The Base-Catalyzed Intermolecular Condensation of α,β-Unsaturated Ketones. Self-Condensation of Styryl Methyl and Styryl Ethyl Ketones to 5-Aryl-3-styryl-2-cyclohexen-1-ones

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Styryl methyl and styryl ethyl ketones, ArCH=CHCOCH$_2$R (R = H, CH$_3$), having suitable aryl substituents (methoxy, dimethylamino) undergo self-condensation in aqueous ethanolic sodium hydroxide to 5-aryl-3-styryl-2-cyclohexen-1-ones (**6a–d**) and 5-aryl-2,4-dimethyl-3-styryl-2-cyclohexen-1-ones (**11a–g**), respectively. Similarly, 1-(2-methoxyphenyl)-2-methyl-1-buten-3-one undergoes self-condensation to 5-(2-methoxyphenyl)-3-[1-methyl-2-(2-methoxyphenyl)vinyl]-6-methyl-2-cyclohexen-1-one (**9**). This behavior contrasts with that of styryl alkyl ketones having R groups larger than methyl; they undergo self-condensation to 4-alkanoyl-2-alkyl-3,5-diarylcyclohexanones (**3**) under the same reaction conditions. Spectral data for all compounds agree with the structural assignments. Retroaldol cleavage of 2,4-dimethyl-5-(2-methoxyphenyl)-3-(2-methoxystyryl)-2-cyclohexen-1-one (**11a**) by heating in aqueous ethanolic sodium hydroxide at 150° led to 2-methoxybenzyl alcohol and epimeric 5-(2-methoxyphenyl)-2,3,4-trimethyl-2-cyclohexen-1-ones, **12a** and **b**. Equilibration data and nmr spectra suggest that cyclohexenones **11a–f** have a *trans* diequatorial C-4 methyl, C-5 aryl configuration. The scope of the reaction is discussed with respect to substituents in the reactant styryl alkyl ketone including number, position, and type of aryl substituents. A comparison is made, with respect to substituents, between the two possible cyclization paths (Michael or aldol) by which the intermediate acyclic olefinic diketone **2** forms cycloalkanones (**3**) or cycloalkenones (**6**, **11**).

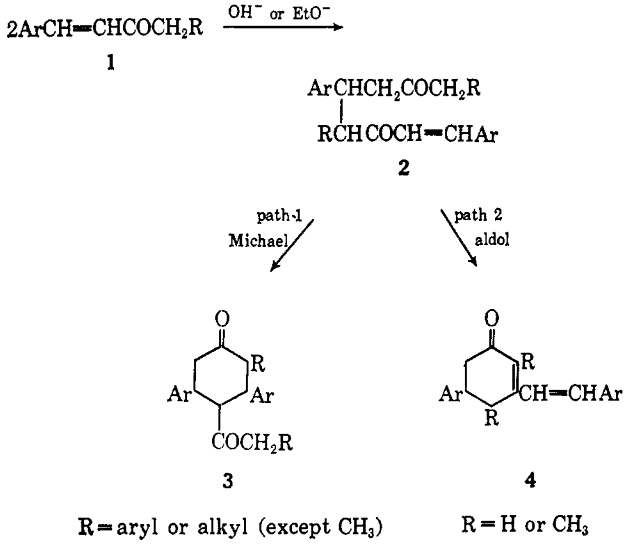
We have extended our studies of the base-catalyzed self-condensation of styryl alkyl ketones to include styryl methyl and styryl ethyl ketones (**1**, R = H, CH$_3$). These ketones are conveniently prepared *in situ* by

$$\mathrm{ArCHO} + \mathrm{CH_3COCH_2R} \xrightarrow{\mathrm{OH^-\ or\ EtO^-}} \underset{\mathbf{1}}{\mathrm{ArCH{=}CHCOCH_2R}} + \mathrm{H_2O}$$

aldol condensation of aromatic aldehydes with methyl ketones. Styryl alkyl ketones having structure **1** may undergo intermolecular Michael addition to an acyclic 1,5-diketone **2** (isolated where Ar = C$_6$H$_5$, R = *i*-C$_3$H$_7$[1]). See Scheme I.

When substituent R is an alkyl group larger than methyl, diketone **2** (obtained *in situ*) undergoes Michael cyclization to 3,5-diaryl-4-alkanoylcyclohexanone **3** (path 1).[2] Styryl methyl and styryl ethyl ketones exhibit different behavior. They have been shown in the present work to form 5-aryl-3-styryl-2-cyclohexen-1-ones (**4**) by aldol cyclization of diketone **2** (path 2). Successful cyclizations by either path depend on the substituents in the aryl group.

SCHEME I



The condensations leading to cyclohexenone **4** are usually run by reaction of an aromatic aldehyde with an excess of methyl ketone to minimize formation of dibenzal ketones. Sodium hydroxide in ethanol is used with 2-butanone, aqueous medium with acetone. Condensations to diketone **3** employ equimolar amounts of aldehyde and ketone (ethanolic sodium hydroxide).[2] Successful condensations require use of pure reagents in a nitrogen atmosphere. The slightly soluble products (both **3** and **4**) crystallize from the reaction mixture after a few days; each is readily purified by recrystallization from ethanol or ethyl acetate. Cyclohexanones (**3**) are colorless and show weak ultraviolet absorption due to isolated aryl groups. The cyclohexenones (**4**) are distinguished by their yellow color and strong ultraviolet absorption near 370 mμ.

The base-catalyzed condensation of aromatic aldehydes with acetone (employed in molar excess) readily leads to styryl methyl ketones, and with 2-butanone to styryl ethyl ketones; yields are often high. Sodium hydroxide, in water or ethanol solvent, is most frequently employed as catalyst. Over 100 examples of these reactions are known.[3–5] There are very few reports of other products resulting from these condensations.[6] In particular, products derived by intermolecular self-condensation of a styryl methyl or styryl ethyl ketone have been mentioned in only a few publica-

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(1) A. T. Nielsen, to be published.

(2) A. T. Nielsen and H. Dubin, *J. Org. Chem.*, **28**, 2120 (1963).

(3) A. T. Nielsen and W. J. Houlihan, *Org. Reactions*, **16**, 186 (1968.

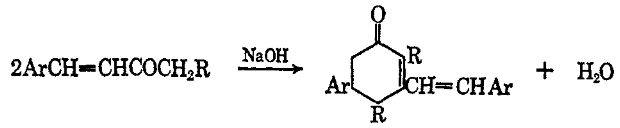
(4) N. L. Drake and P. Allen, Jr., "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1944, p 77.

(5) (a) R. Fabinyi and T. Széki, *Ber.*, **39**, 1211 (1906); (b) H. Bauer and P. Vogel, *J. Prakt. Chem.*, [2] **88**, 329 (1913); (c) N. F. Albertson, *J. Amer. Chem. Soc.*, **72**, 2594 (1950); (d) J. H. Burckhalter and S. H. Johnson, *ibid.*, **73**, 4835 (1951); (e) K. W. Bentley, J. Dominguez, and J. P. Ringe, *J. Org. Chem.*, **22**, 418 (1957); (f) K. W. Bentley and S. F. Dyke, *J. Chem. Soc.*, 3151 (1961); (g) Kalle A.-G., British Patent 943,266; *Chem. Abstr.*, **60**, 14696 (1964).

(6) A. T. Nielsen, H. Dubin, and K. Hise, *J. Org. Chem.*, **32**, 3407 (1967).

TABLE I

SYNTHESIS OF 5-ARYL-3-STYRYL-2-CYCLOHEXEN-1-ONES

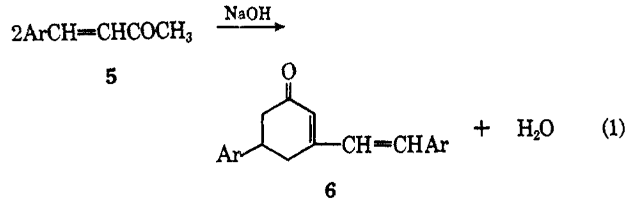


Compd	Ar	R	Yield, %	Mp, °C	Molecular formula	Anal. Calcd C, %	Anal. Calcd H, %	Anal. Calcd Mol wt	Anal. Found C, %	Anal. Found H, %	Anal. Found Mol wt
6a	2,4-$(CH_3O)_2C_6H_3$	H	9	169–170	$C_{24}H_{26}O_5$	73.07	6.64	394.45	72.91	6.54	397
6b	3,4-$(CH_3O)_2C_6H_3$	H	18[a]	168–169[b]	$C_{24}H_{26}O_5$	73.07	6.64	394.45	72.97	6.66	391
6c	3-CH_3O-4-*n*-$C_3H_7OC_6H_3$	H	Low[c]	152–153[c]	$C_{28}H_{34}O_5$	74.64	7.61	450.55	74.5[c]	7.6[c]	
6d	3,4-$(CH_2O_2)C_6H_3$	H	8	177–177.5	$C_{22}H_{18}O_5$	72.92	5.01	362.36	72.88	4.95	362
6e	2,4,5-$(CH_3O)_3C_6H_2$	H	10	191–193	$C_{26}H_{30}O_7$	68.70	6.65	454.50	68.63	6.64	460
11a	2-$CH_3OC_6H_4$	CH_3	64	186–187	$C_{24}H_{26}O_3$	79.53	6.93	378.45	79.42	6.84	370
11a′	2-$CH_3OC_6H_4$	CH_3	*d*	118–120	$C_{24}H_{26}O_3$	79.53	6.93	378.45	79.60	7.14	377
11b	2,4-$(CH_3O)_2C_6H_3$	CH_3	19	186–187	$C_{26}H_{30}O_5$	73.91	7.16	422.50	73.91	7.30	415
11c	2,5-$(CH_3O)_2C_6H_3$	CH_3	29	162–163	$C_{26}H_{30}O_5$	73.91	7.16	422.50	74.07	7.23	427
11d	3,5-$(CH_3O)_2C_6H_3$	CH_3	30	114–115	$C_{26}H_{30}O_5$	73.91	7.16	422.50	74.29	7.07	431
11e	2,4,5-$(CH_3O)_3C_6H_2$	CH_3	50	190–192	$C_{28}H_{34}O_7$	69.69	7.10	482.55	69.76	7.21	488
11f	3,4,5-$(CH_3O)_3C_6H_2$	CH_3	20	191–193	$C_{28}H_{34}O_7$	69.69	7.10	482.55	69.91	7.17	481
11g	4-$(CH_3)_2NC_6H_4$	CH_3	12	174–175	$C_{26}H_{32}N_2O$[e]	80.37	8.30	388.53	80.16	8.53	395

[a] Heilbron[7] reports a yield of 20% under similar conditions. [b] Lit.[7] mp 168°. [c] Data of Heilbron.[7] The preparation of **6c** was not repeated. [d] Isolated by epimerization of **11a** at 180° (aqueous ethanolic sodium bicarbonate). [e] Calcd: N, 7.21. Found: N, 7.47.

tions.[7–9] The present investigation shows the scope of the base-catalyzed self-condensation reactions of styryl alkyl ketones.

Self-Condensation of Styryl Methyl Ketones.—The base-catalyzed intermolecular condensation of styryl methyl ketones (**5**) has been examined previously by Heilbron and coworkers.[7] They found two 3-methoxy-4-alkoxybenzalacetones to give products described as 5-aryl-3-styryl-2-cyclohexen-1-ones (**6**) (eq 1). These



5 **6** (1)

were obtained when 4-alkoxy was methoxy (20% yield of **6b**; *cf.* Table I) and *n*-propoxy (very low yield of **6c** not stated). We have repeated Heilbron's preparation of **6b** and confirm his results. 3-Methoxy-4-alkoxybenzalacetones with 4-alkoxy groups ethoxy, isopropoxy, and benzyloxy failed to produce isolable cyclohexenones.[7] Catalysts tried in these experiments included aqueous sodium hydroxide and piperidine.[7,10] Resinous materials were reported as products of most of the condensations.

We have extended the reaction of eq 1 to the preparation of three new cyclohexenones: **6a**, **d**, and **e** (Table I). Styryl methyl ketones derived from piperonal and 2,4,5-trimethoxybenzaldehyde were produced *in situ* from the aldehyde and excess acetone in dilute aqueous sodium hydroxide. On standing at room temperature or below, the cyclohexenones (**6d** and **e**) crystallized from the reaction mixture. In the preparation of **6a** the pure styryl methyl ketone, 1-(2,4-dimethoxyphenyl)-1-buten-3-one, was allowed to react in aqueous ethanolic sodium hydroxide–acetone. Attempts to self-condense several other styryl methyl ketones to cyclohexenones failed, using a variety of procedures; these experiments are discussed below in a summary of the scope of the reaction.

TABLE II

INFRARED AND ULTRAVIOLET SPECTRA OF 5-ARYL-3-STYRYL-2-CYCLOHEXEN-1-ONES

Compd	ν^{KBr}, cm^{-1}	Principal absorptions in 95% ethanol λ_{max}, $m\mu$ (ϵ_{max})[a]		
6a	1655	260 (12,600)	284 (8,500)	369 (27,500)
6b	1655	260 (10,600)	269 (10,300)	362 (28,800)
6d	1660	242 (10,000)	287 (10,900)	362 (23,500)
6e	1650	266 (10,000)	290 (11,000)	386 (23,000)
9	1640	250 (8,300)	295 (15,000) sh	325 (16,400)
11a	1640	247 (7,700)	278 (6,600)	354 (28,000)
11a′	1640	247 (8,100)	274 (7,200)	355 (25,300)
11b	1655	257 (8,200)	285 (5,640)	372 (19,800)
11c	1660	264 (5,700)	322 (20,200)	372 (16,500)
11d	1650	252 (6,900)	285 (7,700) sh	337 (30,800)
11e	1660	260 (9,150)	295 (10,900)	387 (24,400)
11f	1660	257 (8,300)		352 (29,000)
11g	1640	257 (21,900)		416 (27,600)

[a] Measurements made within a few minutes after preparation of solutions which decompose on standing: **11a**, λ_{max} 352 $m\mu$ (16,600), 280 (6700), 247 (9850), and **11e**, λ_{max} 383 $m\mu$ (ϵ 16,200), 294 (10,900), 257 (10,700), after 15 hr at 25°.

Yields of all cyclohexenones derived from acetone (**6a–e**) are low (8–18%). It is likely that the experimental procedure employed and the scale of most of the runs (*ca.* 0.05 mol) preclude isolation of cyclohexenones formed in very low yields. Yields of cyclohexenones obtained from *in situ*-generated styryl methyl ketones were usually about the same as those obtained from the pure styryl methyl ketone itself. Several modifications of procedure failed to increase the reported yields.

Proof of structure of **6a**, **b**, **d**, and **e** rests on spectral (Table II) and chemical evidence. (Preparation of Heilbron's compound **6c** was not repeated.) Ele-

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(7) R. Dickinson, I. M. Heilbron, and F. Irving, *J. Chem. Soc.*, 1888 (1927).

(8) C. V. Gheorghiu, *Bull. Soc. Chim. Fr.*, (4) **53**, 1442 (1933).

(9) C. V. Gheorghiu and B. Arwentiev, *ibid.*, (4) **47**, 195 (1930).

(10) In two instances Heilbron found that heating styryl methyl ketones on the steam bath with piperidine gave low yields (<5%) of unidentified, white, amorphous substances.[7] From 3,4-dimethoxy-1-buten-3-one there resulted a substance, $C_{24}H_{28}O_2$ (mp 209–210°), and from 4-ethoxy-3-methoxy-1-buten-3-one a substance, $C_{26}H_{32}O_2$ (mp 187°).

TABLE III

NMR SPECTRA OF 5-ARYL-3-STYRYL-2-CYCLOHEXEN-1-ONES[a]

	Chemical shifts, τ					
Compd	CH=[b] (multiplets)	CH=[c] (singlet)	CH_3O (singlets)	CH_2, CH (multiplets)	CH_3[d] (singlet)	CH_3[e] (doublet)
6a	2.30–3.65	3.92	6.20	6.80–7.55		
6b	2.58–3.50	3.87	6.08, 6.12	6.55–7.55		
6d	2.50–3.30	3.88	*f*	6.55–7.55		
6e	2.40–3.75	3.88	6.06, 6.14	6.60–7.55		
9	2.50–3.20	3.69	6.17, 6.19	6.30–7.50	7.95	9.03
11a	2.26–3.28		6.16	5.80–7.80	7.94	9.04
11a′	2.25–3.25		6.15	6.25–7.50	8.00	8.53
11b	2.30–3.70		6.14, 6.16	6.30–7.65	7.96	9.04
11c	2.58–3.50		6.18	6.30–7.50	7.95	9.02
11d	2.50–3.70		6.16	6.40–7.50	7.95	9.02
11e	2.60–3.60		6.13	6.20–7.50	7.96	*g*
11f	2.53–3.60		6.08	6.50–7.70	7.92	8.98
11g	2.45–3.60		*h*	6.50–7.50	8.00	8.57

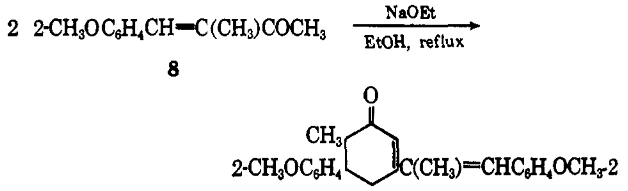
[a] Measurements were taken in $CDCl_3$; tetramethylsilane was the internal reference. [b] Aryl and side-chain vinyl protons. [c] Vinyl hydrogen of cyclohexenone ring at C-2. [d] Vinyl methyl at C-2 except in **9**. [e] Center of doublet; $J = 7$ Hz (three protons); C-4 methyl except in **9**. [f] CH_2O_2 singlets at τ 3.97 (2), 3.99 (2). [g] Complex multiplet centered at τ 8.75. [h] $(CH_3)_2N$ singlets at τ 7.03 (6), 7.15 (6).

mental analyses and molecular weight data support the molecular formulas (Table I). The single oxygen atom is represented in each compound by a conjugated carbonyl group, ν^{KBr} near 1655 cm^{-1} (Table II). The extended conjugation of a 5-aryl-2,4-pentadien-1-one is supported by ultraviolet spectra typical of this chromophore; an intense band is found near 370 mμ (Table II).[11,12] The nmr spectra of cyclohexenones **6a**, **b**, **d**, and **e** (Table III) agree with the structures assigned. A satisfactory alternate synthesis of cyclohexenone **6b** is described by Heilbron.[7]

A useful extension of the styryl methyl ketone condensation would employ α-alkylstyryl methyl ketones (**7**).[13] 1-(2-Methoxyphenyl)-2-methyl-1-buten-3-one

$$ArCHO + RCH_2COCH_3 \xrightarrow{H^+} \underset{\mathbf{7}}{ArCH{=}C(R)COCH_3} + H_2O$$

(**8**) was prepared by condensation of 2-methoxybenzaldehyde with 2-butanone employing hydrogen chloride catalyst (77–81% yield).[14] Heating **8** in ethanolic



8

9

sodium ethoxide led to cyclohexenone **9** (34% yield) The infrared and ultraviolet spectra of the product resemble the spectra of other cyclohexenones (Table II). The nmr spectrum (Table III) reveals the expected characteristic cyclohexenone C-2 vinyl singlet at τ 3.69, a side chain vinyl methyl singlet at 7.95, and a 7-Hz C-6 methyl doublet at 9.03.

Self-Condensation of Styryl Ethyl Ketones.—The base-catalyzed intermolecular condensation of styryl ethyl ketones has not previously been studied systematically. Styryl ethyl ketones are readily formed by condensation of an aromatic aldehyde with 2-butanone in ethanolic or aqueous ethanolic sodium hydroxide solution.[3,5] There are two reported 1:1 condensation products derived from styryl ethyl ketones generated *in situ*. Gheorghiu condensed 2-methoxybenzaldehyde with 2-butanone (ethanolic sodium hydroxide) to produce a yellow crystalline material, mp 178–179°, which he described as a dimer of 2-methoxystyryl ethyl ketone, $C_{24}H_{28}O_4$ (*ca.* 29% yield).[8] His elemental analyses support this molecular formula, but no structure was suggested for the compound. Gheorghiu and Arwentiew[9] reported the formation, in small yield, of a colorless compound, mp 194° (assigned molecular formula $C_{24}H_{28}O_4$), by condensation of 4-methoxybenzaldehyde with 2-butanone (equimolar quantities), using aqueous ethanolic sodium hydroxide catalyst. Following the reported procedure for this latter reaction we were unable to isolate the reported compound, or any crystalline solid from the reaction mixture.

We have repeated Gheorghiu's condensation of 2-methoxybenzaldehyde with 2-butanone (ethanolic sodium hydroxide) and obtained a yellow crystalline material, mp 186–187°, after recrystallization from ethanol (yield, 64%). Elemental analysis and molecular weight data indicate a molecular formula $C_{24}H_{26}O_3$ rather than $C_{24}H_{28}O_4$, reported by Gheorghiu. Only by using pure reagents and a nitrogen atmosphere was it possible to obtain a pure sample of the product which gave satisfactory analyses. We believe our condensation product and Gheorghiu's compound to be samples of the same compound. Impurities, possibly water and/or oxidation products, in Gheorghiu's sample may account for its lower melting point and unsatisfactory elemental analyses.

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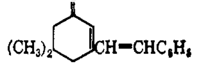
(11) Related dienones are i [(a) A. L. Wilds, L. W. Beck, W. J. Close, C. Djerassi, J. A. Johnson, Jr., T. L. Johnson, and C. H. Shunk, *J. Amer. Chem. Soc.*, **69**, 1985 (1947); (b) R. Kuhn and H. A. Staab, *Ber.*, **87**, 262 (1954)] and ii [(c) G. R. Ensor and W. Wilson, *J. Chem. Soc.*, 4068 (1956)].

$C_6H_5(CH{=}CH)_2COCH_3$

i

λ_{max}^{EtOH} 234 mμ (ε 6750), 319 (36,400)



ii

λ_{max}^{EtOH} 235 mμ (ε 7800), 324 (27,300)

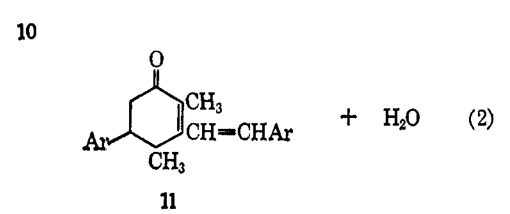
(12) Alkoxy phenyl substituents in compounds listed in Table II are responsible for the expected *ca.* 50-mμ bathochromic shift in the long wavelength band relative to a phenyl substituent: C. N. R. Rao, "Ultraviolet and Visible Spectroscopy," Butterworth and Co., Ltd., London, 1961, pp 40–48. We found 1-(2-methoxyphenyl)-1-penten-3-one to have uv absorptions at λ_{max}^{EtOH} 284 mμ (ε 12,500) and 331 (8500). Compare the spectrum of 1-phenyl-1-penten-3-one: λ_{max}^{MeOH} 220 mμ (ε 11,000), 286 (23,400) [M. Stiles, D. Wolf, and G. V. Hudson, *J. Amer. Chem. Soc.*, **81**, 628 (1959)].

(13) M. T. Bogert and D. Davidson, *ibid.*, **54**, 334 (1932).

(14) E. H. Woodruff and T. W. Conger, *ibid.*, **60**, 465 (1938).

Employing our procedure we have condensed 2,4-, 2,5-, and 3,5-dimethoxybenzaldehydes, 2,4,5- and 3,4,5-trimethoxybenzaldehydes and 4-dimethylaminobenzaldehyde with 2-butanone to yield yellow, crystalline 1:1 condensation products derived *in situ* from the resulting styryl ethyl ketones (compounds **11b–g**, Table I). Yields of these products (12–50%) were all lower than that of **11a** obtained from 2-methoxybenzaldehyde (64%), but generally higher than yields of products **6a–e** derived from styryl methyl ketones (8–18%). Several other aromatic aldehydes failed to yield crystalline condensation products with 2-butanone using a variety of procedures.

The self-condensation products derived from styryl ethyl ketones (**10**) are believed to be 5-aryl-2,4-dimethyl-3-styryl-2-cyclohexen-1-ones (**11**) (eq 2). The structures of compounds **11a–g** were in complete agreement with their infrared, ultraviolet, and nmr spectra, their elemental analyses, and molecular weight data (see Tables I, II, and III).



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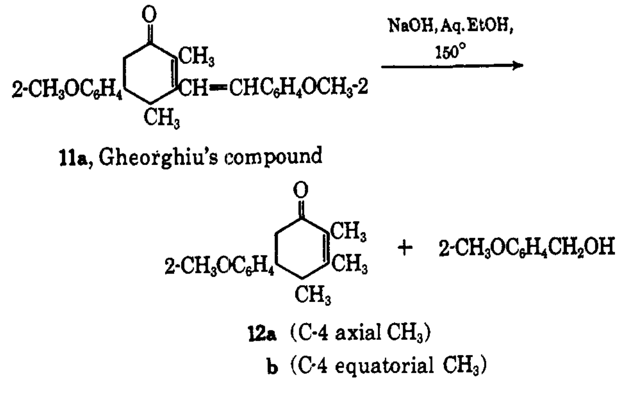
11

(2)

Chemical evidence supporting structure **11a** (Gheorghiu's compound) was provided by retroaldol cleavage in aqueous ethanolic sodium hydroxide at 150° (17 hr). The principal products, separated by distillation and vpc, were 2-methoxybenzyl alcohol (44% yield) and epimeric 5-(2-methoxyphenyl)-2,3,4-trimethyl-2-cyclohexen-1-ones (**12a** and **b**; total yield *ca.* 18%).



11a, Gheorghiu's compound

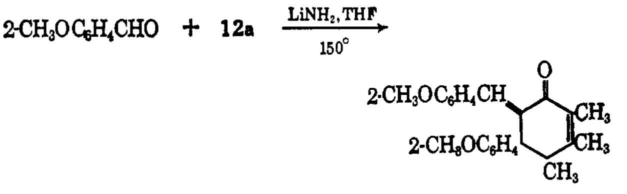
12a (C-4 axial CH$_3$)
b (C-4 equatorial CH$_3$)

2-Methoxybenzyl alcohol was identified by comparison of its infrared spectrum and 1-naphthylurethan derivative with an authentic sample. Neither 2-methoxybenzaldehyde nor 2-methoxybenzoic acid could be detected or isolated as cleavage products; spectra and the material balance suggest that they were not final products. The vigorous reaction conditions required for retroaldol cleavage evidently reduced the initially formed 2-methoxybenzaldehyde by a hydride-transfer process involving solvent ethanol. Milder reaction conditions failed to effect cleavage of **11a**.

Spectra of epimers **12a** and **b** agree with the structures assigned. Elemental analyses and molecular weight data support the molecular formulas, $C_{16}H_{20}O_2$. Nmr spectra indicate an epimer product ratio of **12a**:**12b** of *ca.* 2:1. Epimer **12b** could be separated and purified by vpc. Its nmr spectrum (deuteriochloroform solvent) showed four aryl protons as a complex multiplet at τ 2.5–3.3, a methoxyl singlet at 6.16, four ring-proton multiplets at 6.4–7.9, two vinyl methyl singlets at 7.98, 8.17, and a 7-Hz methyl doublet at 9.18. Its infrared and ultraviolet spectra indicate an α,β,β-trialkyl substituted α,β-unsaturated ketone: ν^{KBr} 1640 cm^{-1}; $\lambda_{\max}^{\text{EtOH}}$ 244 mμ (ε 11,300).[15] Epimer **12a** could not be obtained free of **12b** by vpc. However, a chromatographed sample which contained *ca.* two-thirds **12a** had infrared and ultraviolet spectra identical with pure epimer **12b**. The nmr spectrum of this sample indicated epimer **12a** to differ from **12b** principally in the chemical shifts of the C-3 and C-4 methyl signals; for **12a**, there was a singlet at τ 8.07 and a 7-Hz doublet centered at 8.82. The C-2 methyl singlet appeared at *ca.* τ 8.17 in both epimers. Assuming the C-5 2-methoxyphenyl group to remain equatorial in both isomers, it appears reasonable that they are C-4 epimers. The lower field C-4 methyl signal of epimer **12a** suggests that its C-4 methyl is pseudo-axial and deshielded by the closely adjacent aryl group.[16] Dreiding models show a pseudo-equatorial C-4 methyl in **12b** to be rather far removed from the C-5 aryl group.

The 2,4-dinitrophenylhydrazones of both epimers of **12** were prepared. That of **12a** had mp 159–161° and uv bands at $\lambda_{\max}^{\text{EtOH}}$ 258 mμ (ε 15,000), 385 (23,000); that of **12b** had mp 201.5–202.5° and uv bands at $\lambda_{\max}^{\text{EtOH}}$ 260 mμ (ε 13,000), 386 (21,000).[17]

An attempt to resynthesize cyclohexenone **11a**, or **11a′**, by reaction of 2-methoxybenzaldehyde with epimer mixture **12a** and **b** containing *ca.* two-thirds **12a** (lithium amide, tetrahydrofuran, 150°) led to ketone **13**, mp 190–191°, by aldol condensation on the ring methylene group. Structure **13** is supported by its spectra: ν^{KBr} 1670 (C=O), 1640 cm^{-1} (C=C); $\lambda_{\max}^{\text{EtOH}}$ 328 mμ (ε 11,800), 278 (11,100), 273 (10,700), 244 (10,400).[18] The nmr spectrum of **13** closely resembles that of **12a**: C-4 methyl doublet at τ 8.82 (7-Hz), C-2 methyl singlet at 8.22, C-3 methyl singlet at 8.10. Two methoxy singlets appear at τ 6.13, 6.22; aryl and vinyl protons (9) were at τ 2.5–3.3. Comparison of this nmr spectrum



13

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[15] α,β,β-Trialkyl-substituted α,β-unsaturated ketones have a uv band at $\lambda_{\max}^{\text{EtOH}}$ 247 ± 5 mμ: R. B. Woodward, *J. Amer. Chem. Soc.*, **64**, 76 (1942). For example, $(CH_3)_2C{=}C(CH_3)COCH_3$ has a uv band at $\lambda_{\max}^{\text{EtOH}}$ 247 mμ (ε 7900): R. Mecke and K. Noack, *Angew. Chem.*, **68**, 150 (1956).

[16] In substituted 2- and 4-methylcyclohexanones the axial methyl signal is always observed at lower field (by *ca.* τ 0.1–0.2) relative to the signal for the corresponding equatorial methyl isomer: F. Johnson, N. A. Starkovsky, and W. D. Gurowitz, *J. Amer. Chem. Soc.*, **87**, 3492 (1965); F. Nerdel, D. Frank, and K. Rehse, *Chem. Ber.*, **100**, 2978 (1967).

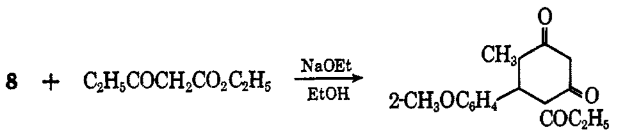
[17] Mesityl oxide 2,4-dinitrophenylhydrazone has a uv band at $\lambda_{\max}^{\text{EtOH}}$ 379 mμ (ε 23,000): J. D. Roberts and C. Green, *J. Amer. Chem. Soc.*, **68**, 214 (1946).

[18] *trans*-2-Benzal-4,4-dimethyl-1-tetralone has uv bands at $\lambda_{\max}^{\text{MeOH}}$ 307 mμ (ε 16,500) and 227 (11,400); the *cis* isomer has bands at $\lambda_{\max}^{\text{MeOH}}$ 311 mμ (ε 11,300), 269 (9300), and 234 (9700): D. N. Kevill, E. D. Weiler, and N. H. Cromwell, *J. Org. Chem.*, **29**, 1276 (1964); *cf.* A. Hassner and T. C. Mead, *Tetrahedron*, **20**, 2201 (1964).

with that of **12a** and **b** suggests an equatorial C-5 aryl, axial C-4 methyl in **13** (condensation product derived from **12a**).[16] It is not clear from our spectral data whether the aryl of the 6-benzal group in **13** is *cis* or *trans* to the carbonyl.[18]

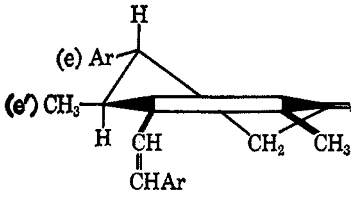
Formation of **13** by aldol condensation is atypical since all reported reactions of aromatic aldehydes with 3-methyl-2-cyclohexen-1-ones (ethanolic sodium ethoxide, 25°, several days) favor a thermodynamically controlled product derived by aldol condensation on the C-3 methyl group, with formation of a 3-styryl derivative.[11c,19] No reaction, to form either **11a**, **11a′** or **13**, occurred between 2-methoxybenzaldehyde and **12** in ethanolic sodium ethoxide, or with potassium *t*-butoxide in tetrahydrofuran, at 25° or at reflux temperatures. Attack at the C-3 methyl (*i.e.*, on the appropriate **12** anion) may be severely hindered by the adjacent C-2 and C-4 methyl groups, as well as by the *ortho* methoxyl group in the aldehyde. The formation of **13** rather than **11a** or **11a′** in our experiment could be a result of rapid irreversible formation of a high concentration of the enolate anion of **12** derived by removal of the most acidic C-6 proton, a process favored by the reaction conditions employed.[20] Also, use of tetrahydrofuran solvent and lithium amide minimizes retroaldol reaction.

An attempt to synthesize ketone **12** by condensation of 1-(2-methoxyphenyl)-2-methyl-1-buten-3-one (**8**) with ethyl propionyl acetate (ethanolic sodium ethoxide) led to a triketone, believed to be an enolic form of **14** (36% yield). Spectral data agree with this structure; see Experimental Section. Intramolecular Claisen condensation is favored over aldol cyclization in this example.[21] Attempted condensation of 1-(2-methoxyphenyl)-1-penten-3-one with ethyl α-methylacetoacetate also failed to yield **12** (reactant styryl ketone recovered).

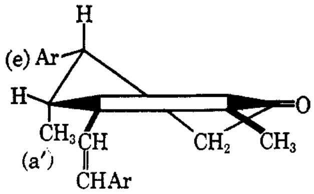


14

The stereochemistry of the 5-aryl-2,4-dimethyl-3-styryl-2-cyclohexen-1-ones **11a–g** is of interest. Assuming in each compound an equatorial aryl group at C-5, epimer pairs should differ in configuration of the methyl group at C-4. Epimerization of the 2-methoxyphenyl derivative **11a**, mp 186–187°, by equilibration in aqueous ethanolic sodium bicarbonate at 180° for 2 hr, led to an 8% conversion into epimer **11a′**, mp 118–120°, with 76% recovery of **11a**. The infrared and ultraviolet spectra of these epimers are virtually identical (Table II). Differences were observed in solubility and nmr spectra. The low melting form is much more soluble in ethanol; it was crystallized from hexane. A difference was observed in the chemical shift of the C-4 methyl doublets which appeared at τ 9.04 in **11a** and at 8.53 in **11a′**, a situation also found with the derived cyclohexenone epimer pair **12a** and **b**. Epimer **11a′** having the lower field C-4 methyl signal is believed to have a pseudo-axial C-4 methyl.[16] The cyclohexenone methylene proton signals in **11a** agree with the assigned stereochemistry: the equatorial proton at C-6 at τ 7.52 (dd, $J_{ae} \cong 5$ Hz and $J_{gem} \cong 18$ Hz), the axial C-6 proton at 6.97 (dd, $J_{aa} \cong 15$ Hz, and $J_{gem} \cong 18$ Hz). The axial C-5 proton at 6.05 and the pseudo-axial C-4 proton at 6.58 each appear as distinct multiplets with splittings characteristic of their assigned stereochemistry.



11a, mp 186–187°



11a′, mp 118–120°

Chemical behavior in basic media agrees with the configuration assignments for **11a** and **11a′**. The lower melting epimer (**11a′**) was found to be partially destroyed under the reaction conditions (53% recovery of **11a′** after 114 hr). With more vigorous conditions (ethanolic sodium ethoxide, 150°, 3 hr) destruction of **11a′** was *ca.* 90% complete, only 10% of **11a′** being recovered. *No significant epimerization of* **11a′** *to the higher melting, less soluble epimer* **11a** *was found in these experiments.* Epimer **11a** is much more stable in basic media and is only slowly epimerized to **11a′** even at 180°. It remained unchanged after refluxing in aqueous sodium hydroxide–tetrahydrofuran for 25 hr (100% recovery). These results suggest a slow axial attack in **11a** (proton removal from C-4) and more rapid equatorial attack in the common intermediate carbanion (protonation at C-4 leading to epimer **11a′**).[22] The converse situation is believed to be true in epimer **11a′** which undergoes a relatively rapid proton removal from C-4 by equatorial attack, followed by destruction of the intermediate carbanion, which evidently occurs much more rapidly than axial protonation required to form **11a**. The accumulation of retroaldol product **12a** (axial C-4 methyl) in favor of **12b** is in agreement with

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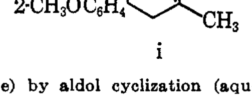
(19) (a) G. Kabas, *Tetrahedron*, **22**, 1213 (1966); (b) J.-M. Conia and U. O'Leary, *Compt. Rend.*, **249**, 1002 (1959); (c) G. Renzi, A. Steuer, and V. Dal Piaz, *Ann. Chim.*, **57**, 279 (1967); (d) J. Dewar, D. R. Morrison, and J. Read, *J. Chem. Soc.*, 1598 (1936).

(20) H. O. House, *Rec. Chem. Progr.*, **28**, 98 (1967).

(21) The course of this type of reaction evidently depends on substituents. 1-(2-Methoxyphenyl)-1-buten-3-one and ethyl acetoacetate lead to i (or the 4-carbethoxy derivative) by aldol cyclization (aqueous ethanolic sodium hydroxide): T. A. Forster and I. M. Heilbron, *J. Chem. Soc.*, **125**, 340 (1924).



i

(22) We believe this interesting example to parallel that found in 2-phenyl-1-nitrocyclohexanes wherein equatorial, relative to axial, attack at C-1 (proton abstraction or insertion) is favored by rate factors of 200–550:1: F. G. Bordwell and M. M. Vestling, *J. Amer. Chem. Soc.*, **89**, 3906 (1967); F. G. Bordwell, W. J. Boyle, Jr., J. A. Hautala, R. H. Imes, K. C. Lee, and E. C. Steiner, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1–5, 1968, p R-10.

these observations. The intermediate carbanion derived from **12** is more stable than that of **11a**. It leads, by equatorial C-4 protonation, to **12a**.

In each condensation leading to cyclohexenones **11a–g** (Table I) only one epimer was isolated. In all compounds the nmr peaks for the C-4 methyl doublet are centered at *ca.* τ 9.03, with the exception of the 4-dimethylamino compound **11g** (τ 8.57). It is suggested that compounds **11a–f** all have a pseudo-equatorial C-4 methyl; **11g** may have a pseudo-axial C-4 methyl.[16]

The exclusive formation of one epimer with *trans* C-4—C-5 stereochemistry may be a consequence of at least three factors favoring the isolated product: (1) its lower solubility and facile crystallizability, (2) its greater stability under the reaction conditions, and (3) its more rapid rate of formation in an irreversible process. As shown with **11a′** one factor is not an equilibration of products which favors one epimer. A more rapid cyclization to the epimer with C-4–C-5 *trans* stereochemistry (believed to be favored thermodynamically) would account for its formation, since the cyclization is irreversible under the reaction conditions. A mixture of equilibrating epimers of precursor diketone **2** would lead to only one product, if rate-limiting cyclization rates leading to product epimers differed sufficiently. Alternatively, and probably less likely, one product would result if only one epimer of **2** were formed initially, or favored at equilibrium.

Scope of the Reaction.—The self-condensation of styryl alkyl ketones to 5-aryl-3-styryl-2-cyclohexen-1-ones is a reaction quite limited in scope. Styryl methyl and styryl ethyl ketones having certain electron-releasing aryl substituents (alkoxy, methylenedioxy, dialkylamino) have been shown to undergo the reaction.

The reaction has been examined with respect to two principal structural features in the reactant ketone ($ArCH{=}CHCOCH_2R$), *i.e.*, the nature of (1) the alkyl group R and (2) the substituents in the aryl group, including type, ring position, and number of substituents. Reaction conditions were limited to catalysts (sodium hydroxide or sodium ethoxide), solvents (water, ethanol, or aqueous ethanol), and temperatures from −15° to reflux (*ca.* 80–90°). The method of isolation of products restricted successful results to formation of products insoluble in aqueous acetone or aqueous ethanol which elected to crystallize from the reaction mixture after standing at −15–25° for periods up to several months. To some degree this simplified isolation procedure has limited the observed reaction scope, but not its major features.

The reaction is clearly limited to styryl methyl and styryl ethyl ketones. Styryl alkyl ketones having larger alkyl groups and suitable aryl substituents undergo Michael cyclization to 4-alkanoyl-2-alkyl-3,5-diarylcyclohexanones (**3**) under similar reaction conditions. It is the failure of intermediate acyclic diketone **2** to undergo aldol cyclization, when R is larger than methyl, which limits the reaction.

Only aryl substituents having negative Hammett σ_{para} substituent constants[23] permit a successful condensation to a cyclohexenone. Condensations were achieved with methoxy, propoxy, methylenedioxy, and dimethylamino substituents in the phenyl group. However, certain other styryl methyl and styryl ethyl ketones with electron-releasing aryl substituents failed to produce crystalline condensation products. Failures resulted with phenyl substituents ethoxy, amino, diethylamino, methyl, isopropyl, and hydroxy, as well as with 2-, 3-, and 4-pyridyl aryl groups. No successful condensation to a cyclohexenone resulted from benzaldehyde itself.[24] Aldehydes with electron-withdrawing substituents (2-chloro- and 2-nitrobenzaldehydes) failed to form a cyclohexenone by reaction with 2-butanone.

The condensation of styryl alkyl ketones (**1**, R larger than methyl) to cyclohexanones (**3**) also is favored by electron-releasing aryl substituents, and disfavored by electron-withdrawing substituents such as nitro. However, the range of electronegativity of substituents allowed for Michael cyclization to **3** is larger, and includes alkoxy, amino, and alkyl substituents as well as chloro, which has a positive σ_{para} substituent constant.

The ring position and number of aryl substituents affect the cyclohexenone forming reaction. *ortho* and *para* substituents favor the reaction relative to *meta*, although *meta* substitution does not prevent reaction. Although 2-methoxystyryl ethyl ketone gave the highest yield of a cyclohexenone, the 3- and 4-methoxystyryl ethyl ketones did not form one; surprisingly, 2-methoxystyryl methyl ketone also failed to react. Only one other monosubstituted ketone was found to react—4-dimethylaminostyryl ethyl ketone. Most dimethoxy and trimethoxystyryl methyl and ethyl ketones underwent reaction rather well. Interesting anomalies were 3,4-dimethoxy and 3,4-methylenedioxy styryl ethyl ketones which failed to produce cyclohexenones, whereas the corresponding methyl ketones did react.

It is of interest to compare the effects of the ring positions and total number of aryl substituents on the two cyclization reactions (paths 1 and 2 leading from diketone **2**). One striking difference is the fact that *ortho* substituents prevent Michael cyclization (Scheme I, path 1) leading to cyclohexanone **3**, but distinctly favor aldol cyclization to **4**. Also, Michael cyclization is often quite successful with a single electron-withdrawing substituent in the *para* position; aldol cyclization occurs best with two or three electron-withdrawing substituents. These observations suggest that electron-releasing effects of aryl substituents are of greater importance in favoring the aldol cyclization (path 2) than in the Michael cyclization.

Experimental Section[25]

Procedure A. Condensation of 2,4,5-Trimethoxybenzaldehyde with Acetone. Formation of 3-(2,4,5-Trimethoxystyryl)-5-(2,4,5-trimethoxyphenyl)-2-cyclohexen-1-one (6e).—A mixture of 1.96 g (0.01 mol) of 2,4,5-trimethoxybenzaldehyde, 15 ml (11.7 g, 0.2 mol) of acetone, 10 ml of water, and 0.4 ml of 10% aqueous sodium hydroxide solution was warmed slightly on the steam bath to secure a clear solution. The glass-stoppered flask was allowed to stand at room temperature (nitrogen atmosphere) for

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[23] G. B. Berlin and D. D. Perrin, *Quart. Rev.* (London), **20**, 75 (1966); H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

[24] Styryl ethyl ketone itself is the only styryl methyl or styryl ethyl ketone which we have found to form a cycloalkanone (**3**, R = CH_3; yield only 1%).[6]

[25] Melting points were determined on a Kofler block and are corrected. Ultraviolet spectra were determined on a Cary Model 11 spectrophotometer, infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer, and nmr spectra were obtained on a Varian A-60 spectrometer (10–20% solutions in deuteriochloroform). Magnesium sulfate was employed as a drying agent.

6 days (crystals slowly deposited during this time), and in the refrigerator (5°) for 2 months. The orange-yellow prisms (0.22 g, 9.6%) were removed by filtration, mp 190–193°. Recrystallization from ethyl acetate gave small prisms which deposited slowly, mp 191–193°. The prolonged reaction time at 5° could be shortened, since most of the product appeared to crystallize from the reaction mixture within *ca.* 2 weeks.

The above procedure was effective in the condensation of piperonal with acetone to yield cyclohexenone **6d** (Table I). The crude product isolated was mixed with a gummy material from which it could be separated by crystallization from ethyl acetate–ethanol.

The procedure of Heilbron[7] was repeated with 3,4-dimethoxybenzaldehyde (0.05 mol) and acetone (same as above procedure, but with *ca.* one-half the relative amount of acetone). The crude product (5.2 g) which separated, mp 105–145°, was crystallized from ethyl acetate to yield cyclohexenone **6b** (1.75 g, 18%), mp 168–169° (lit.[7] mp 168°; yield, 20%[7]).

Attempts to apply procedure A to the preparation of cyclohexenones from certain other aromatic aldehydes and acetone led to styryl methyl ketones which separated from the reaction mixture. The following known styryl methyl ketones were obtained in this manner; substituents, melting points of crude products, and yields (in parentheses) are listed: 4-dimethylamino, mp 133.5–136.5 (91%) (lit.[5g,26] mp 134–135°); 2-methoxy, mp 34–49° (65%) (lit.[26] mp 50°); 4-hydroxy-3-methoxy, mp 123–128° (77%) (lit.[27] mp 128–129°); 2,4-dimethoxy, mp 54–57° (80%) (lit.[28] mp 62°). Benzaldehyde with excess acetone yields styryl methyl ketone itself in 65–78% yield with aqueous sodium hydroxide catalyst.[4] Modification of procedure A by replacement of most or all of the water with ethanol, to increase solubility of styryl methyl ketone intermediates, sometimes gave clear solutions but usually precipitated the styryl methyl ketones from the reaction solution in low yields (<10%). No crystalline cyclohexenones could be isolated subsequently after the solutions had been diluted with water and chilled; oils and/or styryl methyl ketones resulted.

Procedure A gave unidentified oily products (possibly containing low-melting styryl alkyl ketones) when aplied to acetone condensations with substituted benzaldehydes having the following substituents: 3-methoxy, 4-methoxy, 2-ethoxy, 4-diethylamino, 2,3-dimethoxy, 2,5-dimethoxy, 3,5-dimethoxy, and 3,4,5-trimethoxy.

Procedure B. Condensation of 2-Methoxybenzaldehyde with 2-Butanone. Formation of Gheorghiu's Compound, 2,4-Dimethyl-5-(2-methoxyphenyl)-3-(2-methoxystyryl)-2-cyclohexen-1-one (11a).[8]—To a solution of 30.0 g (0.22 mol) of freshly distilled 2-methoxybenzaldehyde in 225 ml of 95% ethanol was added 30 g (0.416 mol) of 2-butanone and 15 ml of 10% aqueous sodium hydroxide solution. By external cooling the temperature was kept below 32°. After the initial reaction had subsided the yellow solution was allowed to stand in an atmosphere of nitrogen, in the dark, for 18 hr at 25°. The yellow crystals which formed were separated (11.1 g, mp 183–187°); chilling the filtrate at 0° for several weeks deposited 15.5 g of additional material, mp 181–185°, to give a total yield of 26.6 g (64%). Recrystallization of the first crop from ethanol gave 8.5 g of yellow prisms, mp 186–187°.

The above procedure, employing a 1- to 2-week reaction time, was effective in condensation of the following substituted benzaldehydes with 2-butanone to yield cyclohexenones **11b**–**11g** listed in Table I: phenyl substituents, 2,4-dimethoxy, 2,5-dimethoxy, 3,5-dimethoxy, 2,4,5-trimethoxy, 3,4,5-trimethoxy, and 4-dimethylamino. In some instances it was necessary to warm the reaction mixture initially in order to dissolve the reactant aldehyde. The crude cyclohexenone product was usually mixed with some styryl alkyl ketone. Purification was readily achieved by crystallization from ethanol or ethyl acetate. With 4-dimethylaminobenzaldehyde a 3-week reaction time was employed resulting in a crude product containing much 4-dimethylaminostyryl ethyl ketone;[5g] the cyclohexenone (**11g**) was isolated with some difficulty by fractional crystallization from ethanol.

Procedure B with 2-butanone and 4-diethylaminobenzaldehyde gave principally an oily product from which a 3% yield of 4-diethylaminostyryl ethyl ketone could be isolated by crystallization from ethanol, mp 71–72°.

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05; mol wt, 231.33. Found: C, 77.75; H, 9.16; N, 6.30; mol wt, 233.

Procedure B with 2-butanone gave oily or gummy products, from which no crystalline product could be isolated, with benzaldehydes having the following substituents: 2-methyl, 4-methyl, 2,3-dimethoxy, 3,4-methylenedioxy, 4-isopropyl, and 3-methoxy.

Procedure B with 2-butanone gave clear solutions from which no product separated, with benzaldehydes having the following substituents: 2-chloro, 2-ethoxy, 4-hydroxy-3-methoxy, 2-amino, 4-hydroxy, 2-nitro, 3,4-dimethoxy, as well as with 2-, 3-, and 4-pyridinecarboxaldehyde. Attempted condensation of 2-pentanone with 2-methoxybenzaldehyde also gave a clear solution with procedure B. Dilution of these solutions with water and/or acidification failed to yield crystalline cyclohexenones.

Attempts to apply procedure B to condensations of aldehydes with acetone failed to yield cyclohexenones. Benzaldehyde and 2-ethoxybenzaldehyde gave gummy products and no crystalline material. Vanillin and 3,4-dimethoxybenzaldehyde gave low yields (<10%) of the styryl methyl ketones. 2-Methoxybenzaldehyde gave *ca.* 15% of di-2-methoxybenzalacetone; the crude product had mp 115–125° (lit.[29] mp 125°).

1-(2-Methoxyphenyl)-2-methyl-1-penten-3-one.—Procedure B applied to condensation of 2-methoxybenzaldehyde with 3-pentanone (reaction time, 11 days; 25°) gave an oil, bp 95–115° (0.1 mm), which was crystallized from hexane to yield the styryl alkyl ketone, mp 39–41° (62% yield). Recrystallization from hexane gave long prisms: mp 42–43°; ν 1670 cm^{-1} (C═O) (measurement on supercooled liquid).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90; mol wt, 204.26. Found: C, 76.63; H, 7.93; mol wt, 210.

1-(2,4-Dimethoxyphenyl)-1-buten-3-one.—A mixture of 2,4-dimethoxybenzaldehyde (8.3 g, 0.05 mol), 30 ml of acetone, 10 ml of water, and 10 ml of 10% sodium hydroxide solution was heated under reflux for 15 min. The solution was chilled to yield 9.55 g (93%) of the styryl ketone, mp 55–60°. Recrystallization from ethanol gave pale yellow needles, mp 62–63 (lit.[28] mp 62°).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; mol wt, 206.23. Found: C, 70.04; H, 7.02; mol wt, 205.

Procedure C. Self-Condensation of 1-(2,4-Dimethoxyphenyl)-1-buten-3-one to 3-(2,4-Dimethoxystyryl)-5-(2,4-dimethoxyphenyl)-2-cyclohexen-1-one (6a).—To a solution of 8.1 g of 1-(2,4-dimethoxyphenyl)-1-buten-3-one in 20 ml each of acetone and ethanol, and 40 ml of water was added 2 ml of 10% sodium hydroxide solution. After standing at room temperature for 1 week and in the refrigerator for 6 weeks, the crystalline cyclohexenone **6a** (0.71 g, 9.1%) was removed by filtration, mp 161–162°. Recrystallization from ethyl acetate gave prisms, mp 169–170°.

The above procedure could not be applied successfully to the preparation of a cyclohexenone from 4-dimethylaminostyryl methyl ketone;[5g,26] 38% of the reactant ketone was recovered. 2-Methoxystyryl methyl ketone[26] gave only an oily product. An unsuccessful attempt was made to improve the yield of cyclohexenone **11g** (Table I) by applying the above procedure to self-condensation of 4-dimethylaminostyryl ethyl ketone;[5g] only recovered ketone (*ca.* 75%) and gummy material could be isolated.

Procedure D. Self-Condensation of 1-(2-Methoxyphenyl)-2-methyl-1-buten-3-one (8) to 5-(2-Methoxyphenyl)-3-[1-methyl-2-(2-methoxyphenyl)vinyl]-6-methyl-2-cyclohexen-1-one (9).—A 3.8-g (0.02 mol) sample of 1-(2-methoxyphenyl)-2-methyl-1-buten-3-one (**8**), mp 23–26°,[14,30] was dissolved in 10 ml of absolute ethanolic sodium ethoxide (prepared from 0.1 g of sodium). The

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(26) I. M. Heilbron and J. S. Buck, *J. Chem. Soc.*, **119**, 1500 (1921).

(27) A. Ya. Berlin and S. M. Sherlin, *Zh. Obshch. Khim.*, **18**, 1386 (1948); *Chem. Abstr.*, **43**, 2185 (1949).

(28) (a) 2,4-Dimethoxystyryl methyl ketone, mp 62°, has been prepared in 14% yield by Friedel–Crafts acylation of 1,3-dimethoxybenzene with 1-chloro-1-buten-3-one employing stannic chloride catalyst: A. N. Mesmeyanov, N. K. Kochetkov, and L. R. Matov, *Dokl. Akad. Nauk SSSR*, **92**, 85 (1953); *Chem. Abstr.*, **48**, 10665 (1954). (b) The compound, prepared by condensation of 2,4-dimethoxybenzaldehyde with acetone and aqueous sodium hydroxide catalyst, is described as an oil, bp 185–190° at 2 mm (no elemental analyses given): A. Ya. Berlin and T. P. Sycheva, *Zh. Obshch. Khim.*, **22**, 1998 (1952); *Chem. Abstr.*, **47**, 8681 (1953). We have repeated this preparation and find mp 62–63° for 2,4-dimethoxystyryl methyl ketone.

(29) A. Baeyer and V. Villiger, *Ber.*, **35**, 3013 (1902).

(30) Woodruff and Conger[14] report ketone **8** as a liquid, bp 162–163° (12 mm). We determined the nmr spectrum of **8** ($CDCl_3$): τ 2.25 (s, 1, CH═), 2.5–3.2 (m, 4, aryl, CH), 6.22 (s, 3, CH_3O), 7.62 (s, 3, CH_3CO), 8.02 (d, 3, J = 1 Hz, CH_3C═); ν_{neat} 1640 cm^{-1} (C═O).

solution was allowed to stand at 25° for 16.5 hr, then heated on the steam bath for 2 hr. The reddish solution was concentrated to remove ethanol and the residue was treated with saturated potassium carbonate solution. The mixture was extracted with methylene chloride, and the extracts were dried and concentrated to remove solvents. The residue was crystallized from ethanol to yield 1.25 g (34%) of cyclohexenone **9**, mp 126–128°. Recrystallization from ethanol gave 1.0 g of nearly colorless prisms, mp 132–133°. Spectral data are given in Tables II and III.

Anal. Calcd for $C_{24}H_{26}O_3$: C, 79.53; H, 7.23; mol wt, 362.45. Found: C, 79.62; H, 7.31; mol wt, 360.

Procedure D was applied to 1-(2-methoxyphenyl)-2-methyl-1-penten-3-one (preparation described above). A gummy product was obtained, soluble in ethanol or benzene. An amorphous solid, mp 125–140°, which could not be obtained in crystalline form, separated on dilution of the benzene solution with heptane.

Condensation of 1-(2-Methoxyphenyl)-2-methyl-1-buten-3-one (8) with Ethyl Propionylacetate.—A solution of 3.80 g (0.02 mol) of ketone **8**[14,30] and ethyl propionylacetate (2.88 g, 0.02 mol) in 20 ml of absolute ethanolic sodium ethoxide (prepared from 0.46 g of sodium) was heated under reflux for 1.5 hr. The solution was concentrated to remove most of the ethanol and the residue was diluted with water and extracted twice with ether. The dried ether extracts gave 2.4 g (63%) of recovered ketone **8** (analysis by vpc on 10 ft × 0.25 in. Chromosorb W-20% Apiezon L at 200°; retention time and infrared spectrum identical with authentic **8**). The aqueous alkaline part was treated with hydrochloric acid to deposit 2.17 g (36%) of crude **5-(2-methoxyphenyl)-6-methyl-4-propionyl-1,3-cyclohexanedione (14)**, mp 155–160°. Recrystallization from benzene gave small prisms, mp 160–170° dec; ethanolic ferric chloride gave a red color: ν^{Nujol} 2400–2600 (enolic OH), 1710 (C=O, nonconjugated), and 1590 and 1530 cm^{-1} (bands due to enolic 1,3-diketone).[31] The nmr spectrum was determined in D_2O–potassium carbonate: τ 2.5–3.5 (m, 3, aryl CH), 6.30 (s, 3, CH_3O), 9.13 (d, 3, CH_3CH), 9.08 (t, 3, CH_3CH_2–), 6.02 (q, 2, CH_3CH_2–), and 5.5–6.0 (m, 1); ring protons (3) which did not appear in the spectrum were exchanged by deuterium in the alkaline medium. The analytical sample was dried at 100° (0.05 mm).

Anal. Calcd for $C_{17}H_{20}O_4 \cdot H_2O$: C, 66.65; H, 7.24; mol wt, 306.35. Found: C, 66.34; H, 7.38; mol wt, 306.

The above procedure was applied, with slight modifications, to the condensation of 1-(2-methoxyphenyl)-1-penten-3-one[8] and ethyl α-methylacetoacetate to yield principally recovered styryl ketone.

1,5-Bis(2-methoxyphenyl)-2-methyl-1,4-pentadien-3-one.—To a solution of 13.6 g (0.1 mol) of 2-methoxybenzaldehyde and 3.6 g (0.05 mol) of 2-butanone in 60 ml of ethanol was added 10 ml of 10% aqueous sodium hydroxide solution. After standing 4 days at room temperature the gummy crystals which deposited were filtered (4.6 g) and recrystallized from ethanol to yield 2.1 g (22%) of cyclohexenone **11a**, mp 183–186°. Chilling the mother liquor gave a low-melting solid which was crystallized from dilute ethanol to yield 1.15 g (7.5%) of the dienone: mp 93–95° (another recrystallization raised the melting point to 94–96°); ν^{KBr} 1645 (conjugated C=O) and 1620 cm^{-1} (conjugated C=C); neither another carbonyl absorption nor a hydroxyl band was present; $\lambda_{\max}^{\text{EtOH}}$ 239 mμ (ϵ 14,900) and 345 (20,800).

Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54; mol wt, 308.3. Found: C, 78.37; H, 6.68; mol wt, 308.

Retroaldol Cleavage of 2,4-Dimethyl-5-(2-methoxyphenyl)-3-(2-methoxystyryl)-2-cyclohexen-1-one (11a). Formation of Epimeric 5-(2-Methoxyphenyl)-2,3,4-trimethyl-2-cyclohexen-1-ones (12a and b).—A mixture of 7.24 g (0.02 mol) of cyclohexenone **11a**, sodium hydroxide (2.0 g), 100 ml 95% ethanol, and 10 ml of water was heated in a 300-ml capacity, stainless steel bomb at 150° for 17 hr. After cooling, the clear orange solution was concentrated under reduced pressure to remove the ethanol. The residue was extracted with ether, and the extracts were washed with 10% aqueous sodium hydroxide solution. The combined, dried extracts were concentrated to yield 7.23 g of yellow viscous oil which was fractionally distilled under reduced pressure.

The first fraction was 2-methoxybenzyl alcohol: 1.22 g (44%); bp 68–70° (0.1 mm); $n^{25}\text{D}$ 1.5440 (lit. $n^{25}\text{D}$ 1.5428,[32] $n^{21}\text{D}$ 1.5470).[33] An authentic sample (Aldrich) had an index of refraction of $n^{25}\text{D}$ 1.5450; its infrared spectrum was identical with authentic sample, ν^{neat} 3200 cm^{-1} (OH); carbonyl absorption was absent. The 1-naphthylurethan derivative was crystallized from cyclohexane and had mp 135–136° which was not depressed when mixed with an authentic sample of 2-methoxybenzyl alcohol 1-naphthylurethan, mp 136–137° (lit.[34] mp 135–136°).

The second fraction (1.7 g), bp 126–130° (0.2 mm), was chromatographed on a 4 ft × 0.25 in. Teflon–5% silicone oil column at 215°. Two major peaks appeared. The first (45% of total) was an unidentified mixture: ν 3300 (OH, weak), 1690 (C=O, weak), and 1640 cm^{-1} (C=O, strong). The last peak (**12a** and **b** mixture, 55% of total, ν^{neat} 1640 cm^{-1}) was used for elemental analysis.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25; mol wt, 244.32. Found: C, 78.94; H, 8.50; mol wt, 243.

Rechromatography of the **12a** and **b** mixture permitted a separation of epimer **12b** (last material to leave the column); **12a** could not be completely freed of **12b** (analysis, based on nmr spectra, is discussed in the text). Epimer **12b** formed a 2,4-dinitrophenylhydrazone: dark-red, flat plates; mp 201.5–202.5°; τ ($CDCl_3$) 2.5–3.3 (m, aryl), 6.15 (s, 3, CH_3O), 6.3–9.0 (m, 4, cyclohexene ring protons), 7.97 (s, 3, CH_3C=), 7.98 (s, 3, CH_3-C=), 9.22 (d, 3, J = 7 Hz, CH_3CH).

Anal. Calcd for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found: C, 62.43; H, 5.55; N, 13.06.

Fractional crystallization of 2,4-dinitrophenylhydrazones prepared from the mixture of **12a** and **b** afforded the derivative of **12a**. It was purified by chromatography on alumina (elution with benzene), and recrystallization from ethanol gave dark red prisms, mp 159–161°.

Anal. Calcd for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found: C, 62.32; H, 5.89; N, 13.18.

The residue from the distillation (4.15 g) failed to yield crystalline material from ethanol or hexane. The aqueous alkaline residue remaining from the ether extractions was acidified with concentrated hydrochloric acid to yield traces of gummy material from which no crystalline material could be isolated.

Condensation of 5-(2-Methoxyphenyl)-2,3,4-trimethyl-2-cyclohexen-1-one (12) with 2-Methoxybenzaldehyde to 6-(2-Methoxybenzal)-5-(2-methoxyphenyl)-2,3,4-trimethyl-2-cyclohexen-1-one (13).—A mixture of a 0.55-g sample of the above unchromatographed fraction 2 (containing *ca.* 0.2 g of **12a** and 0.1 g of **12b**), 0.33 g of 2-methoxybenzaldehyde, 0.05 g of lithium amide, and 2 ml of tetrahydrofuran was heated in a sealed glass tube at 150° for 5 hr. The cooled solution was concentrated to remove the solvent and the residue was extracted with hexane. Ketone **13** separated from the extracts: 22.3 mg, mp 170–185°, and 39.0 mg, mp 185–187°; total yield 61.3 mg, 19% based on assay of **12a** present. Recrystallization from ethanol gave small, pale yellow prisms, mp 190–191°; when mixed with a sample of cyclohexenone **11a** (mp 186–187°) the melting point was depressed to 160–170°. Condensation of 2-methoxybenzaldehyde with crude **12** in parallel experiments, employing ethanolic sodium ethoxide or potassium *t*-butoxide in tetrahydrofuran at 25° or at reflux temperature (16–20 hr), failed to yield **13** or any other crystalline product. Spectra of **13** are discussed in the text.

Anal. Calcd for $C_{24}H_{26}O_3$: C, 79.53; H, 6.93. Found: C, 79.60; H, 7.02.

Epimerization of 2,4-Dimethyl-5-(2-methoxyphenyl)-3-(2-methoxystyryl)-2-cyclohexen-1-one 11a to 11a′.—A mixture of 3.62 g (0.01 mol) of cyclohexenone **11a**, mp 186–187°, 100 ml of 95% ethanol, 50 ml of water, and 0.84 g of sodium bicarbonate was heated in a 300-ml stainless steel bomb at 180° for 2 hr. The cooled mixture deposited 2.75 g (76%) of recovered epimer **11a**, mp 182–186°. The filtrate was concentrated under reduced pressure to remove the ethanol and the residue was extracted with ether. From the ether extracts there was isolated 0.73 g of oil which was extracted with hot hexane. The chilled extracts deposited 0.27 g (8%) of epimer **11a′**, mp 115–120°. Recrystallization from hexane gave 0.14 g of pale yellow prisms, mp 118–120°; see Tables I–III for elemental analyses and spectral data.

Cyclohexenone **11a** was recovered (93%) when a 1.0-g sample was heated under reflux for 28 hr with a solution of 20 ml of ethanol, 10 ml of water, and 1 ml of 10% aqueous sodium hydroxide solution. Heating a 0.51-g sample of **11a** under reflux for 25 hr with a solution of 20 ml of tetrahydrofuran, 2 ml of

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(31) R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattain, *J. Amer. Chem. Soc.*, **71**, 1068 (1949).

(32) E. J. Cragoe, Jr., and A. M. Pietruszkiewicz, *J. Org. Chem.*, **22**, 1338 (1957).

(33) R. Grice and L. N. Owen, *J. Chem. Soc.*, 1947 (1963).

(34) V. T. Bickel and H. E. French, *J. Amer. Chem. Soc.*, **48**, 747 (1926).

water, and 1 ml of 10% aqueous sodium hydroxide solution gave recovered **11a** (100%), mp 183–185°.

A 44.5-mg sample of epimer **11a′**, mp 115–120°, in 2.0 ml of absolute ethanol containing 10 mg of sodium methoxide was heated in a sealed glass tube at 150° for 3 hr. After removal of the ethanol the residue was extracted with hot hexane; the cooled extract deposited 4.4 mg of recovered **11a′**, mp 116–118°; no other crystalline product could be isolated. In a second experiment with 50 mg of **11a′** in 5 ml of 95% ethanol and 0.5 ml of 10% aqueous sodium hydroxide, the solution was allowed to stand at room temperature for 114 hr. From the reaction mixture there was obtained 26.4 mg of recovered **11a′**, mp 116–120°, as the only crystalline product.

Registry No.—**6a**, 16831-37-1; **6b**, 16831-33-7; **6d**, 16831-34-8; **6e**, 16831-35-9; **9**, 16859-74-8; **11a**, 16831-38-2; **11a′**, 16831-39-3; **11b**, 16831-36-0; **11c**, 16831-40-6; **11d**, 16831-41-7; **11e**, 16831-42-8; **11f**, 16831-43-9; **11g**, 16831-44-0; **12a**, 16831-45-1; 2,4-dinitrophenylhydrazone of **12a**, 16831-07-5; **12b**, 16830-99-2; 2,4-dinitrophenylhydrazone of **12b**, 16831-00-8; **13**, 16831-01-9; **14**, 16831-02-0; 4-diethylaminostyryl ethyl ketone, 16831-03-1; 1-(2-methoxyphenyl)-2-methyl-1-penten-3-one, 16831-04-2; 1-(2,4-dimethoxyphenyl)-1-buten-3-one, 16831-05-3; 1,5-bis-(2-methoxyphenyl)-2-methyl-1,4-pentadien-3-one, 14164-68-2.

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The Conformational "Size" of the Methyl Group in 4-, 5-, and 6-Methyl-2-carbomethoxytetrahydropyrans

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The conformational preferences of the methyl group in 4-, 5-, and 6-methyl-2-carbomethoxytetrahydropyran were found to be 1.70, 1.27, and 1.70 kcal/mol, respectively. The value at the 5 position is smaller because of the smaller size of the oxygen with its unshared electron pairs compared to a methylene group. The conformational preference of the carbomethoxy group in 2-carbomethoxy-6-*t*-butyltetrahydropyran was found to be larger than in cyclohexane (1.6 *vs.* 1.1 kcal/mol). This effect is attributed to a dipole–dipole interaction.

Recently Eliel and Knoeber[1] have reported that a series of 2-alkyl-5-*t*-butyl-1,3-dioxanes, where alkyl is methyl, ethyl, isopropyl, and *t*-butyl, show the same equilibrium *cis*/*trans* ratio. In each case, the *cis* isomer was less stable than the *trans* isomer by 1.4–1.5 kcal/mol. It was concluded that in each *cis* isomer the various 2-alkyl groups must be in equatorial conformations; thus the 5-*t*-butyl group must be in an axial conformation. This is a unique situation for the bulky *t*-butyl group which prefers the equatorial conformation in cyclohexane systems by *ca.* 5.6 kcal/mol.[2] In fact the cyclohexane ring is forced into a skew boat conformation, which is unfavorable compared to the chair by 5.3 kcal/mol, rather than have the *t*-butyl axial in the chair conformation.[3]

The 1,3-dioxane chair form has been estimated as 2.2 kcal/mol[4] more stable than the skew boat form although more recently arguments have been advanced in favor of a larger estimate, greater than 3 kcal/mol.[5] Although a boat 1,3-dioxane (even at 3 kcal/mol) may seem to be an energetically feasible alternative explanation to an axial *t*-butyl group, Eliel and Knoeber[1] concluded from an interpretation of nmr coupling constants that the above substituted 1,3-dioxanes must be in chair conformations. The small value of the conformational preference of the 5-*t*-butyl group in the 1,3-dioxane system compared to that in cyclohexane was ascribed to the smaller steric bulk of the unshared electron pairs on the ring oxygens compared to the *syn*, *axial* hydrogens in cyclohexane. A 5-methyl group was observed to have a 0.80-kcal/mol preference for the equatorial conformation in the 1,3-dioxane system.

We have been investigating conformational effects in tetrahydropyran derivatives[6] and were also interested by the steric consequences of the ring oxygen. In order to assess the conformational preference of the methyl group in methyltetrahydropyrans, an epimerizable group is needed which is of steric size comparable to the methyl group. (Otherwise the data are inaccurate as can be shown in the calculation below.) The 2-carbomethoxy group can be epimerized conveniently with sodium methoxide in methanol.

The 2-carbomethoxy-5-methyl- and 2-carbomethoxy-6-methyl-tetrahydropyrans could be obtained in poor yield (2–5%) from the Diels–Alder reaction[7] of methacrolein or methyl vinyl ketone and methyl acrylate. None of the desired 4-methyl product could be obtained from crotonaldehyde and methyl acrylate. A better preparative procedure was found to be the treatment of the alkyldihydropyran with amylsodium followed by treatment with carbon dioxide[8] which yielded, after acidification, hydrogenation, and esterification, the appropriate 2-carbomethoxyalkyltetrahydropyran. The alkyldihydropyrans were obtained by distillation of the corresponding 2-isobutoxymethyltetrahydropyran[6,9] in the presence of toluenesulfonic acid. The respective 2-isobutoxyalkyltetrahydropyrans were obtained by Diels–Alder reaction of isobutyl vinyl ether with crotonaldehyde, methacrolein, or methyl vinyl

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