Oxidation of Furans. 3.[1] Estrogenic Properties of Lactones and Anhydrides Derived from the Oxidation of 17α-[3-Furyl]estradiol Derivatives

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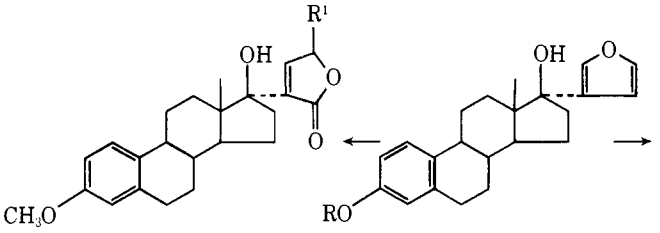
The oxidation of 17α-[3-furyl]estradiol derivatives and the estrogenic properties of the resulting isomeric 17,21- and 17,23-dihydroxy-19,24-dinor-17α-chola-1,3,5(10),20(22)-tetraenoic acid(21→23) γ-lactones as well as those of the related 17-hydroxy-19-nor-17α-pregna-1,3,5(10)-triene-20,21-dicarboxylic acid anhydrides and γ-lactones are described. Of these, only lactones **3c,e,h** and **5b** retained the same degree and profile of estrogenic activity as the starting 17α-[3-furyl]estradiols.

3-Substituted furans may be converted to isomeric butenolides. For example, treatment of 3-isopropylfuran with *N*-bromosuccinimide afforded 4-hydroxy-2-isopropyl-2-butenoic acid γ-lactone, while reaction with peracetic acid gave 4,4-dihydroxy-3-isopropyl-2-butenoic acid γ-lactone.[2] 17β-[3-Furyl]androstanes, derived from digitoxigenin, afforded, when similarly treated, modified cardenolides,[2,3] particularly actodigin, a new isocardenolide with a promising cardiotonic profile of activity different from that of the corresponding digitoxigenin derivative.[4,5]

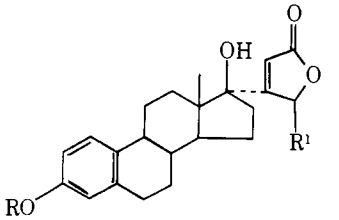
Therefore, in view of the interesting estrogenic properties exhibited by 17-[3-furyl]estradiol[6] and 7α,8α-epoxy-17-[3-furyl]estradiol derivatives,[7] it appeared interesting to convert the furan group into butenolides and to evaluate the effect of this modification on activity. The present paper deals with the preparation and biological properties of the resulting 17,21- and 17,23-dihydroxy-19,24-dinor-17α-chola-1,3,5(10),20(22)-tetraenoic acid(21→23) γ-lactones (**2** and **3**), as well as those of the related maleic and succinic anhydrides **6** and **7** and acid lactones **8**.

Chemistry. Treatment of 17α-[3-furyl]-3-methoxyestra-1,3,5(10)-trien-17-ol[6] (**1a**, R = CH_3) with an excess of *N*-bromosuccinimide in aqueous dioxane followed by reduction of the reaction mixture (lactones **2a** and **2b**) with zinc and acetic acid afforded **2b**. On the other hand, reaction of **1a** with *m*-chloroperbenzoic acid in chloroform in the presence of acetic acid and sodium acetate gave a mixture of isomeric hydroxy lactones **3a** (R = CH_3; R^1 = OH) and **2c** (R^1 = OH), the latter being formed only in minor quantities. The two lactones were separated as the acetates **3b** (R = CH_3; R^1 = OAc) and **2d** (R^1 = OAc).

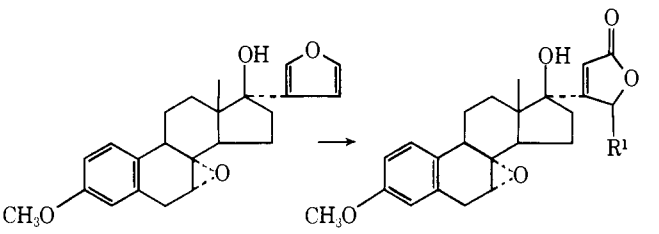


2a, R^1 = Br
b, R^1 = H
c, R^1 = OH
d, R^1 = OAc

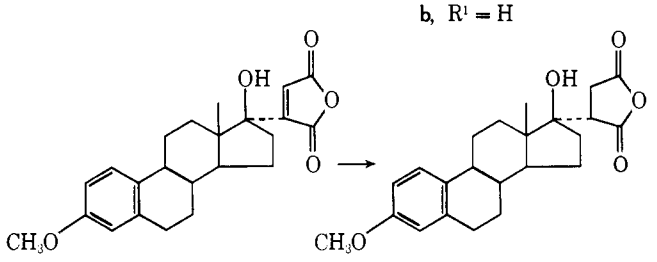
1a, R = CH_3
b, R = c-C_5H_{10}
c, R = Ac



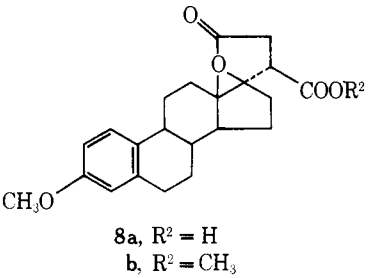
3a, R = CH_3; R^1 = OH
b, R = CH_3; R^1 = OAc
c, R = CH_3; R^1 = H
d, R = c-C_5H_{10}; R^1 = OH
e, R = c-C_5H_{10}; R^1 = H
f, R = Ac; R^1 = OH
g, R = Ac; R^1 = OAc
h, R = Ac; R^1 = H



4 **5a**, R^1 = OH
b, R^1 = H



6 **7**



8a, R^2 = H
b, R^2 = CH_3

Finally oxidation of the hydroxy lactone **3a** with chromic acid yielded the maleic anhydride **6**, which upon reduction with zinc and acetic acid gave the succinic anhydride **7**. The latter compound readily dissolved in aqueous sodium hydroxide and acidification of the alkaline solution afforded the acid lactone **8a** (R^2 = H), readily converted to its methyl ester **8b** (R^2 = CH_3) in a conventional manner.

Reduction of **3b** with sodium borohydride, followed by acidification, afforded lactone **3c** (R = CH_3; R^1 = H), the positional isomer of **2b**. In view of the high degree of estrogenic activity exhibited by **3c** (see below), the analogs **3e, 3h**, and **5b** were similarly prepared from the appropriate furyl derivatives **1b**,[6] **1c**,[6] and **4**.[7]

Pharmacology. The oral estrogenicity of the compounds was determined in two standard assays.

(a) Allen–Doisy Test,[8a] with a Slight Modification.[8b] Cornification of the vaginal epithelial cells in ovariectomized rats was the end point of the experiment. The results

are expressed as the dose necessary to induce cornification in 50% of the animals (ED_{50}). The ED_{50} was calculated by using an average of 40 (20–100) animals per compound. Dose–response curves were used to determine the ED_{50} graphically.[9] There were at least four dose levels for the determination of the ED_{50} for each compound.

(b) Uterotrophic Assay in Immature Intact Mice.[10] This test was done at a minimum of five doses for each compound. Five to ten animals were used at each dose level. The results are expressed as the minimum effective dose at which a threefold increase in uterine weight over that of the controls was obtained.

The results are given in Table I along with data on mestranol which was used as standard. In the Allen–Doisy assay, compounds **3c**, **3e**, **3h**, and **5b** were highly active, being about 4–20 times as potent as mestranol and exhibiting essentially the same degree of activity as the corresponding 17α-[3-furyl]estradiol derivatives.[6,7] With the exception of **3b**, which was weakly active, all the other lactones and the anhydrides were devoid of activity.

In the uterotrophic assay the described lactones and anhydrides were much less active than mestranol.

In summary, the conversion of the furyl group in 17α-[3-furyl]estradiol derivatives into lactones or anhydrides was generally detrimental to the estrogenic activity as determined in the Allen–Doisy assay and only compounds **3c**, **3e**, **3h**, and **5b** retained the same degree and profile of estrogenic activity as the starting 17α-[3-furyl]estradiols.

Table I. Estrogenic Properties of the Lactones and Anhydrides Derived from the Oxidation of 17α-[3-Furyl]estradiol Derivatives

Compd no.	Activity po: Allen–Doisy in rats, ED_{50}, μg	Activity po: Uterotrophic in mice, μg
Mestranol[a]	46	0.5
2b	ND[b]	512
2d	ND[b]	256
3b	120	32
3c	7	128
3e	12	ND[c]
3h	5	256
5b	1.3	256
6	ND[b]	128
7	ND[b]	ND[c]
8b	ND[b]	ND[c]

[a] 17α-Ethynyl-3-methoxyestra-1,3,5(10)-trien-17-ol. [b] ND denotes that the ED_{50} was not determined. The compound was tested up to a dose of 1 mg/kg (five animals) and was found inactive. Such compounds were not investigated further in this assay. [c] ND denotes that the compound was not uterotrophic up to a dose of 512 μg/kg (five animals). Such compounds were not investigated further in this assay.

Experimental Section

The compounds were analyzed for C and H and **2a** also for Br. Where the elements are indicated the results were within 0.4% of the calculated values. The NMR, ir, and uv spectra were in agreement with the proposed structures. The rotations were taken in 1% chloroform or methanol solutions at 24–25°. The melting points are uncorrected.

17,23-Dihydroxy-3-methoxy-19,24-dinor-17α-chola-1,3,5(10),20(22)-tetraen-21-oic Acid(21→23) γ-Lactone (2b). *N*-Bromosuccinimide (5.05 g) was added by portions to a solution of 17α-[3-furyl]3-methoxyestra-1,3,5(10)-trien-17-ol[6] (**1a**, 5.0 g) in dioxane (250 ml) and H_2O (20 ml). The reaction mixture was stirred at room temperature for 30 min, diluted with H_2O, and extracted with Et_2O. The solution was washed to neutrality ($NaHCO_3$–H_2O), dried ($MgSO_4$), and evaporated. The crude residue (6.70 g) was dissolved in AcOH (335 ml) and the solution was stirred for 1 hr at room temperature with Zn dust (33.5 g). The metal was filtered and the filtrate diluted with H_2O. The resulting solid was washed with H_2O and dried. This solid was chromatographed on silica gel and the fractions eluted with C_6H_6–Et_2O (9:1) were combined and crystallized from CH_2Cl_2–MeOH to yield **2b** (2.3 g, 44%): mp 171–174°; [α]D +72.1° ($CHCl_3$). Anal. ($C_{23}H_{28}O_4$) C, H.

In another run the intermediate bromo lactone **2a** was isolated in low yield. *N*-Bromosuccinimide (11.1 g) was added by portions to a solution of **1a** (11.1 g) in dioxane (55 ml) and H_2O (45 ml). The reaction was allowed to proceed as above. After work-up the residue was crystallized from CH_2Cl_2–MeOH and CH_2Cl_2–hexane to afford **2a** (2.6 g, 18%): mp 194–196°; [α]D −27.9° ($CHCl_3$). Anal. ($C_{23}H_{27}O_4Br$) Br; C: calcd, 61.74; found, 62.64. H: calcd, 6.08; found 6.49.

Peracid Oxidations. Preparation of 17,21,21-Trihydroxy-19,24-dinor-17α-chola-1,3,5(10),20(22)-tetraen-23-oic Acid-(21→23) γ-Lactones (3 and 5, R = OH). The general procedure for the preparation of the hydroxy lactones **3** and **5** (R = OH) may be illustrated as follows. *m*-Chloroperbenzoic acid (85%, 23.65 g) was added to a mixture of **1a** (17 g), NaOAc (17 g), AcOH (17 g), and $CHCl_3$ (850 ml). After stirring for 1 hr at room temperature, Et_2O was added and the solution was washed to neutrality ($NaHCO_3$–H_2O), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel. Elution with mixtures of C_6H_6–MeOH (99:1 and 98:2) afforded **3a** (16.4 g, 88%). An analytical sample was obtained from acetone–hexane: mp 214–216°; [α]D +81.9° ($CHCl_3$). Anal. ($C_{23}H_{28}O_5$) C, H.

In the same manner oxidation of **1b**[6] and **4**[7] respectively afforded **3d** [24%; mp 194–196° (Et_2O); [α]D +46.9° (MeOH). Anal. ($C_{27}H_{34}O_5$) C, H] and **5a** [68%; mp 235–236° (acetone–hexane); [α]D +105.1° (MeOH). Anal. ($C_{23}H_{26}O_6$) C, H].

17,23,23-Trihydroxy-3-methoxy-19,24-dinor-17α-chola-1,3,5(10),20(22)-tetraen-21-oic Acid(21→23) γ-Lactone 23-Acetate (2d) and 17,21,21-Trihydroxy-3-methoxy-19,24-dinor-17α-chola-1,3,5(10),20(22)-tetraen-23-oic Acid(21→23) γ-Lactone 21-Acetate (3b). Oxidation of **1a** with *m*-chloroperbenzoic acid as described above afforded, besides **1a**, the isomeric hydroxy lactone **2c**. The compounds were separated and characterized as the corresponding acetates **3b** and **2c**. *m*-Chloroperbenzoic acid (14 g) was added to a mixture of **1a** (10 g), NaOAc (10 g), AcOH (10 g), and $CHCl_3$ (600 ml). The reaction was allowed to proceed as above. After work-up the residue (10 g) was acetylated with Ac_2O (100 ml) and pyridine (100 ml). The mixture was stirred at room temperature for 1 hr, poured on ice–water, and extracted with Et_2O. The solution was washed to neutrality (aqueous H_2SO_4, aqueous $NaHCO_3$, and H_2O), dried, and evaporated. The residue was chromatographed on silica gel. Elution with C_6H_6–EtOAc (19:1) successively afforded **2d** [1.2 g (10%); mp 231–233° (CH_2Cl_2–MeOH); [α]D +68.3° ($CHCl_3$)] and **3b** [5.1 g (42%); mp 206–209° (MeOH); [α]D +129° ($CHCl_3$). Anal. ($C_{25}H_{30}O_3$) C, H].

3,17,21,21-Tetrahydroxy-19,24-dinor-17α-chola-1,3,5(10),20-(22)-tetraen-23-oic Acid(21→23) γ-Lactone 3,21-Diacetate (3g). Similarly as above, reaction of **1c**[6] with *m*-chloroperbenzoic acid afforded the hydroxy lactone **3f** (64%), mp 230–233° (Et_2O), which was purified and characterized as the acetoxy lactone **3g** (84%): mp 224–226° (CH_2Cl_2–MeOH); [α]D +117° ($CHCl_3$). Anal. ($C_{26}H_{30}O_7$) C, H.

17,21-Dihydroxy-19,24-dinor-17α-chola-1,3,5(10),20(22)-tetraen-23-oic Acid(21→23) γ-Lactones (3 and 5, R = H). The general procedure may be illustrated as follows. Sodium borohydride (56.5 g) was added by portions over a period of 30 min to a solution of **3b** (11.3 g) in MeOH (1130 ml). After stirring for 45 min at room temperature, the solvent was removed under reduced pressure. The residue was partitioned between H_2O and Et_2O. The aqueous phase was extracted further with Et_2O and then cooled to 0°. Acidification yielded a solid which was crystallized from MeOH and then CH_2Cl_2–Et_2O to afford **3c** (2.8 g, 24%): mp 217–219°; [α]D +83° ($CHCl_3$). Anal. ($C_{23}H_{28}O_4$) C, H.

Compound **3h** was similarly prepared from **3g**. In the course of the reduction the phenolic acetate was hydrolyzed. Reacetylation was effected in the usual manner: yield of **3h**, 18%; mp 221–223° (MeOH–Et_2O); [α]D +71.4°. Anal. ($C_{24}H_{28}O_5$) C, H.

In a similar manner reduction of the hydroxy lactones **3d** and **5a** respectively afforded **3e** [46%; mp 204–205° (acetone–hexane); [α]D +70.6° ($CHCl_3$). Anal. ($C_{27}H_{34}O_4$) C, H] and **5b** [36%; mp 137–143° (MeOH); [α]D +101.7° ($CHCl_3$). Anal. ($C_{23}H_{26}O_5 \cdot$ MeOH) C, H].

17-Hydroxy-3-methoxy-19-nor-17α-pregna-1,3,5(10),20-tetraene-20,21-dicarboxylic Acid Anhydride (6). An 8 *N* chromic acid solution (6.55 ml) was added slowly to a solution of **3a** (500 mg) in acetone (25 ml) at 10–12°. After stirring for 15 min at room temperature, the excess oxidant was decomposed by the addition of *i*-PrOH. H_2O was added and the solution was evaporated almost to dryness. The residue was extracted with Et_2O and CH_2Cl_2. The organic phase was washed to neutrality ($NaHCO_3$, H_2O), dried ($MgSO_4$), and evaporated. Crystallization of the crude reaction product from $CHCl_3$–Et_2O and then acetone–Et_2O afforded **6** as a pale yellow solid (175 mg, 35%): mp 227–228°; $[\alpha]D$ +96.9°. Anal. ($C_{23}H_{26}O_5$) C, H.

17-Hydroxy-3-methoxy-19-nor-17α-pregna-1,3,5(10)-triene-20,21-dicarboxylic Acid Anhydride (7). A mixture of the maleic anhydride **6** (10 g), $CHCl_3$ (200 ml), AcOH (500 ml), and Zn dust (50 g) was stirred at room temperature for 1 hr. The metal was filtered and washed with $CHCl_3$. The filtrate was thoroughly washed with H_2O, dried ($MgSO_4$), and evaporated. Crystallization of the residue from $CHCl_3$–Et_2O afforded **7** (2.1 g, 21%): mp 234–235°; $[\alpha]D$ +69.9° ($CHCl_3$). Anal. ($C_{23}H_{28}O_5$) C, H.

This product is not very stable and is readily converted into the acid lactone **8a**.

17-Hydroxy-3-methoxy-19-nor-17α-pregna-1,3,5(10)-triene-20,21-dicarboxylic Acid Anhydride (7). A mixture of the dride **7** (8.9 g) was dissolved in 0.1 *N* NaOH. Upon acidification with 1 *N* HCl (100 ml), the solid which formed was filtered, washed with H_2O, and dried. This solid was boiled in the presence of Et_2O for 5 min to yield the acid lactone **8a** (6.72 g, 75%). The analytical sample was obtained from acetone: mp 233–234° dec; $[\alpha]D$ +21.3°. Anal. ($C_{23}H_{28}O_5$) C, H.

17-Hydroxy-3-methoxy-19-nor-17α-pregna-1,3,5(10)-triene-20,21-dicarboxylic Acid γ-Lactone Methyl Ester (8b). Esterification of the acid lactone **8a** in a conventional manner with CH_2N_2 afforded the methyl ester **8b** (73%): mp 135–136° (MeOH); $[\alpha]D$ +10.5° ($CHCl_3$). Anal. ($C_{24}H_{30}O_5$) C, H.

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References and Notes

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Synthesis and Antiinflammatory Activity of Some 1,6-Methano[10]annuleneacetic Acids†

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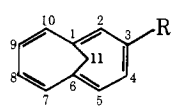
Some new approaches to the 1,6-methano[10]annulene system are described. The routes were used to prepare 1,6-methano[10]annulene-3-acetic acid and the α-methyl analog. The compounds showed antiinflammatory and analgesic activity, though less than that of the corresponding naphthalene compounds; the possible effect of the chirality of the annulene on the observed biological activity is discussed.

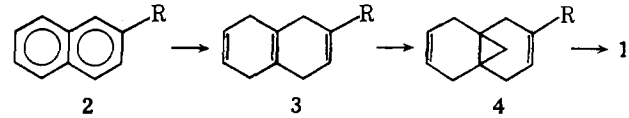
The antiinflammatory activity of arylacetic acids, in which activity is maintained despite wide variations in the nature of the aryl group, has prompted considerable recent research into this class of compounds.[1] In view of the antiinflammatory activity reported[2] for a number of naphthylacetic acids, and also of the spatial similarities between naphthalene and 1,6-methano[10]annulene **1a**,[3] we have synthesized 1,6-methano[10]annulene-3-acetic acid and the α-methyl analog. The syntheses incorporate some novel and efficient approaches to the annulene system.



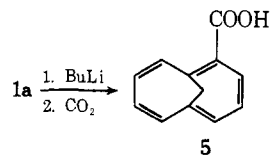
1a, R = H
b, R = CH_2COOCH_3
c, R = $CH(CH_3)COOCH_3$
d, R = CH_2COOH
e, R = $CH(CH_3)COOH$
f, R = CN
1g, R = $COOCH_3$
h, R = COOH
i, R = CH_2OH
j, R = CH_2Cl
k, R = CH_2CN

Chemistry. Since electrophilic substitution has been reported to yield almost exclusively the 2-substituted derivatives,[4] the desired 3-substituted compounds were first synthesized by a modification of the abbreviated synthesis of the parent hydrocarbon which was developed in these laboratories.[5] This synthesis, shown in Scheme I, R = H, is, at least in principle, applicable to 2-substituted naphthalenes in which the substituent R is compatible with Birch reduction, Simmons–Smith methylenation, and dichlorodicyano-*p*-benzoquinone (DDQ) oxidation. Accordingly, 2-naphthylacetic acid and 2-(2-naphthyl)propionic acid were each

Scheme I



2a–4a, R = H
2b–4b, R = CH_2COOH
2c–4c, R = $CH(CH_3)COOH$
2d–4d, R = CH_2CH_2OH



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