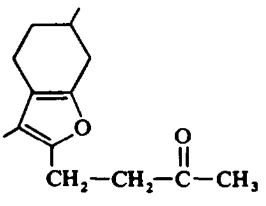
attempt to verify the substitutive addition nature of the major adduct from the reaction of menthofuran with unsaturated ketones and to search for minor products. The expected adduct 5 was obtained in 58% yield, with no other non-polymeric material being present in as much as 5%, consistent with Yur'ev's work.[4, 5]



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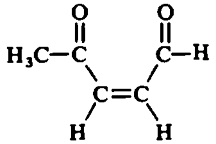
Having supported the idea that substitutive addition is the predominant mode of addition of menthofuran (2) with α,β-unsaturated systems under acidic conditions, it became of interest to us to combine menthofuran with enediones, in which electron withdrawal from the two C atoms of the C=C double bond is essentially balanced. This study utilized three enediones previously prepared in our laboratories,[9] *cis*-β-acetylacrolein (6), *cis*-3-hexene-2,5-dione (7), and *trans*-3-hexene-2,5-dione (8).



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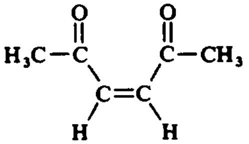

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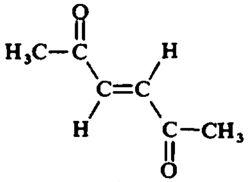

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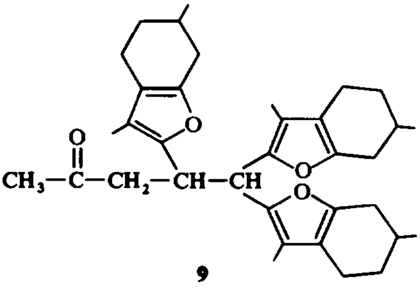
Treatment of *cis*-β-acetylacrolein (6) with menthofuran (2) in acidic ethanol in the absence of air produced an air-sensitive, white solid in 57·9% yield, a minor product in about 5% yield, and considerable polymeric material. The major product was identified as 4,5,5,-tris(4,5,6,7-tetrahydro-3,6-dimethyl-2-benzofuryl)pentan-2-one (**9**), a 3:1 adduct, on the basis of elemental analysis, osmometric molecular weight, infrared spectroscopy (CO groups and furan ring), UV spectroscopy (three furan



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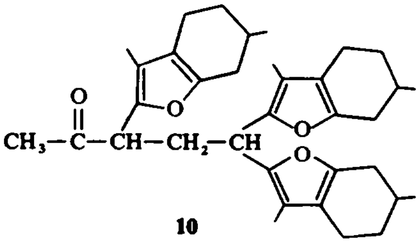

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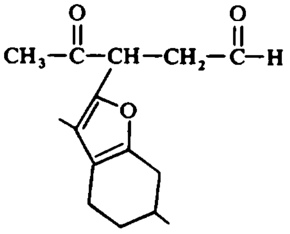
rings), PMR spectroscopy (see below), and mass spectroscopy (molecular ion and fragmentation pattern).

Detailed structural assignment, particularly discrimination between **9** and its isomer **10**, was accomplished with the aid of the mass spectral fragmentations (assuming the absence of extensive rearrangements in the mass spectrometer). The base peak at *m/e* 311 and the peak at *m/e* 219 are consistent with cleavage β to a furan ring in the molecular ion.[10] Alternate β-cleavage with migration of a γ-hydrogen[10] produces an *m/e* 472 fragment. Cleavage of the bond α to the CO group[11] provides the *m/e* 43 species. Loss of the menthofuryl radical or of the net elements of menthofuran provide *m/e* 381 and 380 species, respectively, as well as the menthofuran molecular ion, *m/e* 150, and its main fragment, *m/e* 108.[12] Loss of an acetyl radical from *m/e* 380 produces an *m/e* 337 fragment. Similarly, hydrogen migration in an *m/e* 381 species followed by cleavage leads to *m/e* 325, which can further fragment β to the furan ring[10] to give *m/e* 163 and 311 species. All of these results are consistent only with structure **9** for this adduct.

The 60 MHz PMR spectrum of **9** in deuteriochloroform solution indicated (a) the absence of an aldehydic hydrogen, (b) the presence of more than one kind of methyl ketone residue, (c) increased multiplicity of a tertiary proton signal beyond that expected for **9** (δ 4·08–4·20), and (d) an approximate ratio of 9:6:6 for the secondary Me groups (δ 0·97–1·13), furan Me groups (δ 1·58–1·68), and Me ketone groups (δ 1·73–1·79), respectively, instead of the 9:9:3 ratio predicted for **9**. Points (b) and (c) might be anticipated as the result of the presence of hindered rotation (Dreiding models) or of diastereomers (optically active menthofuran residues). The 100 MHz spectrum provided little assistance. However a 100 MHz spectrum of a benzene solution of this material was significantly different.[13] While integration still indicated relative intensities of 9:6:6, it now became apparent that a significantly deshielded furan Me group (δ 2·02 singlet) was absorbing in the same region as the Me group adjacent to the CO function. It is not difficult to see that the menthofuran residue on C atom four of the adduct might be in a magnetic environment different from that of the two menthofuran residues on C atom five, and that the latter residues themselves are diastereotopic. The PMR spectra taken as a whole are therefore consistent with structure **9** (as a mixture of diastereomers) for this compound.

The minor product from the condensation of **6** and **2** has not been identified.



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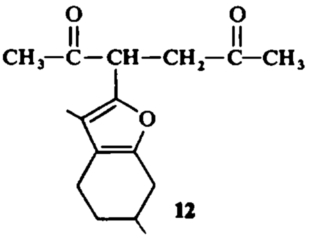
However, it does not appear to be a 1:1 adduct such as **11** (or its isomers) since the PMR spectrum does not exhibit an aldehydic hydrogen.

Reaction of *trans*-3-hexene-2,5-dione (**8**) with menthofuran (**2**) in acidic ethanol produced a 1:1 adduct, 3-(4,5,6,7-tetrahydro-3,6-dimethyl-2-benzofuryl)-2,5-hexanedione (**12**), in 80·4% yield and a 3:1 adduct,**13** or **14**, in 8·8% yield. Similar treatment of *cis*-3-hexene-2,5-dione (**7**) produced **12** in 75·1% yield and the 3:1 adduct (**13** or **14**) in 5·0% yield. In view of the known acid-catalyzed isomerization of the *cis* compound to the *trans*,[9] it appears that all reaction is occurring via the *trans* isomer itself or through a single protonated form accessible from either isomer.



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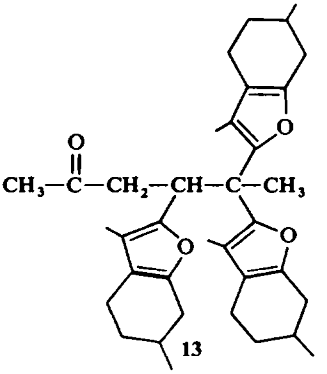

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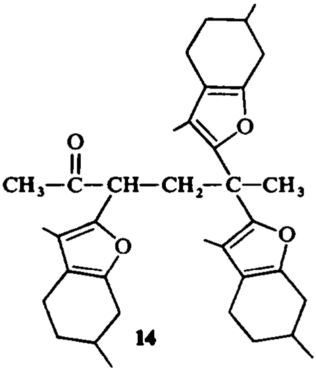

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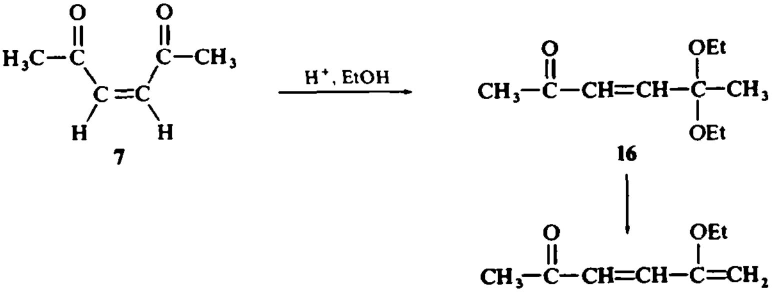
In an attempt to search for *cis–trans* isomerization under these ethanolic reaction conditions,[9] *cis*-3-hexene-2,5-dione (**7**) was placed in acidic ethanol in the absence of menthofuran. On work-up as for the condensation reactions, the crude reaction product was found to decompose to enol ether **15**, presumably by loss of ethanol from ketal **16**. Similar behavior was observed with *trans*-3-hexene-2,5-dione (**8**), indicating the need for aqueous reaction conditions to accomplish clean acid-catalyzed *cis–trans* isomerization.[9]



7 **16** **15**

The available spectroscopic data do not permit unambiguous differentiation between structures **13** and **14** for the minor product. Structure **14** seems more reasonable from steric arguments and from the presence of a peak at m/e 205 in the mass spectrum. Solvent induced changes in the proton magnetic resonance spectra[13] of the 1:1 adduct **12** and the 3:1 adduct **13** or **14** parallel those for the 3:1 adduct **9** (see above).

In summary, the acid-catalyzed reactions of conjugated enediones with menthofuran appear to be extremely sensitive to the aldehydic or ketonic nature of the CO groups. From an analysis of the products obtained from several conjugated enediones, condensation at an aldehyde CO is faster than substitutive addition, which is itself faster than condensation at a ketone CO. This is in marked contrast to the predominance of substitutive addition in the reactions of menthofuran with both α,β-unsaturated ketones and aldehydes. Apparently the essentially balanced electron withdrawal from the two carbons of the double bond in the enediones slows down substitutive addition to a significant enough extent for condensation at the CO to become competitive. The steric differences involved in attack at an aldehyde CO and attack at a ketone CO are large enough to slow down the latter and make this process less favorable than substitutive addition.

EXPERIMENTAL

M.ps are uncorrected. NMR spectra were recorded on a Varian A-60A instrument using 10% solns of $CDCl_3$ unless otherwise indicated and are reported in parts per million downfield from TMS as an internal standard. Only distinct absorptions will be reported herein. IR spectra were determined with a Beckman IR-10 spectrophotometer on 5% solns in $CHCl_3$. Only major absorptions are listed herein. UV spectra were measured with Beckman DK-2 spectrophotometer in absolute EtOH. Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Elbach, West Germany. Mass spectral analyses were performed at Stanford University on a C.E.C. Model 21-103C, an Atlas CH-4, or an A.E.I. MS-9 Mass Spectrometer, at Seton Hall University on a C.E.C. Model 21-104 Mass Spectrometer, or by Morgan-Schaffer Corporation, Montreal, Quebec, Canada.

Reaction of menthofuran (**2**) *with unsaturated carbonyl compounds*

General procedure. A soln of approximately 1 g of the CO compound and a 3–5 fold molar excess of menthofuran in 20 ml of 95% EtOH and a 10 ml soln of 5% H_2SO_4 in 95% EtOH were simultaneously degassed on a vacuum line, combined, and again degassed. The mixture was opened to a N_2 atmosphere and stored in a refrigerator for 44 hr. The mixture was diluted with water, the resulting system extracted with CH_2Cl_2, and the organic layer dried ($MgSO_4$). The solvent was removed and the unreacted menthofuran distilled at reduced pressure. The components of the nondistillable residue were separated by column chromatography on silica gel (Woelm).

Methyl vinyl ketone. Methyl vinyl ketone (**3c**: 1·0 g) and **2** (5·1 g) were combined as described above. Work-up gave 2·9 g menthofuran and 1·6 g (58·4% yield) of a viscous yellow oil identified as **5**: IR 1715, 1650, 1605 cm^{-1}; NMR δ 0·98 (d, 3, *J* = 5 Hz), 1·72 (s, 3), 1·99 (s, 3). (Found: C, 76·10; H, 9·29. Calcd for $C_{14}H_{20}O_2$: C, 76·32; H, 9·15).

cis-β-*Acetylacrolein* (**6**). cis-β-Acetylacrolein (**6**: 1·3 g) and **2** (9·3 g) were treated using the general procedure. Work-up gave 3·8 g menthofuran and 4·2 g (57·9% yield) of **9** (recrystallized from MeOH): m.p. 142–143°; IR 1740, 1645, 1600 cm^{-1}; UV max 235 mμ (ε 24,000); NMR δ 0·97–1·13 (m): 1·58–1·65 (m), 1·73–1·78 (m), 4·08–4·20 (broad split signal); NMR (C_6H_6) δ 0·80 (d), 0·83 (d), 1·57 (s), 1·86 (s), 1·97 (d), 2·02 (s), 4·63–4·83 (broad); mass spectrum molecular ion *m/e* 530, base peak *m/e* 311. (Found: C, 79·00: H, 8·58. Calcd for $C_{35}H_{46}O_4$: C, 79·24: H, 8·68%).

Besides the recovered menthofuran and major product, considerable polymeric material and 220 mg of another product were found.

trans-3-*Hexene*-2,5-*dione* (**8**). *trans*-3-Hexene-2,5-dione (**8**: 1·26 g) and **2** (8·0 g) were combined and worked-up as described. Unreacted menthofuran (5·3 g) was recovered. The major product, **12**, was obtained as a yellow oil in 80·4% yield (2·36 g): $n_D^{24\cdot5}$ 1·5024; IR 1720, 1650, 1595 cm^{-1}: UV max 219 (ε 6430), 286 (ε 1240): NMR δ 1·04 (d, 3, *J* = 5·5 Hz), 1·91 (s, 3), 2·04 (s, 3), 2·14 (s, 3): NMR (C_6H_6) δ 0·84 (d, *J* = 5·5 Hz), 1·71 (s), 1·74 (s), 1·78 (s): mass spectrum molecular ion *m/e* 262, base peak *m/e* 43. (Found: C, 73·05: H, 8·31. Calcd for $C_{16}H_{22}O_3$: C, 73·25: H, 8·45%).

In addition, 530 mg (8·8% yield) of a product tentatively identified as **14** was obtained: IR 1715, 1650, 1460 cm^{-1}. NMR δ 1·05 (d, *J* = 5·5 Hz), 1·48 (m), 1·72 (s), 1·90 (s): NMR (C_6H_6) δ 0·87 (d, *J* = 5·5 Hz), 1·4–1·83 (complex m): mass spectrum molecular ion *m/e* 544, base peak *m/e* 325.

cis-3-*Hexene*-2,5-*dione* (**2**). *cis*-3-Hexene-2,5-dione (**7**: 1·26 g) and **2** (8·0 g) were treated as described above. Work-up gave 5·3 g of recovered menthofuran and 2·2 g (75·1% yield) of **12**: $n_D^{24\cdot5}$ 1·5061, chromatographic behavior. IR, NMR and mass spectra were identical to those obtained for this adduct from the *trans*-3-hexene-2,5-dione.

In addition 310 mg (5·0% yield) of presumed **14** was isolated. Chromatographic behavior, IR, NMR and mass spectra were identical to those obtained for this adduct from the *trans*-3-hexene-2,5-dione.

5-*Ethoxy*-3,5-*hexadien*-2-*one* (**15**). cis-3-Hexene-2,5-dione (**7**: 1·39 g) in 20 ml of 95% EtOH was treated with 10 ml of 5% H_2SO_4 in 95% EtOH as described in the general procedure but in the absence of menthofuran. Work-up gave 1·52 g of a three component mixture. One component was shown to be **8** by chromatographic behavior. Distillation at reduced pressure (85°/5·75 mm) gave 0·4 g of an impure product which was further purified by preparative vapor-phase chromatography (1/4″ × 6′ column of 10% Silicone W-98 on Chromosorb W 60/80, column temp 120°) to yield **15**: IR 1715, 1685, 1365 cm^{-1}; NMR δ 1·15 (t, 3, *J* = 7 Hz), 2·15 (s, 3), 3·34 (q, 2, *J* = 7 Hz), 4·12 (s, 2), 5·59 (m, 1), 5·85 (m, 1). (Found: C, 68·49: H, 8·48. Calcd. for $C_8H_{12}O_2$: C, 68·50: H, 8·61%).

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