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# THE CONDENSATION OF AROMATIC ALDEHYDES WITH ISOPHORONE

G. Kabas[1]
W. R. Grace Research Zurich, Switzerland

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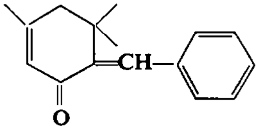
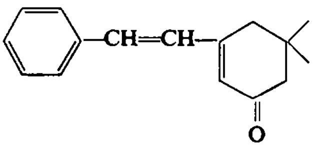
**Abstract**—The Claisen-Schmidt condensation of 7 aromatic aldehydes and furfural with isophorone have been investigated. In three cases a dimer of the styryl compounds was formed for which the two structures IX and X are proposed.

The Claisen-Schmidt condensation between aromatic aldehydes and isophorone has not been thoroughly investigated. Several authors condensed isophorone with differently substituted benzaldehydes and formulated the benzylidene derivatives as I.[2–4] Ensor and Wilson[5] on the basis of UV spectra proposed structure II and Conia[6,7] with an elegant investigation, confirmed the benzylidene isophorone (m.p. 78–79°) structure as represented by II. The latter[6,7] also reinvestigated the work of Cornubert and Berrel[2] and found a second condensation product (m.p. 198–199°) formed as well, but no structure was proposed.



I



II

The nature of this high-melting condensation product ($C_{16}H_{18}O$) seemed to be of particular interest, and consequently, a series of products derived by condensation of isophorone with benzaldehyde, some methoxy derivatives and furfural were prepared. In only three cases was the high-melting isomer found in the reaction mixture. The results obtained are presented in Table 1. A mol. wt. determination of these high melting isomers (both with the Rast and with the osmometric method) revealed their dimeric nature. The condensation was generally carried out with one-mole equivalent each of the aldehyde and isophorone in 95% aqueous ethanol and in the presence of aqueous sodium hydroxide (ca. 0·5 mole equiv in the form of a 45% aqueous solution). The styryl isophorones could be separated from their dimers by taking advantage of their higher solubility in common organic solvents. Dimers were also formed by treating compounds II, VI and VIII with ethanolic sodium hydroxide

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[1] Present address: J. R. Geigy AG., Basle, Switzerland.

[2] R. Cornubert, C. Borel, *C.R. Acad. Sci. Paris* **183**, 296 (1926); *Bull. Soc. Chim. Fr.* **45**, 1148 (1929).

[3] S. C. Dorman, S. A. Ballard, U.S. Pat. 2,465,855 (1949).

[4] H. S. French, *J. Amer. Chem. Soc.* **74**, 514 (1952).

[5] G. R. Ensor, W. Wilson, *J. Chem. Soc.* 4068 (1956).

[6] J. M. Conia, U. O'Leary, *C.R. Acad. Sci. Paris* **249**, 1002 (1959).

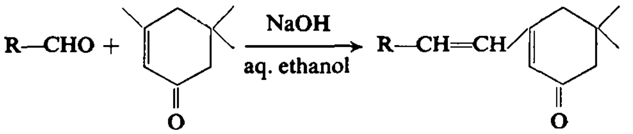
[7] J. M. Conia, A. Le Craz, *Bull. Soc. Chim. Fr.* 1327 (1960).

solution for 48 hr, whereas compounds III, IV, V and VII were recovered unchanged from this treatment. Thus, the dimerization process is hindered by substituents in *ortho* and *meta* positions and the bulky *p*-dimethylamino group.

The formation of these dimers, brought about by bases, may be considered as proceeding by two successive Michael additions analogous to the dimerization of styryl alkyl ketones reported by Nielsen and Dubin.[8] It must be pointed out that no dimer of the isophorone derivatives prepared as described above could be obtained by UV irradiation or heat in the absence of base.

The dimer derived from 2-styryl-5,5-dimethyl-2-cyclohexen-1-one (II) was chosen for detailed structure elucidation. The IR spectrum (observed as a nujol mull) of the monomeric benzylidene isophorone shows the following maxima: 1650 cm$^{-1}$ (olefin conjugated carbonyl), 1620 cm$^{-1}$ (olefinic double bond), 1580 cm$^{-1}$ (aromatic ring), 1295 cm$^{-1}$ and 960 cm$^{-1}$ (*trans* ethylenic double bond). The UV spectrum in EtOH has two maxima $\lambda_{max}$ 236 m$\mu$ ($\varepsilon$ 9,200), $\lambda_{max}$ 324 m$\mu$ ($\varepsilon$ 34,000). The IR spectrum of the dimeric benzylidene isophorone (observed also as a nujol mull) shows the following peaks: 1670 cm$^{-1}$ (olefin conjugated carbonyl), 1640 cm$^{-1}$ (olefinic double bond), 1620 cm$^{-1}$ (aromatic ring). The UV spectrum in ethanol indicated also that in the dimeric benzylidene isophorone the aromatic carbonyl conjugation through the double bond had been destroyed: $\lambda_{max}$ 244·5 m$\mu$ ($\varepsilon$ 10,600).

TABLE 1. SYNTHESIS OF STYRYL TYPE ISOPHORONES



| Compound | R | M.P., °C<br>B.p., °C | D.N.P.,[a]<br>M.p., °C | Dimer<br>M.p., °C |
|---|---|---|---|---|
| II | $C_6H_5$ | 78–79 | 221–222 | 198–199 |
| III | 2-$C_6H_4OH$ | 164–165 | 240–241 | — |
| IV | 2-$C_6H_4OCH_3$ | 125–126 | 245–247 | — |
| V | 3-$C_6H_4OCH_3$ | 182–184[b] | 213–214 | — |
| VI | 4-$C_6H_4OCH_3$ | 69–70 | 232–234 | 194–195 |
| VII | 4-$C_6H_4N(CH_3)_2$ | 124–125 | 270–272 | — |
| VIII | $C_4H_3O$ (2-furyl) | 133–135[b] | 217–218 | 208–209 |

[a] D.N.P. = 2,4-dinitrophenylhydrazone. [b] B.p. at 0·1 mm.

Mass spectrometry revealed the parent peak of the benzylidene isophorone at 226 mass units and thus fixed, accurately, the mol. wt. With the dimeric benzylidene isophorone, the highest peaks appeared at 251 and 239 mass units; below these peaks, the spectra of the dimeric and monomeric II were essentially identical. This is supporting evidence for the dimeric nature of the high-melting benzylidene isophorone.

Two structures are proposed for the dimeric benzylidene isophorone: IX and X (iso = 3-isophoryl radical). Structures containing a cyclobutane or a cyclooctane

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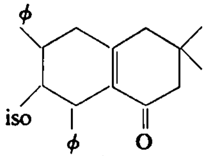
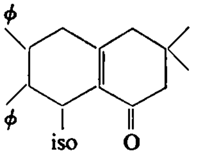
[8] A. T. Nielsen, H. J. Dubin, *J. Org. Chem.* 28, 2120 (1963).



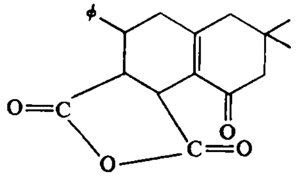
IX



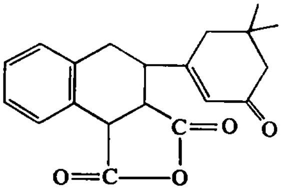
X

ring are ruled out by the NMR spectrum. Moreover, the NMR evidence indicates that there is only one olefinic proton present ($\tau = 4{\cdot}28$), namely, one on an isophorone grouping in a similar environment to isophorone itself. Thus, should there be another double bond, it must be tetrasubstituted. The dimer consumes two moles of bromine in carbon tetrachloride.

3-Styryl-5,5-dimethyl-2-cyclohexen-1-one reacts with N-bromosuccinimide to yield 3-styryl-4-bromo-5,5-dimethyl-2-cyclohexen-1-one, the structure of which was assigned by NMR spectral comparison with pure 4-bromoisophorone.[9] Compound II reacts with maleic anhydride yielding a compound, for which structure XI, and not XII is proposed. In fact, the NMR evidence indicates the absence of olefinic protons. The IR spectrum (observed as a nujol mull) of the maleic anhydride adduct shows the following maxima: 1860 $cm^{-1}$ and 1785 $cm^{-1}$ (anhydride carbonyls), 1670 $cm^{-1}$ (olefin-conjugated carbonyl), 1640 $cm^{-1}$ (olefinic double bond) and 1600 $cm^{-1}$ (aromatic ring). Upon oxidation, benzoic acid and not phthalic acid was obtained thus confirming structure XI.



XI



XII

## EXPERIMENTAL[10]

*3-Styryl-5,5-dimethyl-2-cyclohexen-1-one*

The procedure of Ensor and Wilson[5] was used. A solution of 276 g (2 moles) freshly distilled benzaldehyde in 1000 ml EtOH was treated, under cooling, with 100 ml 45% NaOHaq. The mixture was left at room temp for 6 days, decomposed with water neutralized with dil. HCl and extracted with $CHCl_3$. After removal of solvent from the dried extracts, the residue was treated with 500 ml ether, kept in the freezer overnight and the colourless dimeric compound collected by filtration to yield 264 g (58·5%), m.p. 196–197°. An analytical sample was crystallized from ethyl acetate, m.p. 198–199°. (Found: C, 84·98; H, 7·93. Calc. for $C_{32}H_{36}O_2$: C, 84·91; H, 8·02%. Mol. wt. calc for $C_{32}H_{36}O_2$: 452. Found (Rast): 438: (Osmometric) 455.)

The ethereal mother liquor was concentrated to dryness and the residue distilled. The fraction b.p. 150–155° (0·1 mm) was collected and crystallized from n-hexane to yield 120 g (26·8%) of the pale yellow benzylidine m.p. 78–79° (reported[9] m.p. 78·5°). The 2,4-dinitrophenylhydrazone was prepared in the conventional method and crystallized from ethyla cetate, m.p. 221–222°. (Found: N, 13·81. Calc. for $C_{22}H_{22}N_4O_4$: N, 13·79%.)

The dependence of the yields of II and its dimer (IX) with varying alkali concentration or reaction time using one mole each of the benzaldehyde and of isophorone is shown in Table 2. The procedure as described above was adopted.

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[9] A. J. B. Edgar, S. A. Harper, M. A. Kazi, *J. Chem. Soc.* 1083 (1957).

[10] M.ps and b.ps are uncorrected.

### 3-*Styryl-4-bromo-5,5-dimethyl-2-cyclohexen-1-one*

A mixture consisting of 17·8 g (0·1 mole) NBS, 29 g (0·13 mole) benzylidene isophorone and 0·3 g dibenzoylperoxide in 200 ml dry $CCl_4$ was refluxed until the solid had risen to the surface of the liquid (3 hr). The reaction mixture was cooled, filtered and the filtrate concentrated to dryness. The residue was crystallized from EtOH to yield 27·2 g (67%) of the bromide, m.p. 131–123°. (Found: C, 63·04; H, 5·62; Be, 26·19. Calc. for $C_{16}H_{17}BrO$: C, 62·96; H, 5·62; Br, 26·09%.)

### *Diels-Alder adduct of benzylidene isophorone with maleic anhydride*

A solution of 22·6 g (0·1 mole) benzylidene isophorone and 9·8 g (0·1 mole) maleic anhydride in 100 ml toluene was refluxed for 24 hr Excess toluene was removed and the residue recrystallized from a benzene–chloroform to yield 23·7 g (73·2%) of colourless product, m.p. 135–136° with gas evolution. (Found: C, 74·11; H, 6·17. Calc. for $C_{20}H_{20}O_4$: C, 74·05; H, 6·22%.)

TABLE 2

| NaOH mole | Reaction time | Yields of product, % | |
|---|---|---|---|
| | | II | IX |
| 0·665 | 6 days | 26·8 | 58·5 |
| 0·665 | 2 days | 57·5 | 22·1 |
| 0·33 | 2 days | 77·5 | 13·3 |
| 0·16 | 2 days | 79·5 | 3·6 |
| 0·08 | 2 days | 86·0 | 0·5 |
| 0·66 | 24 hr | 80·6 | 13·2 |
| 0·66 | 4 hr | 85·0 | 0·5 |

### 3-(2-*Hydroxystyryl*)-5,5-*dimethyl-2-cyclohexen-1-one*

A solution of 18·3 g (1·5 moles) salicylaldehyde and 207 g (1·5 moles) isophorone in 750 ml EtOH was cooled to 5°. Under vigorous stirring and temp control, 60 ml 45% NaOHaq was added. Allowing the yellow reaction mixture to reach room temp, stirring was continued for 48 hr. The colour changed from yellow to deep red. The mixture was decomposed with water, neutralized with dil. HCl and extracted with $CHCl_3$. After removal of solvent from the combined and dried extracts, the residue was distilled to remove unreacted isophorone (96 g) and salicylaldehyde (83 g). The residue was dissolved in a minimum amount either of $CHCl_3$, EtOH or benzene, but no insoluble product could be detected. One crystallization of the crude product from a benzene-EtOH gave 181 g (98%) of the yellow phenol III, m.p. 164–165°. (Found: C, 79·26; H, 7·41. Calc. for $C_{16}H_{18}O_2$: C. 79·31; H, 7·49%.)

The 2,4-dinitrophenyldhyrazone was crystallized from ethyl acetate, m.p. 240–241° with dec. (Found: N, 13·37. Calc. for $C_{22}H_{22}N_4O_5$: N, 13·26%.)

### 3-(2-*Methoxystyryl*)-5,5-*dimethyl*-2-*cylclohexen*-1-*one*

(a) The condensation was carried out by reacting 136·1 g (1 mole) *o*-methoxybenzaldehyde with 138 g (1 mole) isophorone in the presence of 40 ml NaHOaq diluted with 500 ml EtOH. After 2 days at room temp, the reaction mixture, as described above, yielded the crude condensation product. A solution of this crude product in the minimum amount of ether did not yield an insoluble dimer. Crystallization from MeOH yielded 225 g (88%) pure IV, m.p. 125–126°. (Found: C, 79·53; H, 7·92. Calc. for $C_{17}H_{20}O_2$: C, 79·65; H, 7·86%.)

The 2,4-dinitrophenylhydrazone melted at 245–247° with dec. (Found: N, 12·78. Calc. for $C_{23}H_{24}N_4O_5$: N, 12·84%.)

(b) Compound was obtained also by methylation of 3-(2-hydroxystyryl-5,5-dimethyl-2-cyclohexen-1-one with dimethylsulfate in methanolic solution in 92% yield.

### 3-(3-*Methoxystyryl*)-5,5-*dimethyl*-2-*cyclohexen*-1-*one*

To a stirred solution of 68 g (0·5 mole) *m*-methoxybenzaldehyde and 69 g (0·5 mole) isophorone in 300 ml EtOH at 0°, 20 ml 45% NaOHaq was added slowly. The reaction mixture was allowed to reach room temp, left at this temp for 2 days and then decomposed with water. After neutralization with dil. HCl, the organic product was extracted with $CHCl_3$. After removal of solvent from the combined and dried extracts, the residue was distilled. The product (76 g, 59·5%) b.p. 182–184° (0·1 mm), after long standing, crystallized, m.p. 52–61°, and was apparently a mixture of two isomers. (Found: C, 79·60; H, 7·86. Calc. for $C_{17}H_{20}O_2$: C, 79·65; H, 7·86%.)

After crystallization from ethyl acetate, the 2,4-dinitrophenylhydrazone melted at 213–214°. (Found: N, 12·91. Calc. for $C_{23}H_{24}N_4O_5$: N, 12·84%.)

The residue (45·8 g) of the above distillation was dissolved in the minimum amount of ether but after several days in the freezer no insoluble product separated.

### 3-(4-*Methoxystyryl*)-5,5-*dimethyl*-2-*cyclohexen*-1-*one*

To a stirred solution of 136 g (1 mole) *p*-methoxybenzaldehyde and 138 g (1 mole) isophorone in 500 ml EtOH at 5°, 40 ml of 45% NaOHaq was added slowly. The resulting solution was allowed to reach room temp and left at this temp for 48 hr. The reaction mixture was poured into ice-water, neutralized with dil. HCl and extracted with $CHCl_3$. After removal of solvent from the combined extracts, the crude concentrated product (255 g) was treated with the minimum amount of ether, left at room temp for 24 hr and filtered yielding 9·2 g of white crystalline product, m.p. 190–192°. Two crystallizations from EtOH gave 7·9 g of colourless crystalline dimer, m.p. 194–195°. (Found: C, 79·52; H, 7·82; Calc. for $C_{34}H_{40}O_4$: C, 79·65; H, 7·86%. Mol. wt. calc, for $C_{34}H_{40}O_4$: 512. Found: (Rast) 495; (osmometric) 506.)

The ethereal mother liquor were concentrated to dryness and the residue crystallized from a benzene-hexane to give 214·3 g (83·5%) pure condensation product VI, m.p. 69–70. (Found: C, 79·66; H, 7·88. Calc. for $C_{17}H_{20}O_2$: C, 79·65; H, 7·86%.)

The 2,4-dinitrophenylhydrazones of VI melted at 234–232° with dec. (Found: N, 12·75. Calc. for $C_{23}H_{24}N_4O_5$: N, 12·84%.)

### 3-(4-*Dimethylaminostyryl*)-5,5-*dimethyl*-2-*cyclohexen*-1-*one*

A solution of 45 g (0·3 mole) *p*-dimethylaminobenzaldehyde and 45·1 g (0·3 mole) isophorone in 500 ml EtOH was cooled at 5° and treated with 20 ml 45% NaOHaq. After 48 hr at room temp, the reaction mixture was decomposed with water, acidified to pH 7·5 with dil. HCl and extracted with $CHCl_3$. After removal of solvent from the combined extracts, the residue was dissolved in the minimum amount EtOH, $CHCl_3$ or benzene, but no insoluble product could be detected. After crystallization from a benzene–hexane, VII was obtained as orange needles in 71% yield, m.p.124–125°. (Found: C, 80·17; H, 8·58; N, 5·25. Calc. for $C_{18}H_{23}NO$: C, 80·25; H, 8·61; N, 5·20%.)

The 2,4-dinitrophenylhydrazone melted at 270–272° with dec. (Found: N, 15·68. Calc. for $C_{24}H_{27}N_5O_4$: N, 15·58%.)

### 3-*Furfurylidenemethyl*-5,5-*dimethyl*-2-*cyclohexen*-1-*one*

To a stirred solution of 96·1 g (1 mole) freshly distilled furfurol and of 138 g (1 mole) isophorone in 500 ml EtOH at 0°, 40 ml of 45% NaOHaq was added slowly. The addition was effected at such a rate that the temp did not rise above 3°. The resulting brown solution was allowed to reach room temp and left at this temp for 24 hr. The reaction mixture was decomposed with water, neutralized with dil. HCl and extracted with $CHCl_3$. After removal of solvent from the combined dried extracts, the residue was distilled. The product (160 g, 74·5%) with b.p. 132–136° (0·1 mm) was collected. An analytical sample showed b.p. 134–135° at 0·1 mm. (Found: C, 77·84; H, 7·38. Calc. for $C_{14}H_{16}O_2$: C, 77·75; H, 7·46%.)

The 2,4-dinitrophenylhydrazone of VIII showed m.p. 217–128°. (Found: N, 14·23. Calc. for $C_{20}H_{20}N_4O_5$: N, 14·14%.)

The residue of the above distillation was treated with 150 ml benzene, allowed to stand at room temp for 24 hr and filtered yielding 24·5 g pale yellow solid. Crystallization from benzene gave 19·3 g pure dimer, m.p. 208–209°. (Found: C, 77·70; H, 7·40. Calc. for $C_{28}H_{32}O_4$: C, 77·75; H, 7·46%. Mol. wt. calc, for $C_{28}H_{32}O_4$: 432. Found: (Rast) 418; (osmometric) 421.)

*Alkali-catalyzed dimerizations*

Compounds II, VI and VIII treated with 0·6 mole equiv. NaOH in ethanolic solution after 48 hr reaction time gave the dimer in yields of 30%, 3% and 31% respectively. On the other hand, compounds III, IV, V and VII were recovered unchanged after even 48 hr refluxing in the presence of 0·6 mole equiv. NaOH.

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