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3-HYDROXYMETHYL-4-ARYL-4-HYDROXYBUTANOIC ACID LACTONES

PODOPHYLLOTOXIN ANALOGS

S. N. LEWIS and T. L. POPPER

Rohm and Haas Company, Philadelphia, Pennsylvania

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Abstract—The biological activity of podophyllotoxin has been expressed in terms of the alkylating potential of its "swinging lactone" functionality. The synthesis and characterization of the two isomeric lactones (X and XI) of 3-hydroxymethyl-4-(3,4-methylenedioxyphenyl)-4-hydroxybutanoic acid, embodying the lowest common denominator of this functionality, are described. The attempted preparation of 4,4-diaryl analogs of these dihydroxyacid lactones revealed a novel oxidation-reduction cycle, relating 3-(4,4'-dimethoxybenzhydrylidene)-4-hydroxybutanoic acid lactone (XX) to 3-(α-hydroxy-4,4'-dimethoxybenzhydryl)-4-hydroxy-2-butenoic acid lactone (XXII).

PRINCIPAL among known mytotic poisons are antimetabolites and a variety of compounds classified chemically as alkylating agents, particularly the nitrogen mustards. Recently in a large number of compounds screened for chemical control of insect populations, a striking parallel between their antineoplastic and chemosterilant activity was evident.[1] Particularly effective in inducing male sterility in several species of insects were alkylating agents, including nitrogen mustards and specifically ethylenimine phosphoramides, presumably because of their ability to interfere in the reproductive process by alkylation of a critical participant. Unfortunately alkylating efficiency usually varies directly with the compound's susceptibility to inactivation by moisture. As a result, practical field application of these materials is difficult.

The antimitotic activity of podophyllotoxin, an extracted component of May apple root has been well documented.[2] Preliminary indications of insect chemosterilant activity in an extract of May apple root suggested that podophyllotoxin might also function in this regard.[3]

Examination of molecular models of podophyllotoxin[4] revealed a unique conformational relationship, which allowed access of its carboxylic acid functionality to either OH of its 1,3-diol system. Recognizing that the benzylic lactone component I of such an equilibrium, however small, provides a stabilized benzylic carbonium ion on carbon–oxygen bond heterolysis (in the direction of the curved arrow), podophyllotoxin could be construed as an alkylating agent. This concept of alkylation

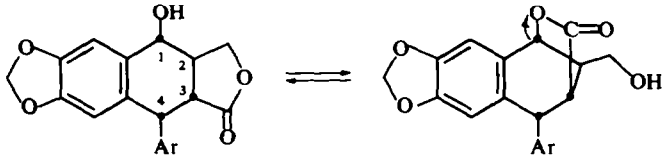
[1] A. B. Bořkovec, *Science* **137**, 1034 (1962).

[2] J. L. Hartwell and M. J. Shear, *Cancer Research* **7**, 716 (1947); J. Leiter, V. Downing, J. L. Hartwell and M. J. Shear *J. National Cancer Inst.* **10**, 1273 (1950); and J. L. Hartwell and W. E. Detty *J. Am. Chem. Soc.* **72**, 246 (1950).

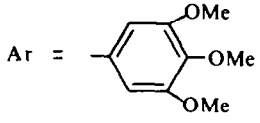
[3] P. L. de Benneville, private communication.

[4] See A. W. Schrecker and J. L. Hartwell, *J. Am. Chem. Soc.* **73**, 2909 (1951) and **75**, 5916 (1953) for elucidation of structure.

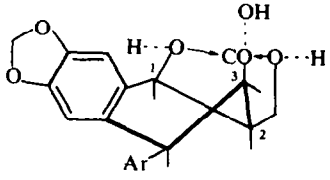
via swinging lactone appeared to be an attractive working hypothesis for both its mitotic and the chemosterilant activity.



Podophyllotoxin I



Podophyllotoxin, however, does not present each of its OH groups for competitive lactonization without some conformational difficulty. Preferred would be its C_2 epimer (illustrated spatially by II) which, models suggest, should allow equal access of its carboxylic acid functionality to either OH-group. Furthermore, the established



II

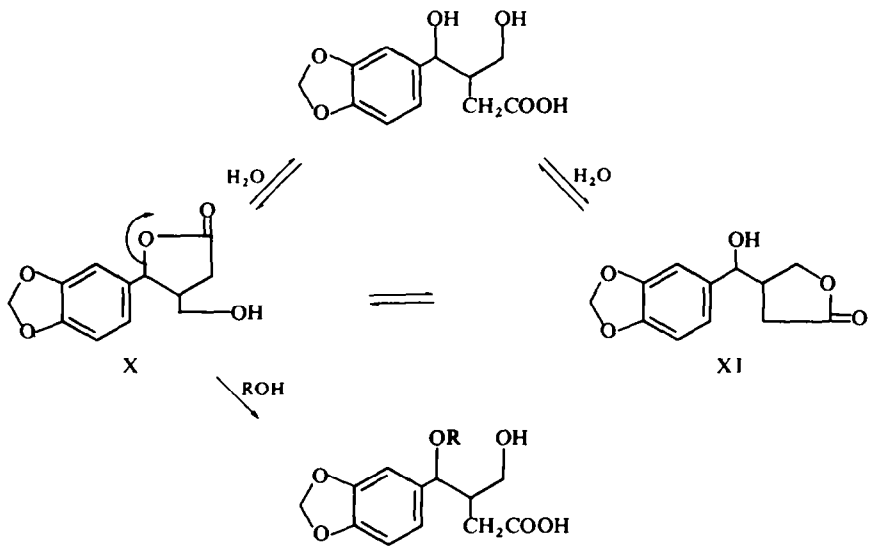
susceptibility of podophyllotoxin to facile epimerization at C_3 to give, irreversibly, the *cis* lactone picrophyllotoxin,[5] an even less spatially favorable conformation for dual closure and, significantly, inactive mitotically, suggested that an acyclic system embodying the requisite functionality but devoid of these sterical restrictions might be an optimal biological alkylator.

A diol system capable of interchange to an activated benzylic lactone may be approximated by a variety of model systems,[6-8] the simplest of which is pictured in Scheme I. Certainly the pendant trimethoxyphenyl group of podophyllotoxin does not appear to be pertinent to the proposed mechanism for alkylation. In this paper, we are reporting the synthesis of the isomeric hydroxylactones X and XI. These structures possess a solvolytically activated leaving group which, in contrast to common alkylators, is retained in close proximity to the cationic center after ionization; and a mechanism is provided for its reintroduction at that same position

[5] J. L. Hartwell and A. W. Schrecker, *Fortschr Chem. Org. Naturstoffe* **17**, 83 (1958).
[6] N. L. Drake and W. B. Tuemmler, *J. Am. Chem. Soc.* **77**, 1204, 1209 (1955).
[7] K. N. Campbell, J. A. Cella, and B. K. Campbell, *J. Am. Chem. Soc.* **75**, 4681 (1953).
[8] G. N. Walker, *J. Am. Chem. Soc.*, **75**, 3393 (1953).

even after the collapse of this cation with water. The consecutive equilibria pictured in Scheme I would be expected to allow a finite concentration of alkylator to be present, even in water. Particularly significant is that this alkylator should not be scavenged by water but only by monovalent active hydrogen compounds such as

Scheme I



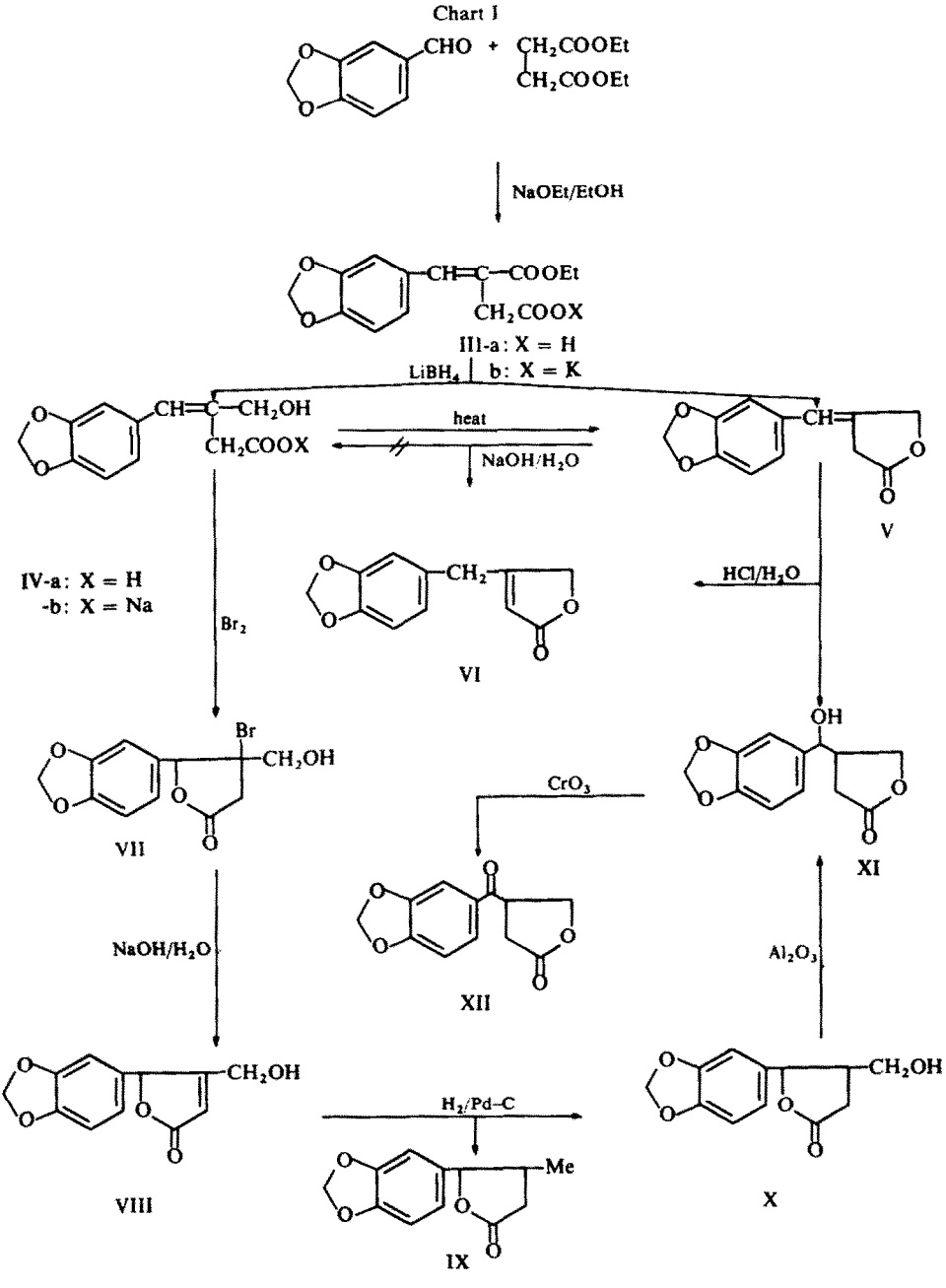
biologically bound hydroxyls (denoted by ROH in Scheme I), thus affording activated alkylation at no expense to hydrolytic stability.

The lactones X and XI were prepared by the reaction sequence illustrated in Chart I. Structural assignments are supported by IR, UV and NMR spectra. All compounds had satisfactory elemental analyses.

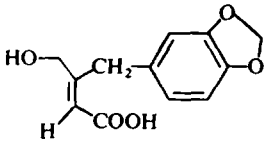
Conversion of the half-ester intermediate III of the Stobbe condensation of piperonal and diethyl succinate to its potassium salt allowed selective reduction of the ester functionality with lithium borohydride in glyme. Surprisingly, the predominant product on acid work up was uncyclized hydroxyacid IV-a, although no particular care was taken to prevent lactonization. The behavior of this hydroxyacid on heating, however, suggested that it was smoothly converted to its corresponding lactone V at its m.p. Interestingly, attempted saponification of this lactone returned little, if any, of the hydroxyacid salt IV-b, but gave instead a substantial quantity of the isomeric α,β-unsaturated lactone VI. A number of attempts to obtain the desired hydroxylactone XI by hydration of V also resulted only in conversion to the isomerized lactone VI.

The surprising stability of the hydroxyacid IV-a suggested that isomerization might have occurred during reduction of III giving a *trans*-hydroxycrotonic acid XIII, no longer amenable to lactonization. This structure, however, was excluded by its UV spectrum. Its absorption maxima (ε_{264}^{MeOH} 12,700, ε_{298}^{MeOH} 6800), characteristic of

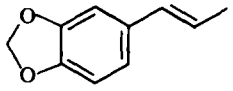
Chart I


CHO + CH2COOEt
CH2COOEt
NaOEt/EtOH
CH=C—COOEt
CH2COOX
III-a: X = H
b: X = K
LiBH4
CH=C—CH2OH
CH2COOX
heat
NaOH/H2O
V
IV-a: X = H
-b: X = Na
Br2
CH2
VI
HCl/H2O
Br
CH2OH
VII
OH
XI
CrO3
NaOH/H2O
Al2O3
XII
CH2OH
VIII
H2/Pd–C
Me
IX
CH2OH
X

styrenes, were in good agreement with isosafrole[9] (ε_{264}^{MeOH} 15,500, ε_{303}^{MeOH} 6600) and thus corroborative for structure IV-a.

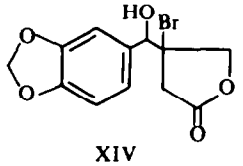


XIII



Isosafrole

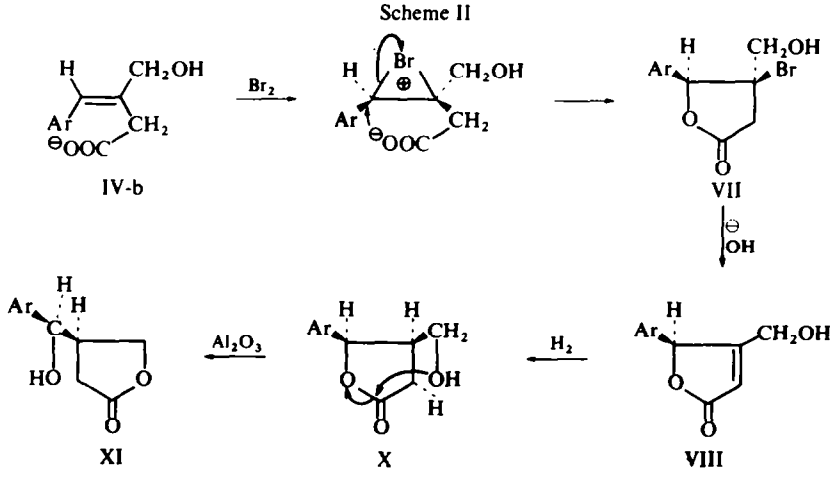
Bromination of the hydroxyacid sodium salt IV-b in aqueous methanol proceeded smoothly,[10] absorbing one equivalent of bromine. The kinetically controlled (see Scheme II) bromolactone VII was obtained, rather than its isomer XIV. Examination



XIV

of Table 1 allows ready distinction of the two possible lactone isomers of these 1,3-dihydroxy systems. It is evident that in the 4-piperonyl-lactone structures, the 4-proton NMR absorption can be expected in the neighborhood of 4·50 τ. In contrast, the isomeric lactones display 4-proton absorption in the neighborhood of 5·5 τ.

Scheme II



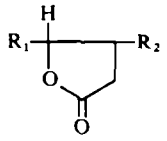
IV-b VII XI X VIII

Dehydrobromination of the bromolactone VII was accomplished titrimetrically with standard NaOH. The resulting unsaturated lactone VIII smoothly reduced at atmospheric pressure to give one of the desired products X. Rearrangement of X to the isomeric lactone XI was effected simply by chromatography on alumina. Its

[9] J. Press and R. Brun, *Helv. Chim. Acta* **37**, 190 (1954).

[10] H. Stobbe, *Liebigs Ann.* **308**, 89, 114 (1899).

TABLE 1. 4-PROTON NMR ASSIGNMENTS FOR 3,4-SUBSTITUTED 4-HYDROXYBUTANOIC ACID LACTONES



Compound	4-R_1[b]	3-R_2[b]	τ[a]
—	H	H	5·63[c]
—	Ph	H	4·67[d]
X	Ar	CH_2OH	4·45
VII	Ar	Br	4·32[e]
VIII	Ar	CH_2OH[f]	4·50[e]
IX	Ar	CH_3	4·49
—	H	C_6H_5	5·61[d]
XI	H	CH(OH)Ar	5·65
V	H	=CHAr	5·07
VI	H	CH_2Ar[f]	5·33
XII	H	COAr	5·35–5·68[g]
—	H	H[h]	5·07[i]

[a] All spectra run using TMS as an external standard; $CDCl_3$ was the solvent unless indicated otherwise.
[b] Ar denotes 3,4-methylenedioxyphenyl.
[c] Varian spectrum #63.
[d] (Ref. 11).
[e] DMSO solvent.
[f] 3,4-disubstituted-4-hydroxy-2-butenoic acid lactone.
[g] Multiplet in indicated range; specific assignment for 4-H difficult.
[h] 4-Hydroxy-2-butenoic acid lactone
[i] Varian spectrum #51.

structure was confirmed by Jones oxidation to the corresponding ketone XII. When the hydrogenation of VIII was performed at 4 atmospheres hydrogen pressure in a Parr apparatus, substantial quantities of the hydrogenolized product IX were obtained.

It is evident that the lactones VII, X and XI contain two asymmetric centers and thus are capable of existence in two diastereomeric forms. The high yields of sharply melting VII and XI isolated suggest a preference for one diastereomer and imply stereospecificity in the reaction sequence which has been summarized in Chart I without reference to stereochemistry. The proposed stereochemical course of these reactions is illustrated in Scheme II.

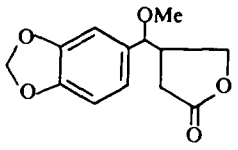
It has been established that a high ratio of *trans/cis* (Ar/COOEt) cinnamic acid

succinate.[12] Thus it is reasonable that lithium borohydride reduction of the sharply melting benzylidene succinate III so obtained gave, with no obvious compromise of

[11] C. H. DePuy, *J. Org. Chem.* **29**, 2810 (1964).
[12] W. S. Johnson and G. H. Daub, *Organic Reactions* Vol. VI. Wiley, New York, N.Y. (1951).

geometrical integrity, the single sharply melting hydroxyacid isomer IV indicated in Scheme II. This geometry predetermines the configuration at the piperonylic position during its stereospecific brominative lactonization[13] also pictured in Scheme II. Predictably only a single diastereomer, presumably the *cis*-4-aryl-3-bromolactone VII, was obtained. Although non-selective hydrogen addition from either side of the 4-arylbutenoic acid lactone VIII again raises the possibility of a pair of diastereomers in the resultant oil X, catalytic hydrogenation *trans* to the bulky aryl substituent would appear to be favored. Indeed, the high yield of the sharply melting XI obtained by what must certainly be a stereospecific process, suggests that X must also be predominantly a single diastereomer.

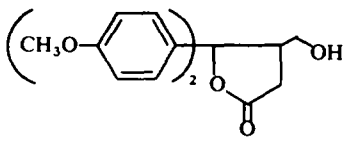
Contrary to expectations, the isomeric hydroxylactones X and XI proved sluggish to methanolysis in 50% aqueous methanol, requiring acidification to pH 1·2 with perchloric acid in order to effect complete hydroxyl loss in 20 hr. Column chromatography gave, in each case, an oil possessed of identical IR and NMR spectra. Each showed a single spot at the same R_f by TLC. The NMR spectra were most consistent with the expected piperonyl methyl ether XV, however, this assignment



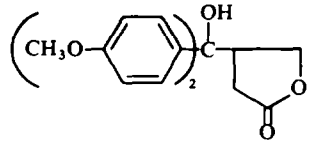
XV

required placing the 4-lactone protons at the abnormally high field of 6·09 τ (Table 1). The spectra were otherwise similar to that of the closely related piperonyl alcohol XI although a general broadening of the peaks was suggestive of the introduction of another diastereomer, an expected consequence of the loss of configurational integrity at the piperonylic position during the methanolysis reaction. The efficacy of the hydroxylactones in biological alkylations is under study.

In order to further enhance the first-order rate of solvolysis of these activated lactones (Scheme I), the preparation of the 4,4-diaryl-3-hydroxymethyl-4-hydroxybutanoic acid lactones, XVI and XVII, was attempted. The synthetic sequence



XVI

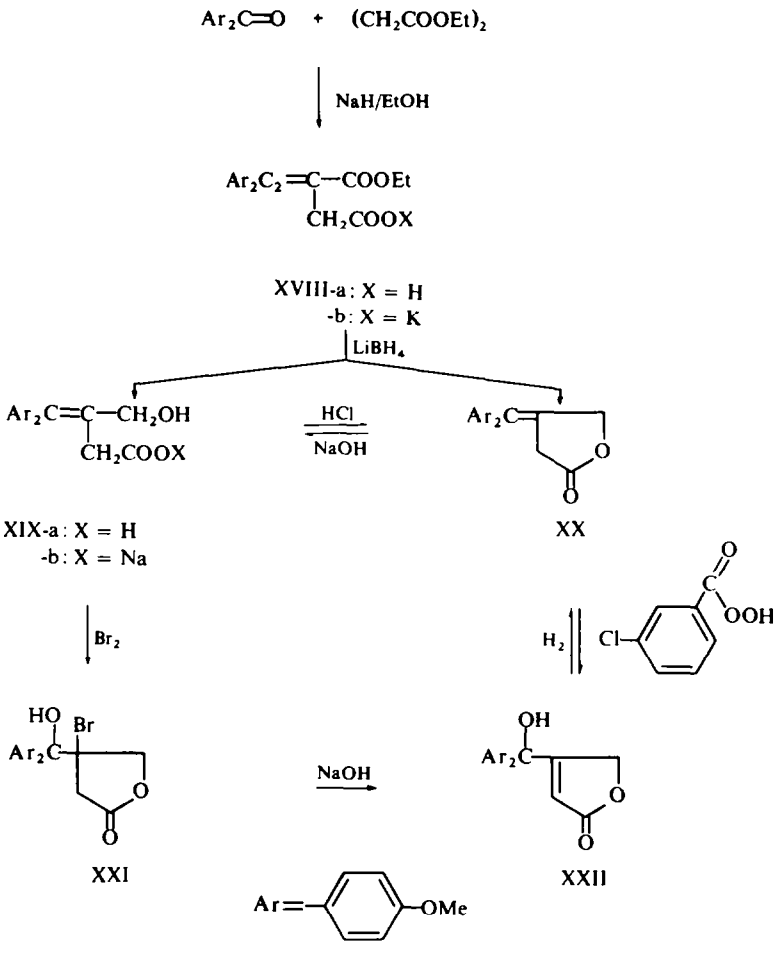


XVII

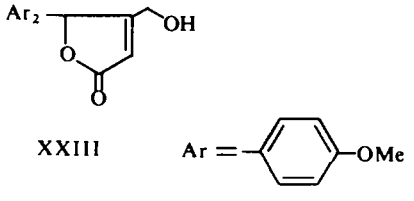
employed was similar to that used successfully for X and XI and is illustrated in Chart II. Structural assignments are supported by IR, UV and NMR spectra. All compounds had satisfactory elemental analyses.

[13] See D. S. Tarbell and P. D. Bartlett, *J. Am. Chem. Soc.* **59**, 407 (1937) for the related stereospecific brominative lactonizations of sodium dimethylmaleate and dimethylfumarate.

Chart II



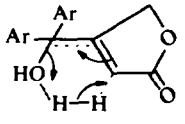
Conversion of the half-ester intermediate XVIII-a from the Stobbe condensation of 4,4'-dimethoxybenzophenone and diethyl succinate to its potassium salt permitted selective reduction of the ester functionality with lithium borohydride. Acidification of the reaction mixture gave the benzhydrylidene-butyrolactone XX in good yield. In contrast to the piperonylidene analog IV-a, the hydroxyacid XIX-a was not isolated. Its sodium salt XIX-b, however, again in contrast to the piperonylidene case, was available by saponification of the lactone XX. Bromination of this sodium salt in aqueous solution with an equivalent of bromine gave a crude bromolactone



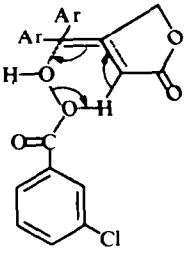
XXI which, without further purification, was dehydrobrominated with aqueous base. The α,β-unsaturated hydroxylactone XXII was obtained in fair yield. Interestingly, again in contrast to the piperonyl series, the thermodynamically favored isomer was obtained directly, rather than the kinetically controlled product XXIII of the brominative lactonization.

Attempted hydrogenation of the unsaturated lactone XXII in ethyl acetate at atmospheric pressure and room temperature, gave not the expected saturated lactone XVII but instead the benzhydrylidenelactone XX in good yield. Oxidation of XX with metachloroperbenzoic acid returned the α,β-unsaturated lactone XXII. Although this novel oxidation-reduction cycle may be rationalized by a number of trivial two-stage reaction sequences, the concerted mechanisms illustrated in Scheme III

Scheme III



XXII



XX

are worthy of note, if only for emphasis of the possible mechanistic similarities of the oxidation and reduction processes. Other than the mild conditions under which the reactions proceed, no definitive evidence supporting their viability is available.

EXPERIMENTAL[14]

Ethyl 2-(3,4-*methylenedioxybenzylidene*) *succinate* (III-a). A crystalline solid, m.p. 85–87°, was prepared in 43% yield from piperonal and diethyl succinate according to the method of Cornforth,[15] using the modification of Johnson and Daub[12] in the isolation of the half ester; ε_{236}^{MeOH} 17,200; ε_{236}^{MeOH} 12,500; ε_{315}^{MeOH} 13,900; ν_{max}^{Nujol} 5·81, 5·91 μ. (Found: C, 60·14; H, 5·14; Neut. Eq. 278. Calc. for $C_{14}H_{14}O_6$: C, 60·43; H, 5·07%; Neut. Eq., 278).

3-(3,4-*Methylenedioxybenzylidene*)4-*hydroxybutanoic acid* (IV-a). A soln of 39·2 g (0·14 mole) of III-a in 150 ml EtOH was neutralized with 282 ml 0·5N alcoholic KOH. After removal of the solvent at reduced press, the glassy residue was suspended in 500 ml dry 1,2-dimethoxyethane and refluxed with 7·5 g (0·36 mole) $LiBH_4$ for 20 hr. After removal of the solvent, the solid residue was dissolved in water, acidified to pH 1, and extracted with $CHCl_3$. Crystallization from $CHCl_3$–ether gave 19·2 g (58%) of a white solid, m.p. 99–101° (transition), resolidifying and melting at 144–145°; ν_{max}^{Nujol} 2·98, 5·90 μ; ε_{264}^{MeOH} 12,700; ε_{298}^{MeOH} 6800. The NMR spectrum in DMSO (vs. Me_4Si) displayed a singlet (1H) at 3·43 τ (ArCH=), a doublet (2H) at 6·05 τ (=C(H)—CH_2OH) and a singlet (2H) at 6·80 τ (—CH_2COOH). (Found: C, 61·34; H, 5·13; O, 33·99; Neut. Eq., 237. Calc. for $C_{12}H_{12}O_5$: C, 61·01; H, 5·12; O, 33·87%; Neut. Eq., 236.)

3-(3,4-*Methylenedioxybenzylidene*)4-*hydroxybutanoic acid lactone* (V). On standing the mother liquor separated 4·0 g (13%) of the crystalline lactone, m.p. 148–150°; ν_{max}^{Nujol} 5·67 μ; ε_{275}^{MeOH} 11,700; ε_{306}^{MeOH} 8700.

[14] All m.ps are uncorrected. IR, UV and NMR spectra were obtained on a Perkin-Elmer Infracord, Perkin-Elmer 202, and Varian HR-60 spectrometer, respectively; only absorption maxima pertinent to structural assignments are indicated.

[15] J. W. Cornforth, G. K. Hughes, and F. Lyons, J. Proc. Roy. Soc. N.S. Wales, **72**, 228 (1939).

The NMR spectrum in $DCCl_3$ (Me_4Si) displayed a quartet (1H, J = 2·1 c/s) at 3·72 τ (ArCH=), a quartet (2H, J = 2·1 c/s) at 5·07 τ (=C—CH_2O—) and a quartet (2H, J = 2·1 c/s) at 6·60 τ (=C—CH_2CO). (Found: C, 65·80; H, 4·65; O, 29·45. Calc. for $C_{12}H_{10}O_4$: C, 66·05; H, 4·62; O, 29·33%.)

3-(3,4-*Methylenedioxybenzyl*)4-*hydroxy-2-butenoic acid lactone* (VI-a). A soln of 600 mg of V (2·75 mmoles) in 20 ml 1,2-dimethoxyethane and 6 ml 10M HCl was stirred under N_2 for 19 hr. After removal of the organic solvent under reduced press, the aqueous residue was extracted with ether. Removal of the ether left a colorless oil which was chromatographed over silica gel. Elution with benzene gave 193 mg (32%) of VI, m.p. 65–66°; ν_{max}^{Nujol} 5·78; ε_{288}^{MeOH} 4800. The NMR spectrum revealed a multiplet (1H) with long range coupling at 4·23 τ (—C=CH—CO), a multiplet (2H) with the same long range coupling pattern at 5·33 τ (=C—CH_2—O—), and a singlet (2H) at 6·35 τ ($ArCH_2$—). (Found: C, 66·21; H, 4·69; O, 29·20. Calc. for $C_{12}H_{20}O_4$: C, 66·05; H, 4·62; O, 29·33%.)

Compound

VI-B. After the addition of 12·4 ml of 0·5N NaOH (6·2 meq) to a suspension of 4·30 g (19·7 mmoles) of V in 30 ml MeOH, the soln turned basic to phenolphthalein. After removal of the MeOH and extraction of the aqueous suspension with $CHCl_3$, 2·37 g (53%) of VI, m.p. 64–65°, crystallized on dilution with ether. Its m.p. was undepressed on admixture with material obtained from method A; the IR spectra of VI-A and VI-B were superimposable.

3-*Hydroxymethyl*-3-*bromo*-4-(3,4-*methylenedioxyphenyl*)4-*hydroxybutanoic acid lactone* (VII). A suspension of 11·5 g (48·5 mmoles) of IV-a in 100 ml water was neutralized with 97 ml 0·5N NaOH and the resulting clear soln diluted with 80 ml MeOH. A soln of 7·8 g (48·5 mmoles) Br_2 in 50 ml MeOH was rapidly added and after 30 min the MeOH removed under reduced press. Extraction of the resulting aqueous suspension with $CHCl_3$ and dilution with ether gave 13·4 g (87%) of VII, m.p. 127–128°; ν_{max}^{Nujol} 2·88, 5·63 μ. The NMR spectrum in DMSO (Me_4Si) displayed a singlet (1H) at 4·32 τ (ArCH—O), a singlet (2H) at 6·21 τ (—CH_2OH), and a singlet (2H) at 7·50 τ (—CH_2CO—). (Found: C, 45·69; H, 3·60; Br, 25·46; O, 25·18. Calc. for $C_{12}H_{11}BrO_5$: C, 45·72; H, 3·52; Br, 25·35; O, 25·37%.)

3-*Hydroxy*-4-(3,4-*methylenedioxyphenyl*)4-*hydroxy-2-butenoic acid lactone* (VIII). A suspension of 11·4 g (36·2 mmoles) of VII in 80 ml acetone was titrated in the presence of phenolphthalein with a stoichiometric equiv of 0·5N NaOH (72·4 ml). After removal of the acetone under reduced press, the resulting yellow emulsion gave, on extraction with $CHCl_3$ and dilution with ether, 6·72 g (80%) of VIII, m.p. 123·5–125°; ν_{max}^{Nujol} 2·98, 5·77 and 6·10 μ; ε_{288}^{MeOH} 4100. The NMR spectrum in DMSO (Me_4Si) displayed a multiplet with very fine splitting (1H) at 3·81 τ (—C=CH—CO), a triplet (1H, J = 6 c/s) at 4·62 τ (ArCH—O), and a broad complex multiplet (2H) at 5·90 τ (—C=C—CH_2OH). (Found: C, 61·67; H, 4·36; O, 34·16. Calc. for $C_{12}H_{10}O_5$: C, 61·54; H, 4·30; O, 34·16%.)

3-*Hydroxymethyl*-4-(3,4-*methylenedioxyphenyl*)4-*hydroxybutanoic acid lactone* (X). A soln of 234 mg (1 mmole) of VIII in 30 ml AcOEt was hydrogenated in the presence of 20 mg 5% Pd–C in a microhydrogenation apparatus at room temp and atm press; a stoichiometric equiv of H_2 was absorbed in 2½ hr. After filtration and evaporation of the solvent under reduced press, 230 mg (97%) of a colorless oil was obtained. Attempts to crystallize this material were unsuccessful; however, it exhibited one spot on TLC over silica gel G. R_f: 0·38 ($CHCl_3$–MeCN, 4:1); ν_{max}^{liq} 2·95, 5·62 μ. No double bond absorption was visible in the IR at 6·10 μ. The NMR spectrum in $DCCl_3$ (Me_4Si) displayed a doublet (1H, J = 6 c/s) at 4·45 τ (ArCH—O—), a doublet (2H, J = 7 c/s) at 6·67 τ (—CH_2OH), a doublet (2H, J = 4·5 c/s) at 7·33 τ (—CH_2—CO), and a broad multiplet (1H) at 7·80 τ (—CH).

3-(α-*Hydroxy*-3,4-*methylenedioxybenzyl*)4-*hydroxybutanoic acid lactone* (XI). When a soln of 1·0 g (4·23 mmoles) of X in 5 ml benzene was chromatographed over 60 g Woelm neutral alumina (activity III), elution with benzene–$CHCl_3$ (1:2) and recrystallization from $CHCl_3$–ether yielded 800 mg (80%) of a crystalline solid, m.p. 133–134°; ν_{max}^{Nujol} 3·00, 5·74 μ; R_f 0·53 on silica gel G ($CHCl_3$–MeCN, 4:1). The

NMR spectrum in $DCCl_3$ (Me_4Si) displayed a doublet (1H, J = 7 c/s) at 5·47 τ (ArCH—OH), a doublet (2H, J = 7 c/s) at 5·65 τ (—CH_2—O—), a doublet (2H, J = 7 c/s) at 7·70 τ (—CH_2—CO), and a broad multiplet (1H) at 7·78 τ (—CH). (Found: C, 61·07; H, 5·07; Sapon. Eq. 236. Calc. for $C_{12}H_{12}O_5$: C, 61·01; H, 5·12%; Sapon. Eq. 236.)

3-Methyl-4-(3,4-methylenedioxyphenyl)4-hydroxybutanoic acid lactone (IX). A soln of 4·88 g (20·8 mmoles) of VIII in 100 ml AcOEt was hydrogenated in a Parr apparatus at 64 psi in the presence of 300 mg 5% Pd–C at room temp. After 4 hr, the catalyst was filtered off and the solvent evaporated under reduced press. The colorless oil residue was chromatographed over Woelm neutral alumina (activity III). Elution with benzene gave 2·0 g (44·5%) of a colorless oil, ν_{max}^{liq} 5·62, 7·26 μ. The NMR spectrum in $DCCl_3$ (Me_4Si) displayed a doublet (1H, J = 7 c/s) at 4·49 τ (ArCH—O), a very complex multiplet (2H) at 7·08 to 7·25 τ (—CH_2—CO), a quartet (1H, J = 11 c/s) with additional fine splitting at 7·56 τ (—CH), and a doublet (3H, J = 7 c/s) at 9·28 τ (—CH_3). (Found: C, 65·30; H, 5·46. Calc. for $C_{12}H_{12}O_4$: C, 65·44; H, 5·49%.)

Further elution with $CHCl_3$ gave on dilution with ether 1·15 g (25%) of a crystalline solid, m.p. 131–132°, identical in all respects to a sample of XI.

3-(3,4-Methylenedioxybenzoyl)4-hydroxybutanoic acid lactone (XII). A soln of 118 mg (0·5 mmoles) of XI in 20 ml acetone distilled from $KMNO_4$ was titrated under N_2 with Jones reagent (4·0 meq/ml).[16] After a permanent orange coloration was obtained, the acetone was removed under reduced press and the residue diluted with water and extracted with $CHCl_3$. Removal of the solvent and crystallization from $CHCl_3$–ether gave 58 mg (51%) of a crystalline solid, m.p. 117–118°, ν_{max}^{Nujol} 5·68, 6·01 μ; ε_{234}^{MeOH} 15,900; ε_{277}^{MeOH} 6910; ε_{314}^{MeOH} 8700. The NMR spectrum in $DCCl_3$ (Me_4Si) displayed a complex multiplet (3H) between 5·35 and 5·68 τ (ArCO—CH—CH_2O) and a doublet (2H) at 7·14 τ (—CH_2COO) with long range coupling: (Found: C, 61·45; H, 4·29. Calc. for $C_{12}H_{10}O_5$: C, 61·54; H, 4·30%.)

3-(α-Methoxy-3,4-methylenedioxybenzyl)4-hydroxybutanoic acid lactone (XV-a). A soln of 276 mg of X (1·17 mmoles) and 60 ml of 50% aqueous MeOH was adjusted to pH 1·2 with perchloric acid and refluxed for 20 hr. The soln was sampled at selected time intervals, spotted on thin layer plates coated with silica gel G, and developed with a 4:1 $CHCl_3$–MeCN soln. Reduction of the original hydroxy lactone spot was accompanied by the development of a new less polar spot (R_f 0·70). At 20 hr only this new spot was evident. The MeOH was removed from the soln under reduced press and the residue extracted with $CHCl_3$. After washing this extract thoroughly with $NaHCO_3$ aq, solvent was removed and the colorless oil residue chromatographed over Woelm neutral alumina. Elution with benzene gave 93 mg (32%) of a colorless oil, ν_{max}^{liq} 5·63, 9·18 μ; no OH absorption was evident in the IR spectrum. The NMR spectrum in $DCCl_3$ (Me_4Si) displayed a broadened doublet (2H, J = 7 c/s) at 6·09 τ (—CH_2—O—) a doublet (1H, J = 7 c/s) at 5·69 τ (ArCH—OMe), a doublet (2H, J = 7 c/s) at 7·37 τ (—CH_2—CO), a slightly broadened singlet (1H) at 7·72 τ (—CH), and a singlet (3H) at 6·87 τ (—OCH_3).

Compound XV-b. A soln of 132 mg (0·56 mmoles) of XI in 40 ml 50% aqueous MeOH was adjusted with perchloric acid to pH 1·2 and refluxed for 20 hr. TLC indicated a disappearance of the original spot and the development of a less polar spot R_f 0·70, under the conditions described above. A similar work-up gave after chromatography over alumina and elution with benzene, 57 mg (41%) of a colorless oil. Its IR spectrum was superimposable with that of XV-a.

Ethyl 2-(4,4'-dimethoxybenzhydrylidene)succinate (XVIII-a). An orange oil ν_{max}^{liq} 5·73, 5·84 μ, neut. equiv. 386 (calc. 370) was prepared from 4,4'-dimethoxybenzophenone and diethyl succinate according to Daub and Johnson[17] in 73% yield. A sample of this oil, maintained at 56° and 0·2 mm overnight, was submitted for elemental analysis. (Found: C, 68·01; H, 5·92; O, 25·92. Calc. for $C_{21}H_{22}O_6$: C, 68·09; H, 5·99; O, 25·92%.)

3-(4,4'-Dimethoxybenzhydrylidene)4-hydroxybutanoic acid lactone (XX). A soln of 92·0 g (0·248 mole) of XVIII-a in 200 ml EtOH was neutralized with 375 ml 0·5N alcoholic KOH. After removal of the solvent at reduced press, the glassy residue XVIII-b was suspended in 600 ml dry 1,2-dimethoxyethane and

[16] K. Bowden, I. M. Heilkon, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

[17] G. H. Daub and W. S. Johnson, *J. Am. Chem. Soc.* **72**, 501 (1950).

refluxed with 10 g (0·48 mole) $LiBH_4$ overnight. After removal of the solvent, the residue was dissolved in water, acidified to pH 1, and extracted with $CHCl_3$. Crystallization from $CHCl_3$–ether gave 53·5 g (69%) of a white solid, m.p. 131–133°, ν_{max}^{Nujol} 5·68 μ; ε_{249}^{MeOH} 17,600; ε_{263}^{MeOH} 16,800. The NMR spectrum in $DCCl_3$ (vs. Me_4Si) displayed a triplet (2H, J = 2·0 c/s) at 5·28 τ (—CH_2—O—), and a triplet (2H, J = 2·0 c/s) at 6·67 τ (—CH_2—CO—). (Found: C, 73·31; H, 5·85; O, 20·67. Calc. for $C_{19}H_{18}O_4$: C, 73·53; H, 5·85; O, 20·62%.)

3-(α-*Hydroxy-4,4'-dimethoxybenzhydryl*)*4-hydroxy-2-butenoic acid lactone* (XXII). A soln of 10·0 g (0·032 mole) XX in 250 ml 1,2-dimethoxyethane was refluxed with 64·5 ml (0·032 equivs) of 0·5N NaOH for 1½ hr. After evaporation of the solvent and extraction of the aqueous residue (XIX-b) with ether, a soln of 5·16 g (0·032 mole) Br_2 in 80 ml CH_2Cl_2 was added dropwise under N_2. Separation of the organic layer and evaporation of the solvent gave 13·1 g of an orange oil, ν_{max}^{liq} 2·98, 5·60 μ. No further purification was attempted.

A suspension of 11·5 g (0·028 mole) of this crude XXI in 200 ml acetone was titrated with a stoichiometric equiv of 0·5N NaOH (56·4 ml). After removal of the acetone under reduced press, the aqueous soln gave, on extraction with ether and dilution with benzene, 2·85 g (31%) of XXII, m.p. 104–110°; ν_{max}^{Nujol} 2·99, 5·78, 6·12 μ; ε_{275}^{MeOH} 4240; ε_{282}^{MeOH} 3470. Recrystallization from EtOH–ether gave a 70% recovery of colorless crystals, m.p. 112–115°, which were spectrally identical (ε_{275}^{MeOH} 4050; ε_{282}^{MeOH} 3320).[18] The NMR spectrum in $DCCl_3$ (vs. Me_4Si) displayed a singlet (1H) at 4·33 τ (=CH—CO—) and a singlet (2H) at 5·25 τ (—CH_2—O—). (Found: C, 69·73; H, 5·43. Calc. for $C_{19}H_{18}O_5$: C, 69·92; H, 5·56%.)

Catalytic hydrogenation of XXII. A soln of 6·52 g (0·020 mole) of XXII in 75 ml AcOEt was hydrogenated in the presence of 300 mg of 5% Pd-C in a micro-hydrogenation apparatus at room temp and atm press; a stoichiometric equiv of H_2 was absorbed in 3½ hr. After filtration and evaporation of the solvent under reduced press, 4·90 g (79%) of the residue crystallized from $CHCl_3$–ether, m.p. 133–134°, undepressed on admixture with XX; its IR spectrum was superimposable with that of XX.

Reaction of XX *with metachloroperbenzoic acid.* A soln of 9·30 g (0·030 mole) of XX and 7·27 g (0·036 mole—85% purity) metachloroperbenzoic acid in 80 ml $CHCl_3$ was stirred at room temp for 22 hr. Thorough washing of the white slurry with Na_2CO_3aq and evaporation of the solvent under reduced press gave an oily residue which was chromatographed over 300 g Woelm neutral alumina (activity I). Elution with $CHCl_3$ and recrystallization from benzene–ether gave 5·4 g (55%) of a white crystalline solid, m.p. 104–110°, undepressed on admixture with XXII; its IR spectrum was superimposable with that of XXII.

Acknowledgement—We are indebted to Dr. Perry Kirklin for assistance in interpreting the NMR spectra.

[18] These ultraviolet absorptions are in accord with that expected for a *bis-p*-alkylanisole and do not indicate conjugated impurities; see, e.g. *p*-methylanisole, *Organic Electronic Spectral Data* Vol. 1, 1946–1952. Interscience, New York (1960).