# α-Pyrones. II.[1] The Synthesis of α-Pyrones From α,β-Unsaturated Aldehydes. Part II[1,2]

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Received April 17, 1973

It is shown that the reaction of acrolein with bromomalonate in the presence of an alkali alkoxide, leading to a 2-formylcyclopropane-1,1-dicarboxylate, may be applied to the steroid series; thus, a 20-methylene 21-aldehyde gives in excellent yield the corresponding cyclopropane derivative. The possibility of converting such systems to α-pyrones was investigated in the case of the acrolein adduct, diethyl 2-formylcyclopropane-1,1-dicarboxylate. While its cyclopropane ring could not be isomerized to an olefin with aluminum chloride or by reactions catalyzed by transition metals and while photolysis led to a dihydrofuran derivative, pyrolysis in high vacuum at 550–575° afforded directly an α-pyrone, ethyl coumalate. Evidence is put forward for the intermediacy of 3-ethoxycarbonyl-α-pyrone in this reaction.

La réaction de l'acroléine avec un bromomalonate en présence d'un alcoolate alcalin, qui conduit à un formyl-2 cyclopropanedicarboxylate-1,1, peut être appliquée à la série stéroïde, un 21-aldéhyde 20-méthylénique donnant en excellent rendement le dérivé cyclopropanique correspondant. Nous avons étudié la possibilité de convertir de tels systèmes en α-pyrones dans le cas du formyl-2 cyclopropanedicarboxylate-1,1 de diéthyle, dérivé de l'acroléine. Tandis que son cycle à trois chaînons ne put être isomérisé en oléfine avec le chlorure d'aluminium ou par des réactions catalysées par des métaux de transition et tandis que sa photolyse conduisit à un dérivé dihydrofurannique, sa pyrolyse, à 550–575° et sous haut vide, donna directement une α-pyrone, le coumalate d'éthyle. Nous suggérons l'α-pyrone 3-éthoxycarbonylée comme intermédiaire dans cette réaction.

Can. J. Chem., **51**, 3263 (1973)

In 1969 our laboratory reported one of the first syntheses of bufadienolides, a class of steroids comprising highly active cardiotonics, which are characterized by an α-pyrone ring whose position 5 is linked to the 17β-position of the steroid nucleus. The salient feature of our synthesis (1, cf. also 2) (compare Scheme 1, pathway *a*) consisted in a Michael addition of diethyl malonate to a 20-methylene 21-aldehyde, the hydrolysis product of the resulting adduct being subsequently subjected to enol-lactonization with concomitant decarboxylation, and the still required double bond, in conjugation with the carbonyl function of the lactone, being then introduced by a variety of methods. This pathway to bufadienolides (and generally to α-pyrones) suffers only from the relatively low yield of the dehydrogenation step which, in our experiments, did not exceed 35% of *pure* product; Pettit *et al.* (3) report yields of 43–60% of *crude* product when the dehydrogenation is carried out with sulfur.

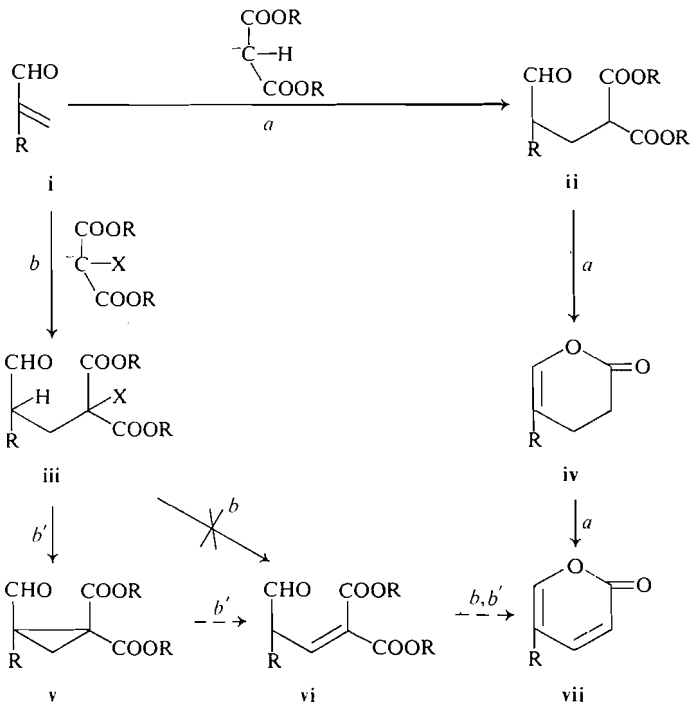
The attempt to "prefigure" the desired double bond in the form of a suitable substituent of the malonate employed (cf. Scheme 1, pathway *b*) is obviously problematic. The olefin-forming elimination from the addition product, involving a leaving group (X in adduct **iii** of Scheme 1) which is α and not β to the ester groups, could hardly be expected to compete successfully with a 1,3-elimination resulting in a cyclopropane; indeed, the hydrogens β to the ester functions show no particular mobility, in contradistinction to the hydrogen α to the aldehyde group. Not surprisingly therefore, Warner and Moe obtained (cf. 4 also 5, 6), by the reaction of acrolein with diethyl bromomalonate not, as they first surmised (7), diethyl 3-formyl-1-propene-1,1-dicarboxylate (cf. **vi** in Scheme 1), but the 2-formylcyclopropane-1,1-dicarboxylate (cf. **v** in Scheme 1). In spite of this, the potential for an α-pyrone synthesis of the addition of a substituted

[1]Paper XXX in our series on Steroids and Related Products (1) has to be considered the first communication of the present series.

[2]The main results of this paper were the subject of a communication presented before the 55th Annual Conference and Exhibition of the Chemical Institute of Canada, Quebec, June 1972.

[3]Some of the results reported here are contained in the B.Sc. thesis of A. Bélanger, presented to the Department of Chemistry, Laval University, April 1970.

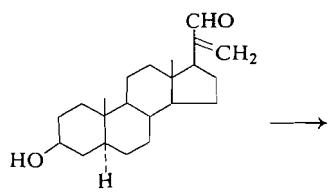
[4]Abbreviated from part of the doctoral thesis of G. Dionne, to be presented to the School of Graduate Studies of Laval University.



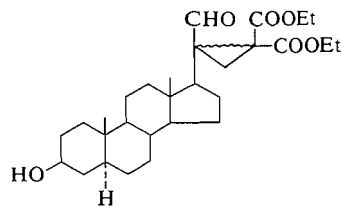

SCHEME 1

malonate such as bromomalonate to an α,β-unsaturated aldehyde still seemed worth exploring since the resulting cyclopropane derivatives (cf. **v**) are valence isomers of 4-formyl 2-butenoic esters (cf. **vi**), the immediate precursors of α-pyrones. If an isomerization of cyclopropanes of type **v** to olefins of type **vi** could be effected, an attractive modification of our first α-pyrone synthesis would be realized.

We at first attempted to apply Warner and Moe's synthesis of cyclopropane derivatives of type **v** (Scheme 1) to steroids, in particular to the 20-methylene 21-aldehyde **1** (1) from which our original bufadienolide synthesis had originated. Treatment of aldehyde **1** with an excess of diethyl bromomalonate in the presence of tertiary sodium butoxide in tertiary butanol afforded in 74% yield the desired cyclopropane derivative **2**. This product gave a marked reaction with tetranitromethane, showed an u.v. absorption maximum (in cyclohexane) at 205 nm (log ε 3.5), attributable to a carbonyl-conjugated cyclopropane, and exhibits in the i.r. (in KBr), apart from the peaks characteristic of the aldehyde, ester, and hydroxyl functions, a band at 1020 $cm^{-1}$ which we assign to the cyclopropyl moiety. In the n.m.r. one proton of the cyclopropyl–methylene group appears as a doublet at 2.20 δ with a coupling constant of 5 Hz. The structure was confirmed by elemental analysis.




**1**




**2**

Since, in preliminary experiments, we were unable to isomerize the cyclopropane ring of the aldehydo ester **2** and even encountered difficulties in hydrolyzing its ester functions, we decided to investigate the valence isomerization

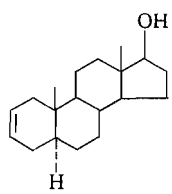
of such systems in the series originally studied by Warner and Moe. Using the American authors' procedure (7), we realized a 64% yield of diethyl 2-formylcyclopropane-1,1-dicarboxylate (**3**). We record in the Experimental its spectroscopic data since the product has not yet been fully characterized in this respect (cf. 4–7). Attention is drawn to the u.v. absorption maximum at 207 nm (log ε 3.3) and to the fact that the n.m.r. signals closely parallel those of cyclopropane-1,1,2-tricarboxylic acid (8): the protons of the cyclopropyl–methylene group form with the cyclopropyl proton of the formyl-substituted carbon atom 2 an ABX system, the $C_2$-proton being, of course, also coupled with the aldehydic proton.[5]

In view of the great ease of the reductive opening of the cyclopropane ring of the 2,4-dinitrophenylhydrazone of compound **3** with a 5% palladium-on-charcoal catalyst at room temperature and 1.8 atm (7), the inertness of the system to isomerization to an olefinic derivative is noteworthy. Treatment with aluminum chloride, even at temperatures exceeding those reported in the literature (cf. 10) gave no results. Neither were reactions catalyzed by transition metals successful. When the cyclopropane derivative was heated in benzene with bis(triphenylphosphine)iridium carbonyl chloride to 130°, following the procedure of Volger *et al.* (11) or when it was treated with *trans*-dichlorobis(tri-*n*-butylphosphine)nickel(II) (12)[6] and diisobutylaluminum chloride according to the method of Miller and Pinke (13), the starting material was recovered unchanged.[7]

Numerous examples of photolytic valence isomerizations to olefins of cyclopropanes conjugated with carbonyl functions (cf. 15–18) or with phenyl or nitro groups (19, 20) have been reported. We therefore irradiated the cyclopropane derivative **3** in benzene solution using a Pyrex filter, according to the method of Beugelmans (18). Instead of obtaining an aliphatic olefin we isolated the dihydrofuran **5**. Its structure was evident from its elemental composition and from its spectral characteristics. In the i.r. the aldehyde band had disappeared, the ester bands were visible at 1750 and 1275 $cm^{-1}$ (in KBr), and the 4,5-double bond at 3122 and 1630 $cm^{-1}$, the latter band having the intensity characteristic of a vinyl ether; the maximum at 1065 $cm^{-1}$ corroborated this structural feature. The n.m.r. spectrum confirmed the absence of the aldehyde group and of the cyclopropane ring and the presence of the ester groups; the two olefinic protons together with the methylene protons of carbon atom 3 form an $AMX_2$-system comprising a multiplet centered at 6.33 δ corresponding to one proton ($H_A = H_5$), a multiplet centered at 4.95 δ also corresponding to one proton ($H_M = H_4$), and finally a multiplet corresponding to two protons centered at 3.18 δ ($2H_X = 2H_3$). The chemical shifts agree well with those reported in the literature for dihydrofuran (21*a*), if one takes into consideration that the deshielding by the neighboring ester groups should result in a downfield shift of the 3-protons (which amounts to 0.65 p.p.m.). The coupling constants (cf. Experimental) correspond well to the expected values (21*b*).

A plausible mechanism for the formation of the dihydrofuran derivative **5** is formally represented in Scheme 2. The participation of the aldehyde carbonyl group in the ring opening is substantiated by the fact that no photolytic ring opening occurs in the case of the ethylenedioxy

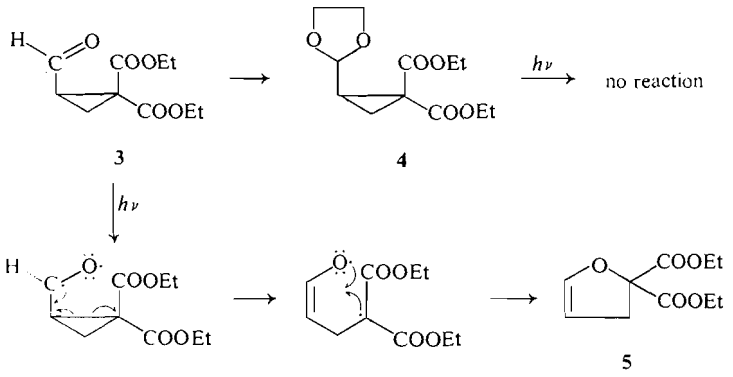
[5]The formation of the three-membered ring by a Perkin cyclization seems perfectly plausible and far more probable than by a reaction involving a carbene, formed by the action of the alcoholate on the bromomalonate. Indeed, while the carbanion formed by proton abstraction from a haloform is only stabilized by inductive effects and converts readily to a carbene, the anion formed from bromomalonate is also significantly stabilized by conjugative effects. We were able to establish the non-intermediacy of a carbene by subjecting a steroid with an unhindered isolated double bond, 5α-androst-2-en-17β-ol (**I**) (9) to the action of excess bromomalonate and sodium *t*-butoxide in *t*-butanol. Even after prolonged reaction periods and at elevated temperatures, the starting material was recovered in almost quantitative yield.




I

[6]We sincerely thank Professor Ray G. Miller for very kindly providing us with the description of the preparation of this reagent.

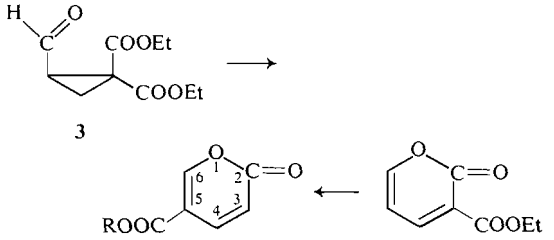
[7]The fact that certain cyclopropane systems cannot be opened by transition metal-catalyzed reactions is, however, not novel; it was discussed in the quoted paper by Volger *et al.* (11) and was recently again demonstrated by Gassman *et al.* (14).




SCHEME 2

derivative **4**. We refer for the preparation of ketal **4** to the Experimental.

We finally succeeded in opening the cyclopropane ring of the diethoxycarbonyl aldehyde **3** by pyrolysis under nitrogen at 0.1 mm Hg at 550–575°. The remarkable feature of this reaction resides in the fact that it is accompanied by cyclization to an α-pyrone and by an apparent 1,3-migration of the remaining ethoxycarbonyl substituent (cf. below), pure ethyl coumalate (**6***a*) being isolated in 20% yield. At 500°, a temperature sufficient for the opening of most cyclopropanes (for instance, for the transformation of cyclopropyl ketones into cyclopentenones (22)), no reaction occurred.

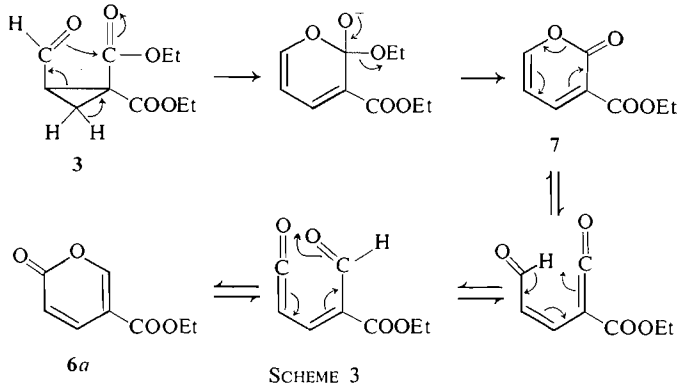



The structure of the coumalic ester was proved by elemental analysis and by its spectral characteristics. In the u.v. it showed maxima at 245 and 288 nm ($\log \varepsilon_{245}$ 3.83, $\log \varepsilon_{288}$ 3.45), in the i.r. (in KBr) maxima at 1760, 1650, and 1565 $cm^{-1}$, typical of the α-pyrone ring, and at 1730 and 1300 $cm^{-1}$, attributable to the ester group. These data agree well with those reported in the literature (23). The n.m.r. spectrum revealed, apart from the signals of the ethyl ester, the 3-, 4-, and 6-protons as three distinct multiplets representing an AMX system. The signal of the 6-proton ($H_X$), centered at 8.35 δ, shows small coupling constants with the vinylic protons 4 ($H_A$) and 3 ($H_M$) ($J_{4,6}$ = 3 Hz, $J_{3,6}$ = 1 Hz), whereas the coupling constant of the 3- and 4-protons (the signals of which are centered respectively at 6.28 and 7.8 δ) amounts to 10 Hz. The identity of the compound was confirmed by its hydrolysis with aqueous sulfuric acid to coumalic acid **6**, an authentic sample of which was prepared according to the method of Wiley and Smith (24, cf. also 25) from malic acid. Conversely, authentic coumalic acid was transformed according to the method of Pechmann (25) into its ethyl ester **6***a* which was found identical to the product arising from the pyrolysis of the cyclopropyl aldehyde **3**.[8]

It seems logical to assume that 3-ethoxycarbonyl-α-pyrone (**7**) is an intermediate in the formation of ethyl coumalate (**6***a*) from the formyl cyclopropane dicarboxylate **3**. While no plausible mechanism for the direct formation of the 5-substituted α-pyrone **6***a* can be advanced, the transformation of the cyclopropane derivative **3** to 3-ethoxycarbonyl-α-pyrone (**7**) can be rationalized readily (cf. Scheme 3);[9] furthermore, Pirkle *et al.* (27) have shown that apparent methyl and bromine 5 → 3 migrations occur upon pyrolytic decarboxylation of 5-methyl and 5-bromo 6-carb-

[8]We recall that coumalic acid may be decarboxylated in excellent yield (cf. 25, 26).

[9]In Scheme 3 the conversion of diethyl 2-formylcyclopropane-1,1-dicarboxylate (**3**) to 3-ethoxycarbonyl-α-pyrone (**7**) is *formally* represented as involving a concerted transformation of the cyclopropane system to an α-pyrone derivative. Naturally, one can also consider that the valence isomerization of the cyclopropane into an olefin precedes the formation of the heterocycle (cf. Scheme 1). Furthermore, while the symbolism employed in Scheme 3 implies ionic reactions, one has to consider that under pyrolytic conditions the reaction may well involve free radicals.



SCHEME 3

oxy-α-pyrones. The American authors explain these apparent migrations by the assumption of a ring opening to a ketene,[10] followed by a 1,5-sigmatropic hydrogen shift and ring closure to an isomeric α-pyrone. Since these transformations have to be regarded as reversible (cf. 27), the formation at high temperatures of ethyl coumalate (**6***a*) from 3-ethoxycarbonyl-α-pyrone (**7**) may be explained as summarily depicted in Scheme 3. In the case of 3- and 5-ethoxycarbonyl-α-pyrones, in contradistinction to the case of 3- and 5-methyl-α-pyrones, the equilibrium is displaced towards the 5-substituted product.

In order to substantiate the intermediacy of 3-ethoxycarbonyl-α-pyrone (**7**) in the formation of ethyl coumalate (**6***a*) from the formylcyclopropane dicarboxylate **3**, we synthesized 3-ethoxycarbonyl-α-pyrone (**7**) from 1,1,3,3-tetraethoxypropane and diethyl malonate (cf. 29) and subjected it to pyrolysis under the conditions used for the preparation of ethyl coumalate (**6***a*) from the cyclopropane derivative **3**. This resulted in a high yield of ethyl coumalate (**6***a*).

Further studies are required and are in progress in our laboratory in order to determine whether or not the two-step synthesis of ethyl coumalate from acrolein can be applied to the synthesis of other α-pyrones.

## Experimental[11]

*Ethyl 3β-Hydroxy-21-oxo-23-ethoxycarbonyl-20,23-cyclo-5α,20ξ-cholanate (2)*

Sodium (80 mg) was dissolved in *t*-butanol (40 ml). To an aliquot of 10 ml of this solution, 790 mg of diethyl bromomalonate was added in a nitrogen atmosphere and, subsequently, 960 mg of 3β-hydroxy-20-methylene-5α-pregnan-21-al (**1**) (1), dissolved in 30 ml of *t*-butanol. A white precipitate formed and the mixture became acidic. The remainder of the sodium *t*-butoxide solution was added slowly and the mixture was stirred for 1 day. Another 15 ml of a sodium *t*-butoxide solution (prepared from 30 mg of sodium) was added, followed by 0.1 ml of diethyl bromomalonate, and the mixture was heated to 30–35° for 3 h. According to thin-layer analysis, the reaction was complete and the mixture was poured into ice water, the precipitate was extracted with dichloromethane, the organic solution was washed with water, and was dried over sodium sulfate. Evaporation of the solvent gave 1.469 g of a product which was chromatographed on 150 g of silica gel. Elutions with benzene – ethyl acetate (90:10) gave 1.029 (74% yield) of the formyl dicarboxylate **2**, m.p. 158–165°. A sample was recrystallized three times from dichloromethane–hexane and sublimed twice in high vacuum at 150–168° for analysis. Fine needles, m.p. 180–180.5°; $[\alpha]_D^{25}$ −36.6° (*c*, 1.000 in $CHCl_3$); $\lambda_{max}$ (cyclohexane) 205 nm (log ε 3.47); $\nu_{max}$ (KBr) 3450 (OH), 2750 (aldehyde), 1740 and 1720 (ester groups), 1712 (aldehyde), 1240 (esters), 1082 and 1050 (hydroxyl), 1020 $cm^{-1}$ (cyclopropyl); δ ($CDCl_3$)[12] 0.69 (s) (18-$CH_3$), 0.81 (s) (19-$CH_3$), 1.22 (t, $J$ = 7 Hz), and 1.29 (t, $J$ = 7 Hz) (ester-$CH_3$), 1.57 (s) (OH, exchanged with $D_2O$), 2.20 (1 H, d, $J$ = 5 Hz) (1 H of cyclopropyl-$CH_2$), 3.68 (1 H, m) (3α-H), 4.10 (q, $J$ = 7 Hz), and 4.22 (q, $J$ = 7 Hz) ($CH_2$ of esters), 9.95 (1 H, s) (aldehyde).

Anal. Calcd. for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08. Found: C, 70.98; H, 8.98.

[10]For the photolytic formation of ketenes from α-pyrones cf. ref. 28.

[11]The melting points were taken in evacuated capillaries and the temperatures were corrected. For elution column chromatography, neutral aluminum oxide Woelm, activity III, and Davison's silica gel no. 923 were employed. Dry-column chromatography was performed with Woelm dry-column chromatography silica gel, activity III; t.l.c. with Merck-Darmstadt silica gel. The i.r. spectra were recorded on Beckman IR-4 and IR-12 spectrophotometers and the u.v. spectra on a Beckman DK-1A instrument. The n.m.r. spectra were taken on a Varian A-60 spectrometer, tetramethylsilane serving as internal standard, if not otherwise stated. The microanalyses were performed by Dr. F. Pascher, Bonn, Germany, and Ayerst Laboratories, Montreal (Director of the Analytical Division: Dr. G. Schilling), to whom we express our sincere appreciation.

[12]Recorded on a Varian HA-100 spectrometer by Prof. G. Just, McGill University, Montreal, to whom we express our sincere appreciation.

*Diethyl 2-Formylcyclopropane-1,1-dicarboxylate (3)*

According to the procedure of Warner and Moe (7), 23 g of acrolein and 95.2 g of diethyl bromomalonate were transformed into 54.2 g (64.1% yield) of purified diethyl 2-formylcyclopropane-1,1-dicarboxylate (3), b.p. 79.5–82°/0.25–0.3 mm Hg; the crude product (70.675 g, 84%) had been purified by fractional vacuum distillation using a Vigreux column. The analytical sample was prepared by two further vacuum distillations; b.p. 78–80°/0.08 mm Hg (lit. (4): 88–90°/0.01 mm Hg); $n^{25}$ 1.4490 (lit. (4), $n^{25}$ 1.4509); $\lambda_{max}$ (cyclohexane) 207 nm (log ε 3.29); $\nu_{max}$ (film) 3120 (cyclopropyl-$CH_2$), 2720 (aldehyde), 1747 and 1732 (esters), 1720 (aldehyde), 1270 and 1205 (esters), 1025 $cm^{-1}$ (cyclopropyl); δ ($CCl_4$) 1.3 (t, $J$ = 7 Hz) (ester-$CH_3$), 1.50–2.10 (m) (cyclopropyl-$CH_2$), 2.45–2.82 (m) (cyclopropyl-CH), 4.12 (q, $J$ = 7 Hz) (ester-$CH_2$), 9.25 (d, $J$ = 5 Hz) (aldehyde).

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.94; H, 6.57.

*2,4-Dinitrophenylhydrazone*

This derivative was prepared in the usual fashion (30); m.p. 146–146.5° (lit. (7): 141.7–142.7°); $\lambda_{max}$ (EtOH) 355 nm (log ε 4.31); $\nu_{max}$ (KBr) 3305 (NH), 3120 (cyclopropyl), 3100 (aromatic C—H), 1730 (esters), 1638 (C=N), 1620 and 1595 (aromatic C=C), 1525 and 1340 (nitro), 1270 and 1210 (esters), 825 $cm^{-1}$ (aromatic C—H deformation); δ($CDCl_3$) 1.28 (t, $J$ = 7 Hz) and 1.32 (t, $J$ = 7 Hz) (ester-$CH_3$), 1.6–2.2 (m) (cyclopropyl-$CH_2$), 2.6–3.1 (cyclopropyl-CH), 4.26 (q, $J$ = 7 Hz) and 4.28 (q, $J$ = 7 Hz) (ester-$CH_2$), 7.32 (s) (C*H*=N), 7.45 (d, $J$ = 10 Hz), 8.20–8.60 (m), and 9.12 (d, $J$ = 2.5 Hz) (aromatic protons), 11.2 (broad s) (NH).

Anal. Calcd. for $C_{16}H_{18}N_4O_8$: C, 48.73; H, 4.60; N, 14.21. Found: C, 48.68; H, 4.65; N, 14.18.

*Diethyl 2-Ethylenedioxymethylcyclopropane-1,1-dicarboxylate (4)*

From a solution of 1.5 g of diethyl 2-formylcyclopropane-1,1-dicarboxylate (3) in 230 ml of absolute benzene, 40 ml of solvent was removed by distillation and 20 ml of freshly distilled ethylene glycol and 93 mg of *p*-toluenesulfonic acid were added. The mixture was refluxed for 10 h and then poured into an iced saturated sodium bicarbonate solution. The product was extracted with ether, the organic solution was washed with a 2 *N* sodium carbonate solution and with water, and was dried over sodium sulfate. Evaporation of the solvent gave 1.6 g (89% yield) of ketal **4**. The product was purified by fractional vacuum distillation, giving 1.32 g (73.5%) of pure material; b.p. 100–103°/0.04 mm Hg. For analysis the product was redistilled *in vacuo*; b.p. 102°/0.04 mm Hg; $n^{25}$ 1.4565; $\nu_{max}$ (film) 3120 (cyclopropyl), 1740 and 1270 (esters), 1140 $cm^{-1}$ (ketal); δ ($CCl_4$) 1.25 (t, $J$ = 7 Hz) (ester-$CH_3$), 3.88 (m) (ketal-$CH_2$), 4.18 (q, $J$ = 7 Hz) (ester-$CH_2$), 4.7 (d, $J$ = 5 Hz) (H on ethylenedioxy-substituted C).

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.80; H, 7.03. Found: C, 55.45; H, 7.02.

*Unsuccessful Attempts at Valence Isomerization of Diethyl 2-Formylcyclopropane-1,1-dicarboxylate (3)*

*(a) With Aluminum Chloride*

For 90 min, 1 g of the formyl cyclopropane dicarboxylate **3** was treated with 1.6 g of aluminum chloride at 100–110°. The usual work-up gave 852 mg of a yellow oil, the u.v., i.r., n.m.r., and thin-layer analyses of which clearly indicated that it consisted of slightly decomposed starting material. There was no evidence for the formation of an olefinic derivative. When the reaction was carried out at 150° for a period of 3 h, a far less pure product was obtained which again showed the characteristics of the starting material but which also indicated the formation of other (in part hydroxylated) products which were not further investigated and which did not contain appreciable amounts of olefins.

*(b) With Bis(triphenylphosphine)iridium Carbonyl Chloride*

A solution of 1 g of the formyl cyclopropane dicarboxylate **3** in 25 ml of absolute benzene was heated with 78 mg of bis(triphenylphosphine)iridium carbonyl chloride to 130° for 18 h. The solution was filtered, washed with water, dried and taken to dryness to give 888 mg of a brownish oil, identified as impure starting material. The same result was obtained when the reaction was carried out at 160° for 24 h.

*(c) With trans-Dichlorobis(tri-n-butylphosphine)-nickel(II) and Diisobutylaluminum Chloride*

A solution of 1 g of the formyl cyclopropane dicarboxylate **3** in 20 ml of absolute toluene was treated with 210 mg of diisobutylaluminum chloride and 87 mg of *trans*-dichlorobis(tri-*n*-butylphosphine)nickel(II) for 3 h. Ice was added and the product was extracted with ether. The ethereal solution was washed with water and dried over sodium sulfate, and the solvent was evaporated. The remaining yellow oil was identified as the starting material. The reaction was repeated at reflux temperature for 5 h with the same result.

*Photolysis of Diethyl 2-Formylcyclopropane-1,1-dicarboxylate (3)*

A solution of 4.429 g of the formyl cyclopropane dicarboxylate **3** in 500 ml of absolute benzene was irradiated under nitrogen with an immersed 450 W Hanovia mercury lamp, using a Pyrex filter and a quartz vessel, cooled by a cold-water jacket. After 30 h the reaction was interrupted and the solvent was removed under reduced pressure. A portion of 3.4 g of the residue (4.435 g of a brownish oil) was subjected to dry-column chromatography (31) on 1 kg of silica gel, using petroleum ether – ether (2:1) as solvent system. Thus 2.039 g (60% yield) of pure diethyl *2,3-dihydrofurane-2,2-dicarboxylate* (**5**) was obtained. Vacuum distillation gave the analytical sample; b.p. 79–80°/0.1 mm Hg; $n^{25}$ 1.4452; $\lambda_{max}$ (cyclohexane) 203 nm (log ε 3.2), $\lambda_{max}$ (EtOH) 203 nm (log ε 3.45); $\nu_{max}$ (film) 3122 (double bond), 1750 (esters), 1635 (strong band of enolic double bond), 1270 $cm^{-1}$ (esters); δ ($CCl_4$) 1.32 (6 H, t, $J$ = 7 Hz) (ester-$CH_3$), 4.30 (4 H, q, $J$ = 7 Hz) (ester-$CH_2$), 3.18 (2 H, d of d, $J_{3,4}$ = 2.5 Hz, $J_{3,5}$ = 2.0 Hz) ($H_2$ of C-3 = 2 $H_X$ of $AMX_2$ system), 4.95 (1 H, d of t, $J_{4,3}$ = 2.5 Hz, $J_{4,5}$ = 2.5 Hz) ($H_4$ = $H_M$ of $AMX_2$ system), 6.32 (1 H, d of t, $J_{5,3}$ = 2.0 Hz, $J_{5,4}$ = 2.5 Hz) ($H_5$ = $H_A$ of $AMX_2$ system).

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.57; H, 6.68.

*Photolysis of Diethyl 2-Ethylenedioxymethylcyclopropane-1,1-dicarboxylate (4)*

A quantity of 1.6 g of the ketal derivative **4** of the aldehydo ester **3** was irradiated as described for the photolysis of the free aldehyde **3**. The work-up gave 1.6 g (quantitative crude yield) of a yellow oil, the i.r. and n.m.r. spectra of which revealed that it only contained the starting material, the cyclopropane derivative **4**. A portion of this product (1.5 g) was dissolved in 300 ml of absolute benzene and was again irradiated, this time without a Pyrex filter and for 17 h. Evaporation of the solvent gave 1.5 g (quantitative crude yield) of a yellowish oil which was again identified by i.r., n.m.r., and thin-layer analyses as unchanged starting material **4**.

*Ethyl Coumalate (6a)*

*(a) By Pyrolysis of Diethyl 2-Formylcyclopropane-1,1-dicarboxylate (3)*

A quantity of 9 g of diethyl 2-formylcyclopropane-1,1-dicarboxylate (**3**) was slowly distilled, in the course of 10 h, under nitrogen at 0.1 mm Hg, and the vapors were passed through a Vycor tube, filled with crushed Vycor glass, preheated to 550–575°. The distillate was collected in a Dry-Ice trap, the dark-brown product (3.728 g) was diluted with ether, the solution was washed with a saturated sodium bicarbonate solution and with water and was dried over sodium sulfate. Evaporation of the solvent gave 3.126 g of a brown oil. A portion of 2 g of this product was purified by dry-column chromatography on 600 g of silica gel, using petroleum ether – ether (1 : 1) as solvent system. Thus, 903 mg (corresponding to an overall yield of 20.2%) of ethyl coumalate (ethyl 2-pyrone-5-carboxylate) (**6a**) was obtained. For analysis, the product was redistilled under vacuum; b.p. 82–83°/0.1 mm Hg; m.p. 35–35.5° (lit. (25): 36°); $n^{25}$ 1.4782; $\lambda_{max}$ (EtOH) 245 (log ε 3.8) and 288 nm (log ε 3.4); $\nu_{max}$ (film) 3100 (double bond), 1760 (lactone), 1730 (ester), 1665 and 1650 (double bonds), 1300 $cm^{-1}$ (ester); δ ($CCl_4$) 1.38 (3 H, t, $J$ = 7 Hz) (ester-$CH_3$), 4.35 (2 H, t, $J$ = 7 Hz) (ester-$CH_2$), 6.28 (1 H, d of d, $J_{3,4}$ = 10 Hz, $J_{3,6}$ = 1 Hz) ($H_3$ = $H_A$ of AMX system), 7.80 (1 H, d of d, $J_{4,3}$ = 10 Hz, $J_{4,6}$ = 3 Hz) ($H_4$ = $H_M$ of AMX system), 8.35 (1 H, d of d, $J_{6,4}$ = 3 Hz, $J_{6,3}$ = 1 Hz) ($H_6$ = $H_X$ of AMX system).

Anal. Calcd. for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 56.69; H, 4.84.

*(b) From Coumalic Acid (6)*

A solution of 10.2 g of coumalic acid (**6**), prepared as described below (cf. 24), in 150 ml of absolute ethanol was refluxed for 1.5 h with 60 ml of concentrated sulfuric acid. The cooled solution was poured onto 100 g of ice and the product was extracted with ether. The organic solution was washed with a saturated sodium bicarbonate solution and with water and was dried over sodium sulfate. Evaporation of the solvent gave 11.9 g of a brown oil which was purified by fractional vacuum distillation. The product (b.p. 72–74°/0.04 mm Hg, m.p. 34–35°) was found identical to a sample prepared as described under (*a*), by the comparison of the u.v., i.r., and n.m.r. spectra.

*(c) By Pyrolysis of Ethyl α-Pyrone-3-carboxylate (7)*

Pyrolysis of 10.2 g of ethyl α-pyrone-3-carboxylate (7) (cf. below), under the conditions described under (*a*), led to 7.8 g (76.5%) of a dark-brown oil, the u.v., i.r., and n.m.r. spectra of which established its identity with ethyl coumalate (**6a**). Vacuum distillation gave 7.05 g (69%) of pure ethyl coumalate (**6a**), b.p. 79–81°/0.08 mm Hg, the spectra of which were superimposable on those of the products described under (*a*) and (*b*).

*Coumalic Acid (6)*

*(a) From Ethyl Coumalate (6a), Obtained by Pyrolysis of the Cyclopropane Derivative 3*

To a solution of 3.36 g of ethyl coumalate (**6a**), prepared from the formyl cyclopropane dicarboxylate **3**, in 40 ml of 95.5% sulfuric acid, 25 cc of water was added slowly. The solution was left for 20 h at room temperature and was then precipitated on 150 g of ice. The product was extracted with ether–chloroform (3 : 1), the organic solution was washed with water and was then extracted with a saturated sodium bicarbonate solution. The alkaline, aqueous extract was acidified to the Congo-blue reaction with concentrated hydrochloric acid and the product was extracted with ether–chloroform (3 : 1). The organic layer was washed with water and dried over sodium sulfate. Removal of the solvent gave 2.41 g (81%) of a light-brown solid, m.p. 190–195°. The product was dissolved in 20 ml of hot methanol and this solution was treated with 250 mg of Norit-A. The hot mixture was filtered and the volume of the filtrate was reduced to approximately 15 ml and cooled in an ice bath. The precipitate was filtered, washed with cold methanol and dried. Thus 1.505 g (50.5% yield) of light yellow crystals, m.p. 208–210°, were obtained. Recrystallization from methanol raised the melting point to 210–212°. A sample was sublimed twice in high vacuum between 120 and 130° for analysis. Almost colorless powder, m.p. 214.5–215° (lit. (24) 209–210°); $\lambda_{max}$ (EtOH) 243 (log ε 3.7) and 288 nm (log ε 3.5); $\nu_{max}$ (KBr) 3200–2500 (acid), 1720 (lactone), 1680 (acid), 1630 and 1550 (double bonds), 1405 and 1230 $cm^{-1}$ (acid); δ ($CF_3COOH$) 6.78 (1 H, d of d, $J_{3,4}$ = 10 Hz, $J_{3,6}$ = 1 Hz) ($H_3$ = $H_A$ of AMX system), 8.25 (1 H, d of d, $J_{4,3}$ = 10 Hz, $J_{4,6}$ = 3 Hz) ($H_4$ = $H_M$ of AMX system), 8.70 (1 H, d of d, $J_{6,4}$ = 3 Hz, $J_{6,3}$ = 1 Hz) ($H_6$ = $H_X$ of AMX system).

Anal. Calcd. for $C_6H_4O_4$: C, 51.44; H, 2.88. Found: C, 51.42; H, 2.97.

*(b) From Malic Acid*

A quantity of 50 g of malic acid was transformed, as described by Wiley and Smith (24), into 21.2 g (80.5% yield) of crude coumalic acid (**6**), m.p. 196–203°. The product was purified in hot methanol with Norit-A and recrystallized twice from methanol to give 16.4 g (62.5% yield) of pure coumalic acid (**6**), m.p. 208–211°, which was found identical with the one prepared as described under (*a*), by the comparison of the u.v., i.r., and n.m.r. spectra, and by the determination of a mixture melting point.

*Ethyl 2-Pyrone-3-carboxylate (7)*

A quantity of 55 g of 1,1,3,3-tetraethoxypropane was transformed, according to the procedure of Windholz *et al.* (29), with 40 g of diethyl malonate, 100 ml of acetic anhydride, and catalytic amounts of zinc chloride, to 58.4 g of *diethyl 3-ethoxyallylidenemalonate*; b.p. 114°/0.08 mm Hg (lit. (29): b.p. 128°/0.2 mm Hg); $\nu_{max}$ ($CH_3OH$) 300 nm (log ε 4.32) (lit. (29): 300 nm (log ε 4.39)); $\nu_{max}$ (film) 1720 (esters), 1630 (double bond), 1245 $cm^{-1}$ (esters); δ ($CCl_4$) 1.28 (3 H, t, $J$ = 7 Hz) (enol ether-$CH_3$), 1.32 (6 H, t, $J$ = 7 Hz) (ester-$CH_3$), 4.22

(2 H, q, $J$ = 7 Hz) (enol ether-$CH_2$), 4.26 (4 H, q, $J$ = 7 Hz) (ester-$CH_2$), 6.20 (1 H, t, $J$ = 12 Hz) (olefinic proton), 7.18 (1 H, d, $J$ = 12 Hz) (olefinic proton), 7.38 (1 H, d, $J$ = 12 Hz) (olefinic proton).

As described by Windholz *et al.* (29), a quantity of 12.6 g of diethyl 3-ethoxyallylidenemalonate was heated in 140 ml of 99% formic acid for 1 h to give 6.1 g (72.7% yield) of *ethyl 2-pyrone-3-carboxylate* (**7**); b.p. 95–97°/0.08 mm Hg (lit. (29): b.p. 122–123°/0.2 mm Hg), $\lambda_{max}$ ($CH_3OH$) 308 nm (log ε 3.72) (lit. (29): 309 nm (log ε 3.87)); $\nu_{max}$ (film) 3110 (double bonds), 1760 (lactone), 1745 (ester), 1630 and 1555 (double bonds), 1270 $cm^{-1}$ (ester); δ ($CCl_4$) 1.37 (3 H, t, $J$ = 7 Hz) (ester-$CH_3$), 4.4 (2 H, q, $J$ = 7 Hz) (ester-$CH_2$), 6.62 (1 H, d of d, $J_{5,4}$ = 7 Hz, $J_{5,6}$ = 5 Hz) ($H_5$ = $H_A$ of AMX system), 7.95 (1 H, d of d, $J_{6,5}$ = 5 Hz, $J_{6,4}$ = 2.5 Hz) ($H_6$ = $H_M$ of AMX system), 8.35 (1 H, d of d, $J_{4,5}$ = 7 Hz, $J_{4,6}$ = 2.5 Hz) ($H_4$ = $H_X$ of AMX system).

Anal. Calcd. for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 57.21; H, 4.73.

*Treatment of 5α-Androst-2-en-17β-ol (I) with Diethyl Bromomalonate*

To 10 ml of a solution prepared from 140 mg of sodium and 100 ml of *t*-butanol, 1.2 ml of diethyl bromomalonate was added and, subsequently, 1 g of 5α-androst-2-en-17β-ol (I) (9), dissolved in 50 ml of *t*-butanol. The rest of the sodium *t*-butoxide solution was added and the mixture was kept for 3 h at room temperature and subsequently at 90° for 5 h. No reaction was observed by thin-layer analysis. The product was poured into ice water and the precipitate was extracted with dichloromethane. The organic solution was washed with water and dried over sodium sulfate. Evaporation of the solvent gave 991 mg of the starting material. The result was analogous when the diethyl bromomalonate was added to a solution containing the steroid and sodium *t*-butoxide. Variations of the reaction conditions did not alter the results.

Sincere thanks are extended to Mrs. J. Capitaine for her assistance in some of the experiments and to Professor G. Just, McGill University, for kindly subjecting one of our products to an n.m.r. analysis at 100 MHz. We gratefully acknowledge the technical cooperation of the late Mr. D. Capitaine and of Mrs. G. Pelletier. Our appreciation is expressed to the National Research Council of Canada, the Ministère de l'Education du Gouvernement du Québec, to Ayerst Laboratories, Montreal, Quebec, and to the Schering Corporation, Bloomfield, New Jersey, for financial assistance. One of us (G. D.) sincerely thanks the National Research Council of Canada for the award of a scholarship.

1. Ch. R. Engel, R. Bouchard, A. F. de Krassny, L. Ruest, and J. Lessard. Steroids, **14**, 637 (1969).
2. W. Haede, W. Fritsch, K. Radscheidt, U. Stache, and H. Ruschig. Justus Liebigs Ann. Chem. **741**, 92 (1970).
3. (*a*) G. R. Pettit, D. C. Fessler, K. D. Pauli, P. Hofer, and J. C. Knight. J. Org. Chem. **35**, 1398 (1970); (*b*) G. R. Pettit and J. R. Dias. J. Org. Chem. **36**, 3207 (1971).
4. D. T. Warner, J. Org. Chem. **24**, 1536 (1959).
5. M. Mousseron, R. Fraisse, R. Jacquier, and G. Bonavent. C. R. Acad. Sci. **248**, 1465 (1959).
6. G. Bonavent, M. Causse, and R. Fraisse-Julien. Bull. Soc. Chim. Fr. 2462 (1964).
7. D. T. Warner and O. A. Moe. J. Am. Chem. Soc. **70**, 3470 (1948).
8. J. D. Graham and M. T. Rogers. J. Am. Chem. Soc. **84**, 2249 (1962).
9. M. M. Janot, A. Khuong-Huu, and R. Goutarel. Bull. Soc. Chim. Fr. 1640 (1960).
10. G. Combaut et L. Giral. Bull. Soc. Chim. Fr. 3258 (1969).
11. H. C. Volger, H. Hogeveen, and M. M. P. Gaasbeek. J. Am. Chem. Soc. **91**, 2137 (1969).
12. K. A. Jensen. Z. Anorg. Chem. **229**, 265 (1936).
13. R. G. Miller and P. A. Pinke. J. Am. Chem. Soc. **90**, 4500 (1968).
14. (*a*) P. G. Gassman and F. J. Williams. J. Am. Chem. Soc. **94**, 7733 (1972); (*b*) P. G. Gassman, G. R. Meyer, and F. J. Williams. J. Am. Chem. Soc. **94**, 7741 (1972); (*c*) P. G. Gassman, T. J. Atkins, and J. T. Lumb. J. Am. Chem. Soc. **94**, 7757 (1972).
15. W. G. Dauben, L. Schutte, and R. E. Wolf. J. Org. Chem. **34**, 1849 (1969).
16. W. G. Dauben, L. Schutte, R. E. Wolf, and E. J. Deviny. J. Org. Chem. **34**, 2512 (1969).
17. C. H. Robinson, O. Gnoj, and F. E. Carlon. Tetrahedron Lett. 2515 (1965).
18. R. Beugelmans. Bull. Soc. Chim. Fr. 3087 (1965).
19. G. W. Griffin, J. Covell, R. C. Petterson, R. M. Dodson, and G. Klose. J. Am. Chem. Soc. **87**, 1410 (1965).
20. G. Brown. U.S. Govt. Res. Rept. **38** [22], 25 (1963).
21. L. M. Jackman and S. Sternhell. *In* Applications of nuclear magnetic resonance spectroscopy in organic chemistry. 2nd Ed. Pergamon Press, Oxford, London, Edinburgh, New York, Toronto, Sydney, Paris, Braunschweig. 1969; (*a*) p. 188; (*b*) pp. 316–317.
22. W. F. Berkowitz and A. A. Ozirio. J. Org. Chem. **36**, 3787 (1971).
23. F. Stitt, G. F. Bailey, G. B. Coppinger, and T. W. Campbell. J. Am. Chem. Soc. **76**, 3642 (1954).
24. R. H. Wiley and N. R. Smith. *In* Organic syntheses, Coll. Vol. IV. John Wiley and Sons Inc., New York. 1963, pp. 201–202.
25. H. von Pechmann. Justus Liebigs Ann. Chem. **264**, 261 (1891).
26. H. E. Zimmerman, G. L. Grunewald, and R. M. Doufler. Org. Synth. **46**, 101 (1966).
27. W. H. Pirkle, H. Seto, and W. V. Turner. J. Am. Chem. Soc. **92**, 6984 (1970).
28. (*a*) P. de Mayo. *In* Advances in organic chemistry. *Edited by* R. A. Raphael. E. C. Taylor, and H. Wynberg. Interscience Publishers, Inc. New York. 1960, p. 394; (*b*) J. P. Guthrie,

C. L. McINTOSH, and P. DE MAYO. Can. J. Chem. **48**, 237 (1970); (*c*) W. H. PIRKLE and L. H. McKENDY. J. Am. Chem. Soc. **91**, 1175 (1969); (*d*) O. L. CHAPMAN, C. L. McINTOSH, and J. PACANSKY. J. Am. Chem. Soc. **95**, 244 (1973); (*e*) C. L. McINTOSH and O. L. CHAPMAN. J. Am. Chem. Soc. **95**, 247 (1973); (*f*) R. G. S. PONG and J. S. SHIRK. J. Am. Chem. Soc. **95**, 248 (1973).

29. T. B. WINDHOLZ, L. H. PETERSON, and G. J. KENT. J. Org. Chem. **28**, 1443 (1963).
30. R. L. SHRINER, R. C. FUSON, and D. Y. CURTIN. *In* The systematic identification of organic compounds. 5th Ed. John Wiley and Sons Inc., New York. 1967. p. 253.
31. (*a*) B. L. LOEV and K. M. SNADER. Chem. Ind. 15 (1965); (*b*) B. LOEV and M. M. GOODMAN. Chem. and Ind. 2026 (1967).