Reactions of Ketene Acetals. IV. A New Synthesis of α-Pyrones. III

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A simple one-step synthesis of α-pyrones and 3-chloro-α-pyrones from β-functionalized α,β-enones and ketene acetals has been devised. The method has also been adapted to the preparation of some 4-methoxy-α-pyrones. Finally the mechanism of the reaction has been investigated.

ALAIN BÉLANGER et PAUL BRASSARD. Can. J. Chem. **53**, 201 (1975).

Une synthèse simple d'α-pyrones et de chloro-3 α-pyrones en une étape à partir d'α,β-énones β-fonctionnalisées a été réalisée. La méthode s'adapte aussi à la préparation de quelques méthoxy-4 α-pyrones. Enfin le mécanisme de la réaction a été étudié.

In a companion paper (1) we described a new synthesis of α-pyrones. This method involved the cycloaddition of chloroketene acetals to α,β-unsaturated carbonyl compounds followed by a dehydrohalogenation which yields α-pyrones. It was then assumed that placing the leaving-group on the enone should facilitate the elimination step, prevent the formation of by-products, and simplify the overall process. This modification uses the more readily accessible ketene dialkyl acetals and produces the α-pyrones directly in moderate to good yields (30–77%) (Scheme 1; R_1 = OAc, OBz, or Cl; R_2 and R_3 = H, alkyl, or aryl). β-Functionalized enals and β-alkylenones are either unreactive or give only exchange reactions.

The great stability of a 2,2,4-trimethoxy-3,4-dihydro-1,2-pyran suggested that the cycloaddition of chloroketene acetals to β-methoxy enones and a subsequent dehydrohalogenation would provide a new synthesis of 4-methoxy-α-pyrones. The 3-chloro-4-methoxy-3,4-dihydro-1,2-pyrans are formed by heating the substrates at about 150° (35–80%) and converted to the expected α-pyrones with yields of 32–90%. (Scheme 2; R_1 = OMe; R_2 = H, R_3 = aryl or styryl; and R_2 = alkyl, R_3 = aryl).

The Reaction of β-*Functionalized Enones with Ketene Acetals (Scheme 1)*

With β-*Acetoxy and* β-*Benzoyloxy Enones*

The β-acetoxy enones **3***a*, **4***a*, **5***a*, and **7***a* react readily with ketene dimethyl acetal (**1**) when heated at about 95° for 3–8 h. Examination of the n.m.r. spectra of the crude product usually reveals the presence of a mixture of the expected 4-acetoxy-2,2-dimethoxy-3,4-dihydro-1,2-pyran and elimination product, the 5,5-dimethoxypentadienone. The magnitude of the coupling constant between the protons in the 2 and 3 positions of the latter (~15 Hz) indicates that the tautomer has the *trans*-configuration (β-acetoxyacrylophenone reacts in 48 h at room temperature and gives only the relatively unstable dihydropyran).

Since all attempts to separate the dihydropyran from the dienone were unsuccessful, the mixture was then heated to 120–130° when a vigorous reaction ensued. The α-pyrone could then be isolated directly by chromatography on Florisil. Most variations of the experimental procedure such as the use of an inert solvent (xylene) or the addition of acetic acid to the reaction mixture produced no appreciable effect; no α-pyrone is obtained when the heating is carried out under vacuum. The use of a benzoyloxy derivative in one case gave analogous results but a somewhat lower yield.

With β-*Chloro Enones*

The reaction was next attempted with 3-chloroacrylophenone (**5***c*) and produced quite different results. At 95° hydrogen chloride was completely eliminated and the mixture after evaporation consisted essentially of the *trans*-pentadienone and the 1,2-pyran. These isomers could not be separated and their nature was deduced solely from spectral data. By subtracting in the n.m.r. spectrum the signals due to the now familiar pentadienone, the structure of the other

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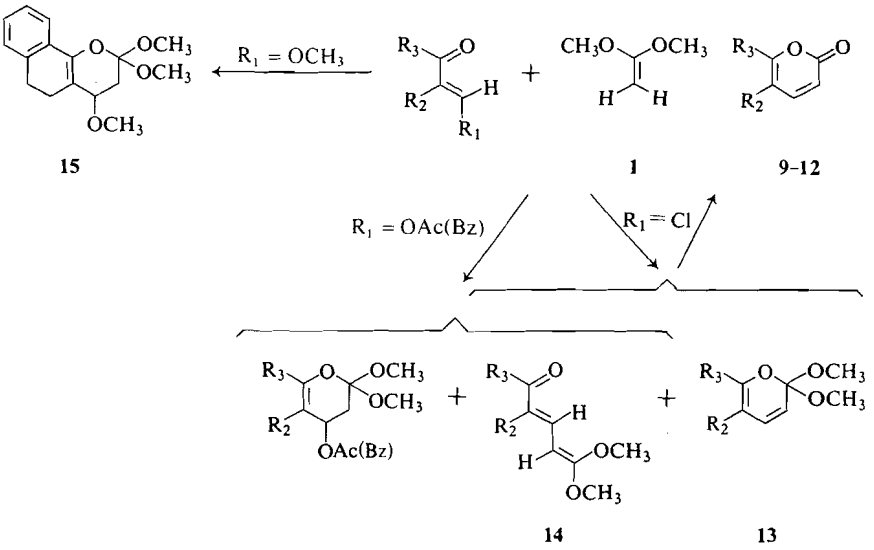
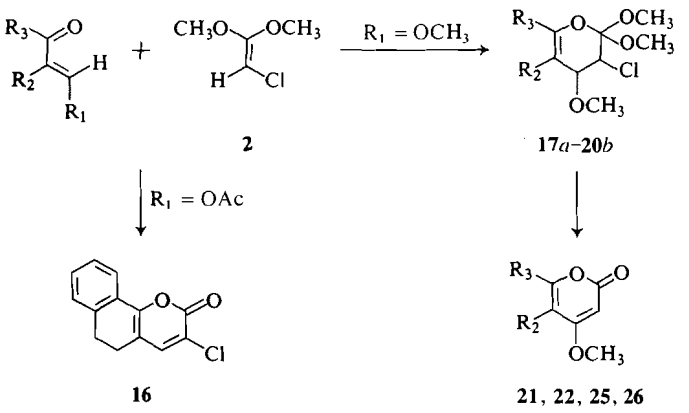


SCHEME 1



SCHEME 2

isomer, 6-phenyl-1,2-pyran, is readily arrived at (a methoxyl peak at δ 3.40 seems characteristic of cyclic structures (1) and the presence of doublets at 5.45 (J = 9.5 Hz) and 6.00 (J = 6.5 Hz) and of a doublet of doublets at 6.50 confirms the proposed structure, *i.e.* the coupling constants are the same as in the corresponding α-pyrone but the chemical shifts are quite different).

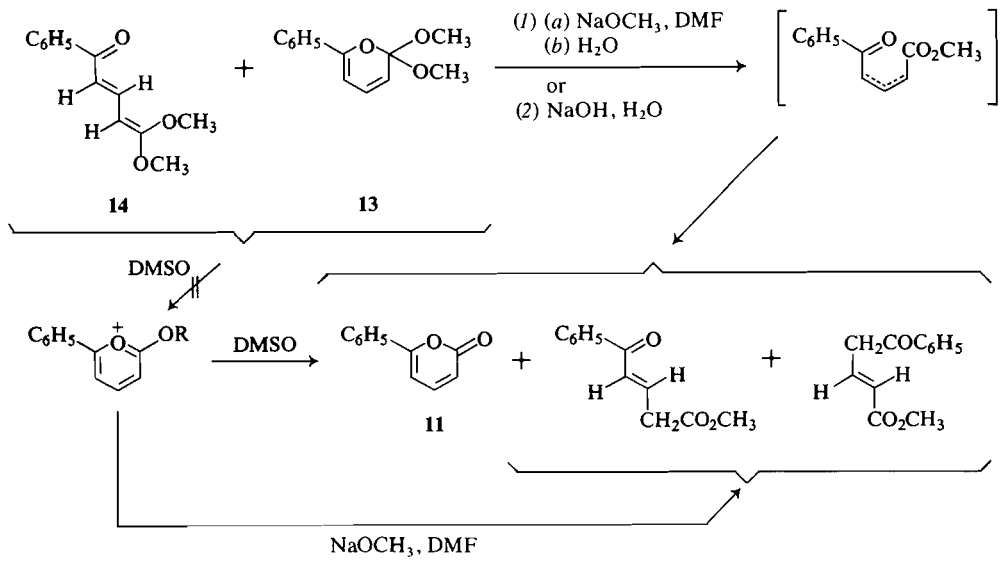
A subsequent heating of the mixture of isomers at 120° resulted in extensive decomposition and in the formation of only a trace of the α-pyrone. Chromatography on silica gel also decomposed these products but the addition of benzoic acid followed by heating at the same temperature gave good yields of 6-phenyl-α-pyrone and methyl benzoate.

With β-Methoxy Enones

These enones were significantly less reactive than the foregoing and the cycloaddition had to be carried out at 135° in a sealed tube. Only the 4-methoxydihydropyran was obtained and heating it progressively to 200° only caused decomposition; moreover it was quite inert to alkoxides under the usual conditions. This negative result suggested that analogous 4-methoxydihydropyrans could be used in the synthesis of 4-methoxy-α-pyrones, many derivatives of which are naturally occurring compounds.

With Chloroketene Dimethyl Acetal (Scheme 2)

When 2-acetoxymethylene-α-tetralone (**4***b*) was heated to 130° for 24 h with chloroketene dimethyl acetal (**2**) an 82% yield of the correspond-



SCHEME 3

ing 3-chloro-α-pyrone **16** was obtained. Although the procedure was not further explored it undoubtedly constitutes an excellent method of preparing certain compounds of this type.

The Reaction of β-Methoxy Enones with Chloroketene Acetals (Scheme 2)

In this procedure 2-methoxymethylene-α-tetralone (**4***b*), 3-methoxyacrylophenone (**5***b*), 2-methoxyvinyl styryl ketone (**7***b*), and 3′,4′-methylenedioxystyryl 2-methoxyvinyl ketone (**8**) were successfully added to chloroketene dimethyl acetal (**2**) at the boiling point of the latter; 2-methoxymethylenecyclohexanone (**3***b*) and 3-methoxy-2-isopropylacrolein were found to be unreactive whereas 2-methoxyvinyl 3′-pyridyl ketone (**6**) gave a variety of products, none of which seemed to be the expected dihydropyran. In most cases, both diastereoisomers were obtained and the *cis*-compounds are thought to be usually predominant; however only the *cis*-isomer **20***a* was observed but the yield was low in this instance and the *trans*-isomer could have remained undetected. These isomers can be partially separated by chromatography on Florisil but, with the exception of those of **17***a* and *b*, the configurations cannot be assigned with certainty since the signals for the protons in positions 3,4 of the dihydropyran system are usually superimposed. The 6-phenyl isomers **18***a* and *b* show very different reaction rates in the presence of sodium methoxide and the more reactive one is assumed to be the *cis*-compound. Other mixtures do not show this characteristic and structures have been tentatively assigned on the basis of small differences in chemical shifts and coupling constants, and of chromatographic behavior.

The dehydrohalogenation of the 3-chloro-2,2,4-trimethoxydihydropyrans was attempted under the usual conditions (4.5 equiv. of methoxide in DMSO). The mixture of isomers **17***a* and *b* gave a 90% yield of the corresponding α-pyrone but a similar reaction with the 6-phenyl compounds **18***a* and *b* showed the rapid disappearance of the *cis*-isomer while a large amount of the *trans*-isomer remained unaffected (a prolonged reaction increases the proportion of by-products) The pure *trans*-compound **18***b* gave a very low yield (14%) which could not be improved but the *cis*-isomer **18***a* at $-10°$ could be converted more efficiently to the α-pyrone (40%). Finally the 6-styryl derivatives **19***a* and *b* and **20***a* reacted readily at low temperatures but provided only moderate yields of the expected products (37–43%).

The Mechanism of the Reaction (Scheme 3)

The conversion of 3- or 4-functionalized dihydropyrans to α-pyrones in the presence of alkoxide or by heating raises a number of mechanistic problems. There seems to be little doubt that an elimination occurs in the first step of the process, that the 1,2-pyran is the initial intermediate, and that an equilibrium then exists between the latter and the oxodienes since all of these are occasionally observed (the fact that

the 1,2-pyran appears only when hydrogen chloride is eliminated by a thermal reaction remains unexplained). We have elucidated two main problems: (*a*) whether the α-pyrones are produced by a nucleophilic attack on the 1,2-pyran-oxodiene mixture or by the formation and subsequent conversion of the corresponding pyrilium salt and (*b*) whether the ketoester by-products are formed during the reaction or by subsequent hydrolysis (these compounds are not observed in the thermal procedure).

It has been shown that 1,2-pyrans exist mainly in the oxodiene form and that substituents capable of enhancing the resonance in this isomer also displace the equilibrium in its favor (2–5). The formation of α-pyrones was thought at first to proceed through the pyrilium salt because of the ease with which 5,5-dimethoxy-2-*n*-decyl-penta-2,4-dienal (1) was converted to such a compound and since the intermediate 1,2-pyrans (orthoesters) were expected to be stable in basic media. The postulate which assumed that pyrilium salts were formed from the 1,2-pyrans and that a lowering of the reaction temperature would increase the concentration of the latter and thence facilitate the formation of the specific intermediate presented certain difficulties at the outset. Indeed there seemed to be no valid reason why the 4-phenyl-, 4-alkyl-, and 4,6-diphenyldihydropyrans should yield α-pyrones quite readily whereas the 6-phenyl and 5-alkyl derivatives having comparable electronic effects behaved abnormally (1). The difficulty in effecting the conversion and the occurrence of appreciable amounts of ketoester by-products in the last instances seemed related rather to steric factors and a greater ease of isomerization (in the case of the 4-methoxy dihydropyrans the ease of isomerization could be due to an electronic effect). It should be noted here that 2-*n*-decyl-pentadienal is only encountered when a large excess of methoxide is used and it is possible that this structure is stabilized by a Michael-type addition and is regenerated during hydrolysis.

The initial assumption that 1,2-pyrans are the first intermediates even in the base-induced reaction was tested by treating the mixtures of isomers **13** and **14** with sodium methoxide in dimethylformamide at −10°. Hydrolysis and chromatography of the reaction mixture gave 6-phenyl-α-pyrone (**11**) and a small amount of the usual ketoesters. The next step in the elucidation of the mechanism consisted in determining whether preformed pyrilium salts were capable of undergoing the conversion to α-pyrones under similar conditions. Pirkle and Dines (6) had previously proposed the intermediacy of pyrilium salts in the nitration of α-pyrones and confirmed this possibility by thermally converting the former to dienolides (4-methoxy pyrilium salts are known to be stable under analogous conditions) (7). We prepared 2-ethoxy-6-phenyl-pyrilium fluoroborate (**27**) and dissolved it in dimethylsulfoxide. Examination of the reaction mixture both before hydrolysis (DMSO-d_6) and after revealed efficient conversion to the α-pyrone; when a similar reaction was carried out with the usual amount of methoxide (DMF, −10°) only a trace of compound **11** was obtained (the reaction mixture consisted mainly of the ketoester by-products). However, by dissolving the mixture of isomers **13** and **14** in deuterated dimethylsulfoxide, a progressive decomposition of the substrates was observed but neither the pyrilium salt nor the α-pyrone could be detected.

It now seems quite obvious that pyrilium salts must be discounted as intermediates in the new synthesis of α-pyrones that we describe. The latter compounds can only result from the hydrolysis of or the nucleophilic attack on the oxodiene. This was confirmed when hydrolysis of the mixture of isomers **13** and **14** with aqueous sodium hydroxide was found to yield the α-pyrone and the usual ketoesters. The configuration of the oxodiene also seems to enter into consideration. Although it could not be established which isomer was present in the case of the 2-*n*-decylpenta-2,4-dienals, the ease with which they are converted to the α-pyrone seems to indicate a *cis*-configuration; on the other hand some dienones produced at higher temperatures are undoubtedly *trans*. The *cis*-oxodienes are therefore hydrolyzed to a mixture of *cis*- and *trans*-oxopentenoates and the *cis*-esters then cyclize spontaneously to the α-pyrones. The improved yields we have observed at low temperature undoubtedly result from slower rates of isomerization. As to the thermal formation of α-pyrones, McElvain (8) has proposed a mechanism for the conversion of ketene acetals to esters and this seems a plausible process for the transformation we have observed. Indeed the elimination of hydrogen chloride from chlorodihydropyran at 95° prevents the formation of the α-pyrone since the reagent would be

volatilized under these conditions and a similar situation is observed when the corresponding acetoxy compounds are heated under vacuum.

Experimental

The melting points were taken in capillary tubes using a calibrated thermometer (Thomas-Hoover Apparatus). The i.r. spectra were recorded on a Beckman IR-12 instrument, u.v. spectra on a Beckman DK-1A spectrophotometer, and the n.m.r. on a Varian A60 spectrometer with tetramethylsilane as internal standard.

The Preparation of β-Functionalized α,β-Enones

No attempt has been made to determine the configuration of these compounds since (*a*) in most cases only one isomer is obtained, (*b*) the β-hydrogen is not always discernible in the n.m.r. spectrum, and (*c*) compounds of this type are known to isomerize readily under the reaction conditions used. However the chemical shifts, when visible, and the coupling constants of the olefinic protons suggest that the configurations are *cis*.

2-Methoxymethylenecyclohexanone (3b)

A mixture of the sodium salt of 2-hydroxymethylenecyclohexanone (10.0 g) (9), dimethylsulfate (7.0 ml), anhydrous potassium carbonate (10.0 g), and acetone (100 ml) was refluxed for 24 h. The methyl ester **3***b* was isolated in the usual way, b.p. 110–115°/10 mm (34%) (lit. (10) b.p. 85°/3.2 mm); ν_{max} (film) 1685, 1600 cm^{-1}; δ ($CDCl_3$) 1.50–2.50 m ($(CH_2)_4$), 3.90 s (OCH_3), 7.18 t (J = 2.0 Hz) (C=CH).

2-Chloromethylene-α-tetralone (4c)

A solution of 2-hydroxymethylene-α-tetralone (2.6 g) (11), thionyl chloride (1.2 ml), and benzene (10 ml) was refluxed for 4 h. Evaporation of the mixture under vacuum gave the chloro compound **4***c*, m.p. 61–62° (ether – petroleum ether) (90%); λ_{max} (ethanol) 272 nm (log ε 4.29); ν_{max} (KBr) 1670 cm^{-1}; δ ($CDCl_3$) 3.03 s ($(CH_2)_2$), 7.20–7.50 and 7.80–8.40 2 m (aromatic and vinyl CH).

Anal. Calcd. for $C_{11}H_9OCl$: C, 68.57; H, 4.71. Found: C, 68.70; H, 4.81.

3-Methoxyacrylophenone (5b)

A mixture of the sodium salt of 3-hydroxyacrylophenone (15.0 g) (12), dimethylsulfate (8 ml), anhydrous potassium carbonate (10.0 g), and acetone (50 ml) was refluxed for 3 h. The methyl ether **5***b* was isolated in the usual way, b.p. 100–105°/0.1 mm (88%) (lit. (10) b.p. 112°/1.8 mm); λ_{max} (ethanol) 274 nm (log ε 4.12); ν_{max} (film) 1670 cm^{-1}; δ ($CDCl_3$) 3.80 s (OCH_3), 6.43 d (J = 12.5 Hz) (2-CH), 7.40–7.70 and 7.85–8.15 2 m (aromatic CH), 7.90 d (J = 12.5 Hz) (3-CH).

2-Methoxyvinyl 3′-Pyridyl Ketone (6)

A solution of hydrogen chloride (7.8 g) in anhydrous methanol (10 ml) was added dropwise at 0° to a suspension of the sodium salt of 3′-pyridyl 2-hydroxyvinyl ketone (10.0 g) (13) in methanol (10 ml). After allowing the reaction to rest for 1/2 h at the same temperature and evaporating it under vacuum, the methyl ether **6** was obtained by pouring the residue into a 5% solution of sodium carbonate, extracting the latter with ether and distilling the residue over sodium carbonate (50 mg), b.p. 170–175°/0.9 mm, m.p. 74–75° (47%); λ_{max} (ethanol) 240, 278 nm (log ε 4.00, 4.08); ν_{max} (KBr) 1670, 1640 cm^{-1}; δ ($CDCl_3$) 3.89 s (OCH_3) 6.38 d (J = 12.0 Hz) (1-CH), 7.45 dd (J = 4.5, 8.5 Hz) (5′-CH), 7.92 d (J = 12.0 Hz) (2-CH), 8.25 dt (J = 2.0, 8.5 Hz) (4′-CH), 8.82 dd (J = 2.0, 4.5 Hz) (6′-CH), 9.20 d (J = 2.0 Hz) (2′-CH).

Anal. Calcd. for $C_9H_9O_2N$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.32; H, 5.84; N, 8.32.

2-Methoxyvinyl Styryl Ketone (7b)

A mixture of the sodium salt of 2-hydroxyvinyl styryl ketone (10.0 g) (14), dimethylsulfate (5.5 ml), anhydrous potassium carbonate (6.0 g), and acetone (50 ml) was refluxed for 5 h. The methyl ether **7***b* was isolated in the usual way, b.p. 140–145°/0.2 mm, m.p. 89–90° (ether – petroleum ether) (57%); λ_{max} (ethanol) 226, 309 nm (log ε 4.13, 4.32); ν_{max} (KBr) 1650 cm^{-1}; δ ($CDCl_3$) 3.70 s (OCH_3), 5.95 d (J = 12.5 Hz) (1-CH), 6.92 d (J = 16.0 Hz) (α-styryl CH), 7.25–7.65 m (aromatic CH), 7.74 d (J = 16.0 Hz) (β-styryl CH), 7.86 d (J = 12.5 Hz) (2-CH).

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.59; H, 6.43. Found: C, 76.85; H, 6.60.

3′,4′-Methylenedioxystyryl 2-Methoxyvinyl Ketone (8)

A suspension of the sodium salt of 3′,4′-methylenedioxystyryl 2-hydroxyvinyl ketone (4.0 g), dimethylsulfate (2.0 ml), potassium carbonate (2.18 g), and acetone (20 ml) was refluxed for 3 h. The methyl ether **8** was obtained in the usual way, m.p. 90–91° (carbon tetrachloride) (50%); λ_{max} (ethanol) 259, 304, 348 nm (log ε 4.12, 4.20, 4.37); ν_{max} (KBr) 1650 cm^{-1}; δ ($CDCl_3$) 3.82 s (OCH_3), 5.95 d (J = 12.5 Hz) (1-CH), 6.08 s (—OCH_2O—), 6.75 d (J = 16.0 Hz) (α-styryl CH), 6.80–7.35 m) (aromatic CH), 7.65 d (J = 16.0 Hz) (β-styryl CH), 7.86 d (J = 12.5 Hz) (2-CH).

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.50; H, 5.08.

The Synthesis of α-Pyrones from β-Functionalized α,β-Enones

From β-Acetoxy or β-Benzoyloxy Enones

A mixture of the β-acetoxy or β-benzoyloxy enone and ketene dimethyl acetal (**1**) (3–5 equiv.) (in this procedure (15) benzene was replaced by xylene) was heated under nitrogen. The excess of the acetal and the volatile by-products were evaporated under vacuum and the residue heated at 120–130° for 10–15 min. The following products were obtained.

5,6,7,8-Tetrahydrocoumarin (**9**) from 2-acetoxymethylenecyclohexanone (**3***a*) (3.09 g) (16) (110°; 15 h) was chromatographed on Florisil (107 g) (benzene–ether, 23:2), m.p. 64–65° (ether – petroleum ether) (30%) (lit. (17) m.p. 64.5–65°); λ_{max} (ethanol) 304 nm (log ε 3.88); ν_{max} ($CHCl_3$) 1740, 1720, 1649, 1560 cm^{-1}; δ ($CDCl_3$) 1.50–1.90 m (6,7-CH_2), 2.20–2.60 m (5,8-CH_2) 6.12 d (J = 9.5 Hz) (3-CH), 7.10 d (J = 9.5 Hz) (4-CH).

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 72.36; H, 6.69.

5,6-Dihydro-2-naphtho[1,2-*b*]pyrone (**10**) from 2-acetoxymethylene-α-tetralone (**4***a*) (200 mg) (18) (95°; 8 h) (preparative t.l.c.; benzene – ethyl acetate, 7:3), m.p. 102–103° (ether) (76%) (lit. (19) m.p. 96–97°); λ_{max} (ethanol) 237, 354 nm (log ε 4.15, 4.27); ν_{max} (KBr) 1720, 1630, 1540 cm^{-1}; δ ($CDCl_3$) 2.60–3.10 m (5,6-CH_2), 6.28 d (J = 9.5 Hz) (3-CH), 7.10–7.60 and 7.70–8.20 2 m (3- and aromatic CH).

Anal. Calcd. $C_{13}H_{10}O_2$: C, 78.77; H, 5.09. Found: C, 78.78; H, 5.13.

6-Phenyl-α-pyrone (**11**) from 3-acetoxyacrylophenone (**5***a*) (300 mg) (11) (95°; 2 h) (preparative t.l.c.; benzene – ethyl acetate, 7:3; and filtration on Florisil), m.p. 64–65° (77%) (lit. (20) m.p. 63–64°) and from 3-benzoyloxyacrylophenone (200 mg) (24) (95°; 2 h) (61%).

6-Styryl-α-pyrone (**12**) from 2-acetoxyvinyl styryl ketone (7*a*) (200 mg) (21) (95°; 2 h) (preparative t.l.c.; dichloromethane–benzene, 1:1), m.p. 112.5–113° (ether – petroleum ether) (67%) (lit. (22) m.p. 115–116°); λ_{max} (ethanol) 262, 270, 370 (log ε 4.21, 4.22, 4.29); ν_{max} (KBr) 1730, 1630, 1530 cm^{-1}; δ ($CDCl_3$) 6.19 d (J = 7.0 Hz) (5-CH), 6.23 d (J = 9.0 Hz) (3-CH), 6.68 d (J = 16.0 Hz) (α-styryl CH), 7.20–7.70 m (4-, β-styryl and aromatic CH).

Anal. Calcd. for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09. Found: C, 78.79; H, 5.12.

From β-*Chloro Enones*

*6-Phenyl-α-pyrone (**11**)*. The condensation of 3-chloroacrylophenone (**5***c*) (200 mg) (23) with ketene dimethyl acetal (1.00 g) under nitrogen at 95° for 5 h gave, after evaporation, a mixture of 2,2-dimethoxy-6-phenyl-1,2-pyran (**13**); δ ($CDCl_3$) 3.40 s (OCH_3), 5.45 d (J = 9.5 Hz) (3-CH), 6.00 d (J = 6.5 Hz) (5-CH), 6.52 dd (J = 6.5, 9.5 Hz) (4-CH)) and *trans*-5,5-dimethoxy-1-phenylpenta-2,4-dien-1-one (**14**); δ 3.71 s (OCH_3), 4.80 d (J = 11.5 Hz) (4-CH), 6.79 d (J = 15.0 Hz) (5-CH). After heating this mixture with benzoic acid (180 mg) for 10 min at 120°, 6-phenyl-α-pyrone, m.p. 64–65° (80%) and methyl benzoate (125 mg) were isolated in the usual way.

*5,6-Dihydro-2-naphtho[1,2-b]pyrone (**10**)*. This pyrone is obtained as in the preceding paragraph from 2-chloromethylene-α-tetralone (**4***c*) (200 mg), **1** (1.00 g) (95°; 10 h) and benzoic acid (180 mg), m.p. 102–103° (preparative t.l.c.; benzene – ethyl acetate, 7:3) (79%).

From β-*Methoxy Enones*

*2,2,4-Trimethoxy-3,4,5,6-tetrahydro-2-naphtho[1,2-b]-pyran (**15**)*. This pyran **15** was obtained by heating a mixture of 2-methoxymethylene-α-tetralone (**4***b*) (1.0 g) (24) and **1** (1.40 g) for 30 h at 135°, m.p. 68–69° (ether – petroleum ether) (92%); ν_{max} (KBr) 1665, 1120, 1095, 1050 cm^{-1}; δ ($CDCl_3$) 1.80–2.90 m (3,5,6-CH_2) 3.38, 3.43 and 3.48 3s (OCH_3), 4.11 bt (J = ~7.5 Hz) (4-CH), 7.10–7.80 m (aromatic CH).

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.65; H, 7.52.

From β-*Acetoxy Enones and Chloroketene Dimethyl Acetal*

A mixture of 2-acetoxymethylene-α-tetralone (**4***a*) (3.6 g) and chloroketen dimethyl acetal (**2**) (7.3 g) (25) was heated at 130° for 24 h, and evaporated under vacuum. The residue gave 3-chloro-5,6-dihydro-2-naphtho[1,2-*b*]-pyrone (**16**), m.p. 142–143° (ether) (82%); λ_{max} (ethanol) 245, 252, 370 (log ε 4.11, 4.17, 4.16); ν_{max} (KBr) 1740, 1720, 1640, 1535 cm^{-1}.

Anal. Calcd. $C_{13}H_9O_2Cl$: C, 67.10; H, 3.89; Cl, 15.22. Found: C, 67.31; H, 3.93; Cl, 15.34.

The Preparation of 3-chloro-2,2,4-trimethoxy-3,4-dihydro-1,2-pyrans

A mixture of the β-methoxy enone and chloroketene dimethyl acetal (**2**) (25) (2–4 equiv.) was heated at 150° under nitrogen. After evaporation of the volatile products under vacuum, the residue was chromatographed on Florisil.

cis- and *trans*-3-Chloro-2,2,4-trimethoxy-3,4,5,6-tetrahydro-2-naphtho[1,2-*b*]pyrans (**17***a* and *b*) were obtained from 2-methoxymethylene-2-tetralone (**4***b*) (900 mg) and **2** (48 h). Chromatography (benzene then benzene–ether 19:1) gave the *trans*-isomer **17***b*, m.p. 107–109° (ether – petroleum ether) (19%); ν_{max} (KBr) 1661, 1130, 1108, 1070, 990 cm^{-1}; δ ($CDCl_3$) 2.30–3.10 2m (5,6-CH_2), 3.49, 3.58 and 3.65 3s (2,2,4-OCH_3), 4.24 bd (J = 8.0 Hz) (4-CH), 4.49 d (J = 8.0 Hz) (3-CH), 7.20–7.70 2m (aromatic CH).

Anal. Calcd. for $C_{16}H_{19}O_4Cl$: C, 61.83; H, 6.16. Found: C, 62.14; H, 6.10.

Later fractions gave a mixture of the *cis*- and *trans*-isomers (8%) and the *cis*-isomer **17***a* (an oil) (53%); ν_{max} (film) 1660, 1135, 1100, 1065, 1055 cm^{-1}; δ ($CDCl_3$) 2.30–3.20 2m (5,6-CH_2), 3.38, 3.55 and 3.59 3s (2,2,4-OCH_3), 4.39 bd (J = 5.0 Hz) (4-CH), 4.62 d (J = 5.0 Hz) (3-CH), 7.20–7.80 2m (aromatic CH).

cis- and *trans*-3-Chloro-2,2,4-trimethoxy 6-phenyl-3,4-dihydro-1,2-pyrans (**18***a* and *b*) were prepared from 3-methoxyacrylophenone (**5***b*) (2.0 g) and **2** (36 h). Chromatography (benzene) gave successively: the *trans*-isomer **18***b* (an oil) (20%); ν_{max} (film) 1665, 1100, 1052, 1025 cm^{-1}; δ ($CDCl_3$) 3.50, 3.56 and 3.58 3s (2,2,4-OCH_3), 4.36 d (J = 1.5 Hz) (3,4-CH), 5.63 t (J = 1.5 Hz) (5-CH), 7.40–7.90 2m (aromatic CH); a mixture of the *cis*- and *trans*-isomers (16%); the *cis*-isomer **18***a* (an oil) (53%); δ ($CDCl_3$) 3.41, 3.52, and 3.58 3s (2,2,4-OCH_3), 4.56 d (J = 2.0 Hz) (3,4-CH), 5.50 t (J = 2.0 Hz) (5-CH), 7.30–7.90 2m (6-C_6H_5).

cis- and *trans*-3-Chloro-2,2,4-trimethoxy-6-styryl-3,4-dihydro-1,2-pyrans (**19***a* and *b*) were obtained from 2-methoxyvinyl styryl ketone (7*b*) (1.0 g) and **2** (48 h). Chromatography (benzene) gave successively: a mixture of the *cis*- and *trans*-isomers (38%); the *cis*-isomer **19***a*, m.p. 109–110° (ether – petroleum ether) (24%); ν_{max} (KBr) 1650, 1130, 1091, 1071, 1050 cm^{-1}; δ ($CDCl_3$) 3.39, 3.49, and 3.54 3s (2,2,4-OCH_3), 4.49 d (J = 2.0 Hz) (3,4-CH), 5.03 t (J = 2.0 Hz) (5-CH), 6.47 d (J = 16.0 Hz) (α-styryl CH), 7.00–7.80 m (β-styryl and aromatic CH).

Anal. Calcd. for $C_{16}H_{19}O_4Cl$: C, 61.83; H, 6.16. Found: C, 62.12; H, 6.28.

cis-3-Chloro-2,2,4-trimethoxy-3′,4′-methylenedioxystyryl-3,4-dihydro-1,2-pyran (**20***a*) was prepared from 2-methoxyvinyl 3′,4′-methylenedioxystyryl ketone (**8**) (1.0 g) and **2** (32 h). Chromatography (benzene) gave only the *cis*-isomer **20***a*, m.p. 124–125° (ether) (35%); ν_{max} 1655, 1120, 1091, 1071, 1050 cm^{-1}; δ ($CDCl_3$) 3.35, 3.46, and 3.52 3s (2,2,4-OCH_3), 4.48 d (J = 2.0 Hz) (3,4-CH), 4.98 t (J = 2.0 Hz) (5-CH), 5.97 s (—OCH_2O—), 6.31 d (J = 16.0 Hz) (α-styryl CH), 6.80–7.40 m (β-styryl and aromatic CH).

Anal. Calcd. for $C_{17}H_{19}O_6Cl$: C, 57.55; H, 5.39. Found: C, 57.79; H, 5.30.

The Synthesis of 4-Methoxy-α-pyrones

A solution of the chlorodihydropyran and sodium methoxide (4.5 equiv.) in the appropriate solvent was stirred under nitrogen, diluted by addition of ice and extracted with ether.

4-Methoxy-5,6-dihydro-2-naphtho[1,2-*b*]pyrone (**21**) was obtained from the mixture of *cis*- and *trans*-pyrans **17***a* and *b* (420 mg) (25 ml of DMSO; 25°; 15 h), m.p. 173–174° (ether) (90%); λ_{max} (ethanol) 222, 228, 260, 270, 330, 340 nm (log ε 4.27, 4.29, 3.81, 3.81, 4.23, 4.23); ν_{max} (KBr) 1705, 1640, 1555 cm^{-1}; δ ($CDCl_3$) 2.40–3.10 m

(5,6-CH_2), 3.86 s (4-OCH_3), 5.58 s (3-CH), 7.10–8.10 2m (5- and aromatic CH).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.66; H, 5.31. Found: C, 73.78; H, 5.21.

4-Methoxy-6-phenyl-α-pyrone (**22**) from the *trans*-pyran **18***b* (640 mg) (50 ml of DMSO; 25°; 24 h) (preparative t.l.c.; chloroform), m.p. 125–126° (ether) (14%) (lit. (26) m.p. 129.5–131.5°); λ_{max} (ethanol) 220, 233, 315 nm (log ε 4.23, 4.21, 4.19); ν_{max} (KBr) 1708, 1645, 1569 cm^{-1}; δ ($CDCl_3$) 3.90 s (4-OCH_3), 5.62 d (J = 2.0 Hz) (3-CH), 6.51 d (J = 2.0 Hz) (5-CH), 7.40–8.10 2m (6-C_6H_5).

Anal. Calcd. for $C_{12}H_{10}O_2$: C, 71.28; H, 4.98. Found: C, 71.08, H, 4.92.

Compound **22** was also obtained from the *cis*-isomer **18***a* (500 mg) (40 ml of DMF; −10°; 12 h), m.p. 125–126° (40%) along with a mixture of the methyl *trans*-4-benzoyl-3-methoxybut-2- and 3-en-1-oates (**23** and **24**) (23%); ν_{max} (film) 1740, 1700, 1665, 1640 cm^{-1}; δ ($CDCl_3$) 3.62, 3.68, 3.75, and 3.83 4s (OCH_3 and CO_2CH_3), 3.95 s (4-CH_2), 4.50 s (2-CH_2), 5.30 s (2-CH), 6.38 s (4-CH), 7.40–7.70 and 7.85–8.20 2m (aromatic CH).

4-Methoxy-6-styryl-α-pyrone (**25**) from the mixture of *cis*- and *trans*-pyrans **18***a* and *b* (207 mg) (30 ml of DMF; −20°; 20 h) (preparative t.l.c.; chloroform), m.p. 136–137° (ether) (43%) (lit. (27) m.p. 138–140°); λ_{max} (ethanol) 226, 233, 255, 343 nm (log ε 4.32, 4.33, 4.28, 4.42); ν_{max} ($CHCl_3$) 1710, 1641, 1560 cm^{-1}; δ ($CDCl_3$) 3.87 s (4-OCH_3), 5.60 d (J = 2.0 Hz) (3-CH), 6.05 d (J = 2.0 Hz) (5-CH), 6.70 d (J = 16.0 Hz) (α-styryl CH), 7.30–7.70 m (β-styryl and aromatic CH).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.66; H, 5.30. Found: C, 73.90; H, 5.35.

6-(3′,4′-Methylenedioxystyryl)-4-methoxy-α-pyrone (**26**) from the *cis*-pyran **20***a* (280 mg) (30 ml of DMF; −20°; 5 h), m.p. 233–234° (ether) (37%) (lit. (28) m.p. 233°); λ_{max} (ethanol) 221, 248, 370 nm (log ε 4.24, 3.91, 4.37); ν_{max} (KBr) 1720, 1640, 1555 cm^{-1}; δ ($(CD_3)_2SO$) 3.88 (4-OCH_3), 5.68 d (J = 2.0 Hz) (3-CH), 6.13 s (—OCH_2O—), 6.32 d (J = 2.0 Hz) (5-CH), 6.63 d (J = 16.0 Hz), 6.90–7.50 m (β-styryl and aromatic CH).

Anal. Calcd. for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.10; H, 4.26.

Miscellaneous Reactions

2-Ethoxy-6-phenylpyrilium Fluoroborate (27)

A mixture of 6-phenyl-α-pyrone (**11**) (240 mg) and of a solution of triethyloxonium fluoroborate (methylene chloride, 0.01 *M*) (1.4 ml) was stirred at room temperature for 48 h, filtered and evaporated. The residue upon crystallization from acrylonitrile – methylene chloride gave 2-ethoxy-6-phenylpyrilium fluoroborate, m.p. 147.5–148° (86%); λ_{max} (ethanol) 238, 332 nm (log ε 4.23, 4.14); ν_{max} (KBr) 1641, 1519 cm^{-1}.

Anal. Calcd. for $C_{13}H_{13}O_2BF_4$: C, 54.20; H, 4.54. Found: C, 54.07; H, 4.41.

Reactions of 2-Ethoxy-6-phenylpyrilium Fluoroborate

With Sodium Methoxide. A solution of 2-ethoxy-6-phenylpyrilium fluoroborate (200 mg) and sodium methoxide (167 mg) in dimethylformamide (20 ml) was stirred for 15 min at −15°. The n.m.r. spectrum of the crude product showed the presence of the corresponding methyl ketoesters. Thin-layer chromatography revealed only a trace of the α-pyrone **11**.

With Dimethylsulfoxide. 2-Ethoxy-6-phenylpyrilium fluoroborate (50 mg) was dissolved in deuterated dimethylsulfoxide (0.8 ml). After 10 min, the n.m.r. spectrum of the reaction mixture revealed mainly 6-phenyl-α-pyrone and the usual working up gave a 90% yield of the pyrone **11**.

With Acetic Acid. A mixture of 2-ethoxy-6-phenylpyrilium fluoroborate (200 mg) and acetic acid (1 ml) was heated at 120° for 10 min, dissolved in ether and washed with water. Evaporation of the solvent gave 6-phenyl-α-pyrone (**11**) (83%).

Reactions of the Mixture of Isomers 13 and 14

With Sodium Methoxide. The mixture of isomers **13** and **14** prepared as before from 3-chloroacrylophenone (**5***c*) (1.0 g) and **1** (1.7 g) was treated with sodium methoxide (280 mg) in dimethylformamide (20 ml) at −10° for 10 min. The reaction medium after dilution by addition of ice gave 6-phenyl-α-pyrone (**11**) (34%) and a mixture of the corresponding ketoesters (7%) (1), (preparative t.l.c.; benzene – methylene chloride – ethyl acetate, 5:4:1). The n.m.r. spectrum of a similar reaction on a small scale in deuterated dimethylsulfoxide shows the presence of the 1,2-pyran **13** and another substance which is probably one of the open-chain dienones.

With Aqueous Base. The mixture of the isomers **13** and **14** obtained as above was dissolved in ether (40 ml) and extracted several times with a 2% aqueous solution of sodium hydroxide. Evaporation of the ethereal layer gave a mixture of the pyrone **11** (78%) and of the corresponding ketoesters (15%).

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