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OXYGENATED DIENES AND THE SYNTHESIS OF METHYLENEDIOXYBIPHENYL DERIVATIVES*

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Abstract—New dienoate and trienoate esters **5**, **8**, **9** and **10** are described. Their preparation by the two standard variants of the Wittig reaction led to an uncommon reversal of utility in that the phosphorane procedure proved much superior to the phosphonate anion procedure. Reactivities of the new dienoate esters **8** and **10** and of the related diene aldehyde derivatives **3** and **4** toward several dienophiles were explored. Through the halolactonization reaction, selective protection of one carboxyl function in a tetrahydrophthalic acid derivative was achieved, allowing esterification of the other and removal of the first in an oxidative decarboxylation. The oxidative decarboxylation was brought about by 2,3-dichloro-5,6-dicyanobenzoquinone, a novel reaction for quinones. The combination of these reactions allowed selective syntheses of 2- and 3-piperonylbenzoic acids (**17** and **19**) and their ethyl esters (**18** and **20**) and of the parent 3,4-methylenedioxybiphenyl (**16**). Aspects of the NMR spectra of a number of these compounds are discussed, as they shed light on the rigid conformation expected for bridged halolactones.

FOR our research directed toward the synthesis of members of a particular structural family of *Amaryllidaceae* alkaloids, we required a number of substituted dienes bearing in the 1- and 4-positions a carboxyl function actual or masked and a masked OH group. Treatment of several such dienes with 3,4-methylenedioxy-β-nitrostyrene led to a number of new methylenedioxybiphenyl derivatives.[1] This paper presents the syntheses and some of the properties of the new dienes, and unequivocal syntheses, for the purpose of structure proofs, of the new methylenedioxybiphenyl derivatives. The latter syntheses illustrate the use of dichlorodicyanobenzoquinone in a novel role to effect oxidative decarboxylation.

Syntheses and characterization of the dienes. The dienes **3**, **4**, **8**, and **10** were prepared by extensions of known methods. Thus, hydrolysis of pyridine gave the known,[2] versatile intermediate sodio glutacondialdehyde (**1**); its lower homologue sodio malondialdehyde (**2**) was prepared by either of two reported hydrolyses,[3,4] of tetraethoxypropane or dimethylaminoacrolein. The known acetyl (**3**) and benzoyl (**4**) derivatives were prepared; and, in a test of the usefulness of the Wittig reaction applied to these sensitive aldehydes, the benzoyloxypentadienal was converted to the triene ester **5**. Even though **5** was obtained in poor yield, we studied the preparation of the related carboxylic esters **8** and **10** because of the great lability (see below) of Diels–Alder adducts of **3** and **4**.

* This work is taken in part from the Ph.D. Dissertation (1965) of E.J.J.G.

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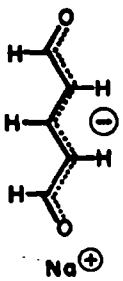

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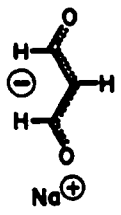

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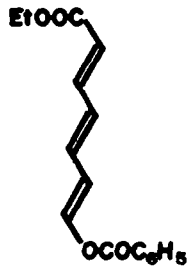
3: R = Ac
4: R = COC_6H_5



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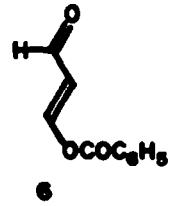

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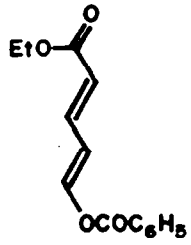

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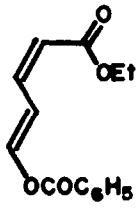

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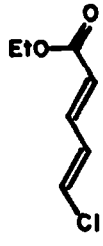

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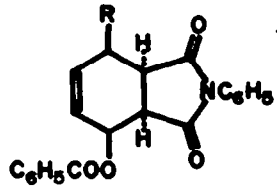
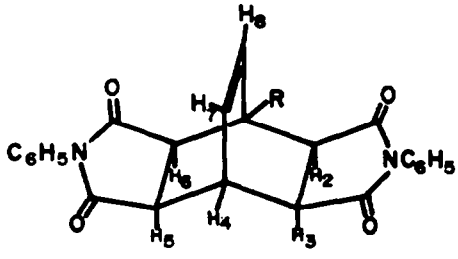
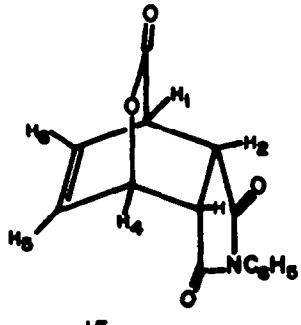


11: R = CHO
12: R = COOEt



13: R = CHO
14: R = COOEt



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Application of the Wittig reaction to the synthesis of esters **8** and **10** required the precursor aldehydes **6** and **7**, compounds which were readily made from the sodio malondialdehyde (**2**) by treatment, respectively, with benzoyl chloride and with phosgene.[5] We studied first the Wittig reaction of **6** with the anion of triethylphosphonoacetate, since the customary advantages of the phosphonate procedure[6] are well known. This reaction provides a clear exception to that generalization. Although the *trans : cis* isomer ratio (formation of **8** *vs* **9**) was solvent dependent, the combined yield was not appreciably so. The ratio of **8** to **9** varied from 11 : 1 in benzene to 4 : 1 in ether, to 1 : 1 in dimethoxyethane. But, as determined by VPC, the total diene yield was always in the range 10–12%, with the starting materials making up almost all the remainder. We do not have a proven explanation for this peculiar result, but it cannot

be attributed to low reactivity of the aldehyde carbonyl of **6**, because the normal Wittig procedure gives a good yield. We observed that, quite early in the addition of a solution of phosphonate anion to a solution of **6**, a yellow solid separated. We speculate that this solid arises by addition of the highly active phosphonate anion at some point other than the aldehyde carbonyl: perhaps in the Michael sense, to give an insoluble complex incapable of leading to product; and that this complex is destroyed by the subsequent aqueous treatment of the reaction mixture with regeneration of the starting materials. In any event, isolation of the desired *trans,trans* pentadienoate ester **8** from the reaction mixture, though possible, was not synthetically useful, and we turned to the original Wittig procedure using carbethoxymethylenetriphenylphosphorane.

The condensation of benzoyloxyacrolein (**6**) with carbethoxymethylenetriphenylphosphorane was examined at reflux in six solvents of various polarity from benzene to methanol, and the result was monitored by VPC. The condensation was appreciably more successful than that with the phosphonate anion, but the ratio of **8** to **9** was 1 : 1 and not particularly influenced by solvents. Since the mechanism of the condensation is known,[7] and formation of the betaine leading to the desired *trans* olefin is thought to be favored by a lower activation energy, we reasoned that the temperature of the boiling solvents was high enough to mask the energy differences in the formation of the two betaines. Consequently, we conducted the reaction in benzene at 0°, obtaining an isomer mixture in which the desired *trans* isomer was favored by a factor of at least 4 : 1, from which the product could readily be isolated pure in 50% yield.

Application of the same reaction conditions to the chloroacrolein (**7**) gave the ethyl 5-chloropentadienoate (**10**) in 55% yield.

For characterization and to gain insight into the Diels–Alder reactivity, several of the dienes discussed above were treated with phenylmaleimide. (Neither **3** nor **4** gave an adduct with maleic anhydride.) The difference in stability between the adducts of **4** and of **8** with phenylmaleimide is illuminating: in boiling benzene the initial adduct (**12**) with the diene ester **8** was stable, whereas that (**11**) expected from the diene aldehyde **4** was not found. It lost benzoic acid to give a new diene trapped by the addition of a second molecule of phenylmaleimide to give **13**. The corresponding loss of benzoic acid from **12** required the temperature of boiling xylene to proceed even slowly: bisadduct **14** was the product. The reaction of phenylmaleimide with diene ester **10** was much slower, and even at the low temperature of boiling benzene the loss of hydrogen chloride was sufficiently facile that only bisadduct **14** was obtained.

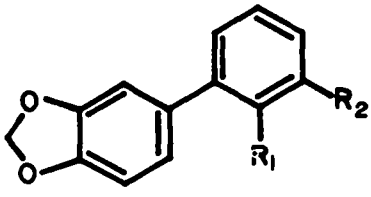
Though a number of these compounds had been previously prepared and characterized by classical means, we examined their NMR spectra for instructive points. The simplicity of the NMR spectrum of **1** in DMSO solution attests to its depicted symmetry. It shows only three resonances: a doublet, $J=9$ Hz, at $\delta=8{\cdot}70$ ppm for H-1,5; a triplet, $J=13$ Hz, at 7·17 ppm for the central H; a doublet of doublets at 5·20 ppm for H-2,4. NMR spectra of the acetyl and benzoyl derivatives (**3** and **4**) were consistent with their being pure compounds (and therefore almost certainly only *trans,trans* isomers): the respective aldehyde hydrogens appeared as simple doublets, at 9·54 ppm, $J=8$ Hz; and at 9·61, $J=7{\cdot}5$ Hz.

The same simplicity characterizes the spectra of **6** and **7**. The coupling constant for H-3, a doublet, proves the *trans* stereochemistry: in **6**, H-3 appears at 8·38 ppm, $J=12{\cdot}7$ Hz; in **7** it appears at 7·48, $J=13{\cdot}5$ Hz. The NMR spectra of the three

diene esters **8**, **9** and **10** were too complex for analysis by inspection. Structures were assigned to **8** and **9** on the basis of differences in m.p., UV absorption, and absence from the IR spectrum of **8** of a strong band at 11·61 μm characteristic of out-of-plane vibrations of hydrogen on a *cis*-disubstituted double bond, present in the spectrum of **9**.

NMR spectra of Diels–Alder derivatives **13** and **14** were difficult to obtain, owing to their low solubility. Features only poorly distinguishable in trifluoroacetic acid solution spectra of the two taken on a Varian A-60 were finally seen clearly in computer accumulated spectra of a $CDCl_3$ solution of **14** At 100 MHz. They were: 1·35 ppm, triplet: $\underline{CH_3}CH_2O$—; 3·24, doublet of doublets: H-3,5, $J_{2,3}=J_{5,6}=8{\cdot}5$ Hz, $J_{3,4}=J_{4,5}=3{\cdot}0$; 3·62, doublet: H-2,6, $J_{2,3}=J_{5,6}=8{\cdot}8$; 3·99, two overlapping triplets of doublets: H-4, $J_{3,4}=J_{4,5}=3{\cdot}0$, $J_{4,7}=6{\cdot}0$, $J_{4,8}=1{\cdot}2$; 4·40, quartet: $CH_3\underline{CH_2}O$—; 6·32, doublet of doublets: H-7, $J_{4,7}=6{\cdot}5$, $J_{7,8}=8{\cdot}5$; 6·83, poorly resolved doublet of doublets: H-8, $J_{7,8}=9{\cdot}0$, $J_{4,8}$ not directly determinable; 7·04–7·42, multiplet, $NC_6\underline{H_5}$.

Synthesis of methylenedioxyphenyl derivatives. Dienes **3** and **4** were too unstable to react with methylenedioxynitrostyrene. Dienes **8** and **10** gave adducts which were not stable to the reaction conditions, and gave rise to ethyl 2- and 3-piperonylbenzoate (**18** and **20**).[1] Despite the simplicity of these compounds, they were unknown prior to this work, and we sought an unequivocal synthesis of them.



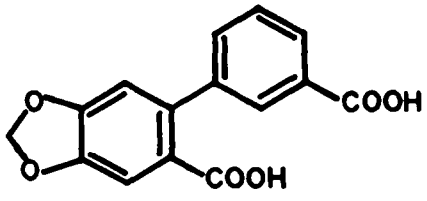
16: $R_1 = R_2 = H$

17: R_1 = COOH, R_2 = H

18: R_1 = COOEt, R_2 = H

19: R_1 = H, R_2 = COOH

20: R_1 = H, R_2 = COOEt



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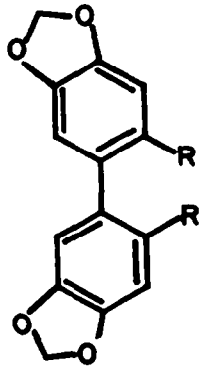

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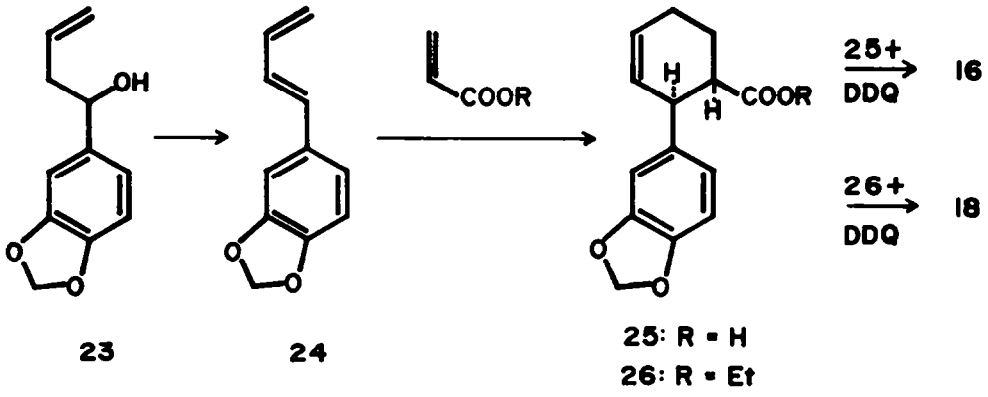
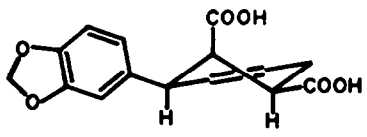


There are a number of syntheses for compounds containing a methylenedioxyphenyl ring. Compounds of the type represented by **22** have been intensively investigated by Dallacker and his colleagues.[8] The Ullmann reaction is a principal tool in this field; and it was used in the synthesis, for structure proof, of 4,5-methylenedioxybiphenyl-2,3′-dicarboxylic acid (**21**),[9] the known compound closest in structure to those described herein. A different, useful route to compounds in this series is that based on Diels–Alder additions to 1,4-diacetoxybutadiene.[10]

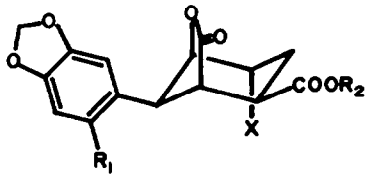
Our synthesis involved addition of acrylic acid or maleic anhydride to 1-piperonylbutadiene (**24**) generated *in situ* from 1-piperonylbut-3-enol-1 (**23**).[11] The former addition led smoothly, as one would expect from the addition of acrylic acid to 1-phenylbutadiene,[12] to *cis*-2-piperonyl-1,2,5,6-tetrahydrobenzoic acid (**25**). Addition of ethyl acrylate to **24**, followed by distillation of the product at 160°, gave a stereoisomeric mixture of **26** and its *trans* epimer (two ethoxyl groups in the NMR spectrum). The acid **25** was stereochemically homogeneous, however: esterification with diazoethane gave only **26**. Dehydrogenation of the epimeric mixture of esters or of pure **26** with dichlorodicyanobenzoquinone (DDQ) gave authentic **18**, identical to the suspected ethyl 2-piperonylbenzoate obtained from the reaction of methylenedioxynitrostyrene with dienes **8** and **10**.[1] Saponification of the aromatic ester afforded the crystalline 2-piperonylbenzoic acid (**17**).

A key observation making possible a synthesis of ethyl 3-piperonylbenzoate (**20**) was an attempted preparation of 2-piperonylbenzoic acid directly by the DDQ oxidation of the tetrahydrobenzoic acid **25**. The result was an oxidative decarboxylation to 3,4-methylenedioxybiphenyl (**16**). We know of no report to date of an oxidative decarboxylation by DDQ or similar reagent, but Jackman, in his review of dehydrogenation reactions,[13] suggested that a hydroaromatic carboxylate anion might so react.

The application of such an oxidative decarboxylation to a suitable derivative of the piperonylbutadiene–maleic anhydride adduct (**27**) should lead to the desired ethyl 3-piperonylbenzoate. The obvious derivative would be 1-ethoxycarbonyl-3-piperonyl-1,2,3,6-tetrahydro-2-benzoic acid (**33**). This dicarboxylic acid mono ester was selectively prepared by protection of the 2-carboxyl function as a halolactone, esterification of the 1-carboxyl, and regeneration of the 2-carboxyl from the halolactone.



27



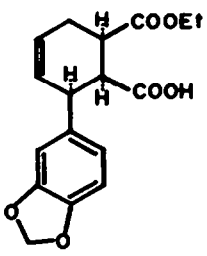
28: R_2 = H, R_1 = X = Br

29: R_1 = R_2 = H, X = I

30: R_1 = H, R_2 = Et, X = Br

31: R_1 = H, R_2 = Et, X = I

32: R_1 = H, R_2 = OtBu, X = I



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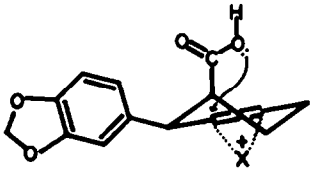

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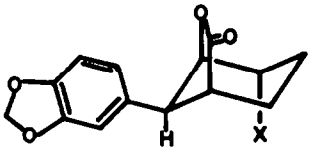
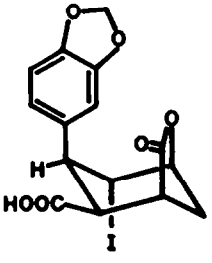


35: X = Br

36: X = I



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Thus, the known,[11] all *cis* adduct **27** gave, on suitable treatment with halogen or equivalent, haloketone acid **28–30**. van Tamelen and Shamma[14] have shown that the γ-lactone is formed even when there is apparent possibility of δ-lactone formation. That such a lactone formation would be facile in our system was first suggested to us by the formation of bromolactone **35** when we attempted to obtain **17** by NBS oxidation of **25** in CCl_4. That lactone, **35**, was of course obtained in much better yield by the use of bromine in mixed $CHCl_3$—CCl_4. Owing to the much lower solubility of the dicarboxylic acid **27** in halogenated solvents, we treated **27** first with bromine in aq. bicarbonate. While this gave bromolactonization, it led also to bromination of the aromatic ring, to give **28** [NMR spectrum: 2 aromatic hydrogens only, sharp singlets at 6·78 and 7·32 ppm, width at half-eight <0·8 Hz; from inferred very small *J*, hydrogens must be *para*].

To avoid halogen attack on the activated piperonyl ring, we then tried iodolactone formation. Formation of the simple iodolactone **36** by reaction of **25** with potassium triiodide in aqueous bicarbonate was satisfactory. Application of the same transformation to **27** gave the lactone acid **29** in 70% yield. Although both theoretical considerations and NMR spectroscopy (*vide infra*) indicated that the reaction had proceeded uniquely in the desired sense to tie up only the 2-carboxyl, we chose to interrelate **29** and **36** chemically. To that end we prepared the t-butyl perester **32** and subjected it to the free radical decomposition—decarboxylation to afford the same iodolactone **36** as that obtained from the simple monoacid **25**.

Iodolactone acid **29** was converted to its ethyl ester **31**, opened readily by zinc to the cyclohexenecarboxylic acid **33**, and smoothly oxidized and decarboxylated by

DDQ to authentic **20**. The identity of suspected **20** from the reaction of methylenedioxynitrostyrene with dienes **8** and **10** was thus demonstrated. The ester was readily saponified to the crystalline 3-piperonylbenzoic acid (**19**).

The preparation of the biphenyl ester **20** was performed with yield comparable to that from the stepwise procedure above, but with much less time and effort, as follows. To bring about bromolactonization of **27** without attendant ring bromination, it was necessary to avoid the highly polar aqueous reaction conditions. Diacid **27** dissolved slowly, as it reacted, at the boiling point in a large volume of $CHCl_3$. Bromination was thus performed; the attendant hydrogen bromide released served to catalyze the esterification of the remaining carboxyl directly using the 0·75% of ethanol present as preservative in the large volume of $CHCl_3$. The identity of the product ester bromolactone **30** was checked by IR and NMR spectroscopy, but it was most readily carried directly on by treatment with zinc, followed by DDQ oxidation of the crude monoester **33** to give **20** in 22% overall yield from **27**.

Evidence for the halolactone structures. As is uniformly the case for simple β,γ- or γ,δ-unsaturated acids,[14] or for more complex substances in which the two ends of the γ,δ-double bond are fixed in space at quite different distances from the carboxyl group,[15] the halolactones we prepared were all γ-lactones, as was readily demonstrated by their IR spectra. This fact, together with the concept of axial addition to olefins, uniquely defines the structure and stereochemistry of the two simple halolactones **35** and **36**. Their NMR spectra were very informative of their molecular geometry. The most salient feature of the spectrum (Fig. 1) is an apparent singlet at 3·94 ppm. Since there is no possibility, barring a deep-seated rearrangement, for a carbon bearing a single hydrogen to be present and not flanked by adjacent carbons bearing hydrogens, some special angular distortion must exist such that one hydrogen falls near zero J on the Karplus curve.[16] Consideration of this observation, together with the chemical shifts and multiplicities of the various peaks leads to the assignments in Table 1. It is apparent from models that both dihedral angles H_1—C—C—H_2 and H_2—C—C—H_3 are close to 90°. Owing to the presence of the axial bromine atom and to the

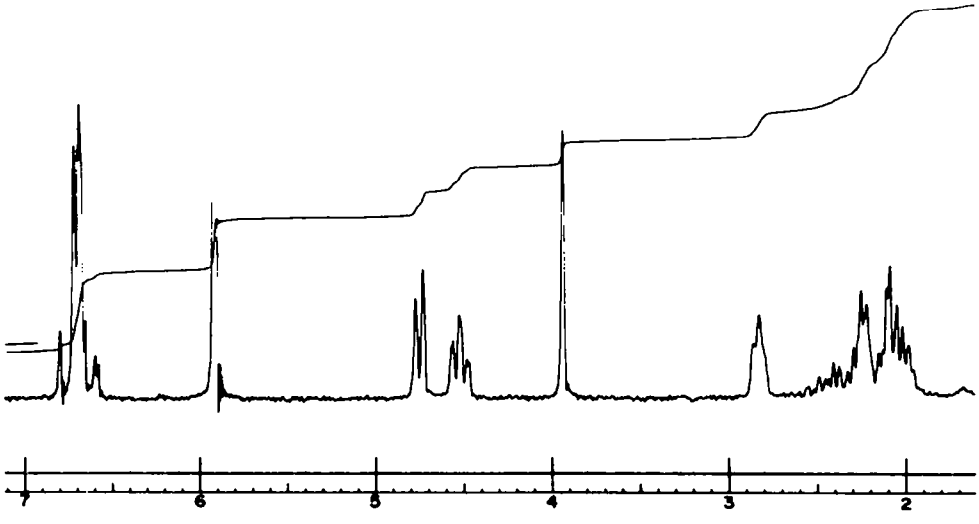

FIG. 1

different bond lengths and angles around oxygen *vs* those around carbonyl, the two angles are not the same. Including van der Waals interaction with the bromine and measuring on a Cenco–Petersen model, we estimate the angles to be H_1—C—C—H_2: $80 \pm 3°$, H_2—C—C—H_3: $74 \pm 3°$. If angle strain imposed by the bromine is ignored, the angles are even closer to 90°. The near-zero couplings to H-2 are thus plausible and the other assignments follow logically. Conclusions similar to these have recently been published.[17]

For halolactones from diacid **27** we must consider, *a priori*, four possibilities. Two of these are δ-lactones and may be excluded both on the basis of prior experience[14] and on examination of the IR spectra of the products. The two possible γ-lactones may not be thus distinguished, however, but the product of closure of the 1-carboxyl to C-5, as in **37**, was not expected to form. Reaction of the carboxyl with the developing electrophilic π-complex of the double bond and halogen (cf. **34**) requires it to be axial on the ψ-chair ring. Of the two ψ-chair conformations available to **27**, the favored one (shown) has the 2-carboxyl axial, the 1-carboxyl equatorial and the bulky piperonyl group ψ-equatorial. For the 1-carboxyl group to participate in lactonization, the ring would have to flip, not only forcing the 1-carboxyl axial but up against the 3-piperonyl

TABLE 1.[a] NMR SPECTRUM OF **35** AT 100 MHz

H	δ	J	Multiplicity[b]
5, 6	1·95–2·60		m
1	2·84		m
2	3·95	~0·0	s
4	4·53		m
3	4·76	4·4	d
OCH_2O	5·93		s
AR–H	6·10		m

[a] Compound in $CDCl_3$ solution unless otherwise stated; dissolved TMS as internal standard. Chemical shift in ppm downfield from TMS signal.

[b] s = singlet; d = doublet; m = multiplet.

TABLE 2. SELECTED NMR ABSORPTIONS OF HALOLACTONES

Compound	H-2	H-3	
	δ[a]	δ	J (Hz)
28[b]	4·15	5·20	4·5
29[b]	4·13	5·02	4·5
30	3·98	4·79	4·5
31	4·10	4·78	4·0
35	3·95	4·76	4·4
36	4·08	4·78	4·0

[a] singlet: width at half-height $\leqslant 2$ Hz.

[b] In DMSO soln.

group in a ψ-axial conformation. Such a strained conformation, required to lead to the transition state necessary for **37**, was expected to contribute insignificantly at moderate temperatures. That this was so was borne out by the NMR spectra of lactones **28–31**, all of which bore striking resemblance to those of **35** and **36**: they showed, in particular, the apparent singlet at $4{\cdot}06 \pm 0{\cdot}11$ ppm (see Table 2). The spectrum of **37** would not be expected to show such a singlet.

EXPERIMENTAL

M.ps and b.ps are uncorrected. M.ps were observed on a Nalge hot stage; except those marked (vac), which were observed with Anschütz thermometers in a modified Hershberg apparatus. IR spectra were measured on a Perkin–Elmer model 421 spectrophotometer; UV spectra were measured on a Cary model 11 MS spectrophotometer. The piperonyl bands seen in the IR spectra are those shown to be characteristic.[18] Microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

Solvent abbreviations: DME. 1,2-Dimethoxyethane; DMF. dimethyl formamide; DMSO. dimethylsulfoxide; THF. tetrahydrofuran.

Sodio 5-oxopenta-2,4-dienal (**1**)

This salt was prepared on a 2·5 mole scale as described by Baumgarten[2] and purified by the method of Schöpf.[19] Yellow-orange plates, m.p. >360°, were obtained in 37% yield; UV spectrum (water): 363 nm (52,100); NMR spectrum: see text.

Sodio 3-oxoacrolein (**2**)

Method A. 1,1,3,3-Tetraethoxypropane (200·8 g), 75 ml 1N HCl and 100 ml water were stirred vigorously for 1·25 hr at room temp. The resulting homogenous yellow soln was cooled in ice and adjusted to pH 10 with 5N NaOH. To the red soln was gradually added 2·0 l. acetone and colorless crystals separated. The ppt was filtered, washed with acetone and dried at room temp/15 mm for 12 hr. The salt was dissolved in 500 ml boiling MeOH, treated with charcoal and filtered. To the filtrate was slowly added 1·6 l. ether. The resulting colorless ppt was filtered and dried at 100°/15 mm for 24 hr to yield 42·2 g (49%) of sodio 3-oxoacrolein. The purity of the salt thus prepared[3] was demonstrated by comparison of its UV spectrum (in MeOH: 266 nm, (22,700)) with that obtained by Method B.

Method B. The salt was also prepared in 25% yield on a 15 mmole scale by the hydrolysis of 3-(N,N-dimethylamino)acrolein,[4] wherein NaOH was substituted for KOH. The pure sample was thrice recrystallized from EtOH and dried at 100°/1 mm; UV spectrum (MeOH): 266 nm (22,800); lit.[4] (H_2O) 267 nm (27,100) for potassio 3-oxoacrolein.

5-Acetoxypenta-trans-2-trans-4-*dieneal* (**3**)

Sodio 5-oxopenta-2,4-dieneal (2·66 g) was dissolved in 50 ml distilled water. The soln was cooled to 0° and 2·53 g Ac_2O was added. The reaction mixture was vigorously shaken for 5 min. The resulting brown ppt was filtered, dried and recrystallized from pet. ether (b.p. 30–60°) decolorizing carbon used) to yield 1·04 g (33%) of 5-acetoxypenta-*trans*-2-*trans*-4-dieneal as colorless needles: m.p. 74–75°, lit.[2] m.p. 75°; IR spectrum (CCl_4): 3·57, 3·68, 5·94 (—CHO), 5·67 (Ac) and 6·10 μm (enol double bond); UV spectrum (EtOH): 278 (37,000), 363 nm (4700); NMR ($CDCl_3$): 2·20 (s, 3H), 6·15–7·91 (m, 4H), 9·54 ppm (d, J = 8 Hz, 1H, —CHO).

An attempt to prepare an ethylene ketal by the usual method was unsuccessful: no water separated azeotropically and the reaction soln seemed to contain, in addition to starting materials, only tar.

5-Benzoyloxypenta-trans-2-trans-4-*dieneal* (**4**)

To a slurry of 2·99 g of anhyd sodio 5-oxopenta-2,4-dieneal in 20 ml pyridine was added 4·63 g benzoyl chloride. The reaction mixture was stirred for 5 min and the resulting yellow soln was poured onto 65 g crushed ice. A cream-colored ppt formed immediately. It was filtered, washed with water and recrystallized from EtOH–water to yield 4·32 g (86%) of 5-benzoyloxypenta-*trans*-2-*trans*-4-dieneal as yellow needles: m.p. 120–121°, lit.[2] m.p. 118°; IR spectrum (CCl_4): 3·56, 3·65, 5·86 (—CHO), 5·67 (C_6H_5CO), 6·03 μm (enol double bond); UV spectrum (MeOH): 238 (8600), 284 (34,000), 362 nm (3300);

NMR ($CDCl_3$): 6·00–8·30 (m, 9H, vinyl and aromatic protons), 9·61 ppm (d, J=7·5 Hz, 1H, —CHO).

Ethyl 7-*benzoyloxyhepta*-trans-2-trans-4-trans-6-*trieneoate* (**5**)

Triethyl phosphonoacetate (1·127 g) was added dropwise to a slurry of 0·121 g NaH in 5 ml n-heptane. The resulting yellow soln was stirred for 1 hr. A soln of 5-benzoyloxypenta-*trans*-2-*trans*-4-dieneal (1·008 g) in 20 ml n-heptane and 20 ml THF was added dropwise to the phosphonate anion soln. The resulting black soln was stirred for 1 hr, then concentrated to 25 ml *in vacuo*. To it 50 ml brine was added and the system was then extracted with 2 × 100 ml ether. The combined ether soln were washed with $NaHSO_3$ aq. then $NaHCO_3$ aq. The ether soln was dried over Na_2SO_4. Filtration followed by removal of the ether *in vacuo* yielded a yellow solid which was twice recrystallized from EtOH-water, then from $CHCl_3$–pet. ether (b.p. 30–60°) to yield 0·239 g (18%) ethyl 7-benzoyloxyhepta-*trans*-2-*trans*-4-*trans*-6-trieneoate as yellowish needles: m.p. 115–116°; IR spectrum (CCl_4): 3·25, 5·71, 5·81, 6·06, 6·14, 10·02, 10·47, 10·96, 14·18 μm; UV spectrum (MeOH): 235 (11,800), 308 nm (52,000); NMR spectrum ($CDCl_3$): 1·29 (t, J=7·5 Hz), 4·22 (q, J=7·5 Hz), 5·70–8·20 ppm (m, 11H, vinyl and phenyl H's). (Found: C, 70·35; H, 5·93. Calc for $C_{16}H_{16}O_4$: C, 70·58; H, 5·92%).

trans-3-*Benzoyloxyacrolein* (**6**)

To a rapidly stirred slurry, at 0°, of 17·8 g of sodio 3-oxoacrolein in 350 ml anhyd ether was added 22·5 g benzoyl chloride over a period of 15 min. The reaction mixture was stirred for 30 min at 0° and then for 45 min at room temp. After the addition of 1·0 ml pyridine the reaction mixture was stirred for 10 min and filtered. To the filtrate was added 1·5 l. pet. ether (b.p. 30–60°) and the resulting white crystalline material was filtered. Repeated concentration of the filtrate yielded additional crystals. The combined solids were recrystallized from pet. ether (b.p. 30–60°) to yield 19·5 g (69%) *trans*-3-benzoyloxyacrolein: m.p. 63·5–65°, lit.[3] 63°; IR spectrum (CCl_4): 3·26, 3·55, 3·66, 5·68, 5·90, 6·07, 10·55, 14·29 μm; UV spectrum (MeOH): 247 nm (28,600); NMR spectrum (CCl_4): 6·07 (d.d, $J_{1,2}$ = 7·9 Hz, $J_{2,3}$ = 12·7 Hz, 1H, —OCH=CH—), 8·38 (d, $J_{2,3}$ = 12·7 Hz, 1H, —OCH=CH—), 9·62 (d, $J_{1,2}$ = 7·9 Hz, 1H, —CHO), 7·27–8·27 ppm (m, 5H, Ph). The material displayed a marked tendency towards decomposition and was consequently stored on dry ice under N_2.

trans-3-*Chloroacrolein* (**7**)

trans-3-Chloroacrolein was prepared in 34% yield (b.p. 37–40°/30 mm, Lit.[5] 37–41/36 mm) on a 0·287 mole scale as described.[5] Because the compound showed a marked tendency to decomposition, a small quantity of hydroquinone was dissolved in it and it was stored over dry ice; IR spectrum (CCl_4): 5·94, 10·58, 11·72 μm; NMR spectrum (CCl_4): 6·45 (d.d, $J_{1,2}$ = 7·5 Hz, $J_{2,3}$ = 13·5 Hz, 1H, ClCH=CH—), 7·48 (d, $J_{2,3}$ = 13·5 Hz, 1H, ClCH=CH—), 9·57 ppm (d, $J_{1,2}$ = 7·5 Hz, 1H, —CHO).

Ethyl 5-*benzoyloxypenta*-trans-2-trans-4-*dienoate* (**8**)

An ice cold soln of 24·7 g *trans*-3-benzoyloxyacrolein and 48·7 g ethoxycarbonylmethylenetriphenylphosphorane in 200 ml dry benzene was stirred for 3 hr, during which time a deep red color developed. The soln was stirred for an additional 15 hr at room temp. Examination of the crude reaction mixture by TLC showed (lower limit) a 4 : 1 *trans,trans*- to *cis,trans*-diene isomer ratio. The benzene was removed *in vacuo*. The remaining red solid was thoroughly mashed with 200 ml ether and the insoluble triphenylphosphine oxide (29·4 g, 76% crude yield) was filtered. Concentration of the ether soln *in vacuo* to half its volume yielded 16·1 g crude diene, m.p. 65–75°, isolated by filtration. Repetition of the process yielded an additional 9·4 g m.p. 60–72°. Further concentration of the ether soln yielded no additional solid. The combined solids were recrystallized from EtOH–water to yield 17·1 g (50%) ethyl 5-benzoyloxypenta-*trans*-2-*trans*-4-dieneoate as colorless needles, m.p. 75·76°; IR spectrum (CCl_4): 5·72, 5·83, 6·06, 10·14 μm; UV spectrum (MeOH): 242 (shoulder; 16,000), 275 nm (38,700); NMR spectrum ($CDCl_3$): 5·70–6·60 (m, —CH=CH—CH=CH—), 7·00–8·20 ppm (m, —CH=CH—CH=CH— and phenyl H). (Found: C, 68·25; H, 5·90. Calc. for $C_{14}H_{14}O_4$: C, 68·28; H, 5·73%).

Ethyl 5-*benzoyloxypenta*-cis-2-trans-4-*dienoate* (**9**)

In 75 ml DME was slurried 2·28 g 53·2% NaH in mineral oil; thereto was added dropwise 11·15 g triethyl phosphonoacetate over 30 min. After 2 hrs' stirring, the phosphonate anion thus formed was

added dropwise to a soln of 8·80 g benzoyloxyacrolein in 100 ml DME. A yellow ppt began to form after the addition of the first few drops of phosphonate soln. By the end of the addition the mixture was dark and viscous. It was stirred 21 hr at room temp, then poured into water and extracted with ether. The dried ether extract yielded 11·0 g brown oil which was distilled at reduced pressure. The first fraction, 3·9 g (b.p. 100–125°/0·5 mm), was proven by VPC to consist principally of triethyl phosphonoacetate and 3-benzoyloxyacrolein. The second fraction, 3·0 g (b.p. 125–160°/0·5 mm) was shown by VPC to contain 50% of a 1:1 mixture of **8** and **9**. The all *trans*-isomer (yield estimated by VPC, 6%) was identified by retention time and IR spectrum, both identical with those of an authentic sample. The *cis,trans*-isomer was separated by VPC; it solidified to colorless needles (6% by VPC) on standing: m.p. 54–60°; IR spectrum (CS_2): 5·73, 5·82, 6·06, 10·15 and 11·61 μm; UV spectrum (MeOH): 235 (17,700), 273 nm (24,700); NMR spectrum ($CDCl_3$): 5·50–6·20 (m, —CH=C<u>H</u>—C<u>H</u>=CH—), 7·20–8·30 (m, —C<u>H</u>=CH—CH=C<u>H</u>— and phenyl H). The multiplets for the vinyl protons of the *trans*, *trans*- and *cis,trans*-isomers were distinctly different, but too complex for simple analysis.

Repetition of the experiment in solvent ether gave a 10% yield of the isomer mixture: 4:1 *trans,trans*- to *cis,trans*- by VPC. In benzene at 50° the experiment gave a 10% yield of an 11:1 mixture. Substantial quantities of the starting materials were present.

Ethyl 5-chloropenta-trans-2-trans-4-*dieneoate* (**10**)

To a soln of 8·5 g *trans*-3-chloroacrolein in 20 ml benzene at 0° was added a soln of 32·7 g ethoxycarbonylmethylenetriphenylphosphorane in 100 ml benzene over 1 hr. The cold bath was removed and the deep red reaction soln was stirred for 22 hr at room temp. Removal of the benzene *in vacuo* left a red semi-solid. This was thoroughly mashed with 200 ml ether and filtered to remove the insoluble triphenylphosphine oxide (19·5 g, 75%). The viscous red oil left on removal of the ether was distilled *in vacuo* to afford 8·3 g (55%) ethyl 5-chloropenta-*trans*-2-*trans*-4-dieneoate as a colorless liquid: b.p. 67–68°/1·5 mm. Examination of the diene by VPC showed it to be 97% pure. The analytical sample was prepared by VPC; m.p. 17–18·5°; $n_D^{25} = 1{\cdot}5127$; IR spectrum (CCl_4): 5·81, 6·11, 10·16 μm; UV spectrum (EtOH): 258 nm (31,000); (Found: C, 52·37; H, 5·57; Cl, 22·03. Calc. for $C_7H_9ClO_2$: C, 52·35; H, 5·65; Cl, 22·07%).

N-*Phenyl*-6-*benzoyloxy*-3-*carbethoxy*-cis-1,2,3,6-*tetrahydrophthalimide* (**12**)

A soln of 4·921 g ethyl 5-benzoyloxypenta-*trans*-2-*trans*-4-dieneoate, 3·474 g N-phenylmaleimide and 50 mg hydroquinone in 20 ml benzene was boiled under reflux for 29 hr. To the reaction soln was added 100 ml pet. ether (b.p. 30–60°) and the resulting gum was scratched until it solidified. The crude solid (7·8 g, m.p. 85–105°) was filtered off and recrystallized from MeOH–water to yield 5·567 g (67%) of **12** as colorless prisms: m.p. 130–131·5° and 160·5–162° (two polymorphs? identical spectra); IR spectrum (CCl_4): 5·63 (shoulder), 5·71, 7·14 μm; UV spectrum (EtOH): 227 (20,300), 275 (1400), 282 nm (1200); NMR ($CDCl_3$): 1·25 (t, J = 7 Hz, C<u>H</u>$_3$—), 3·45 (m, 1H, C<u>H</u>COO—), 3·75–3·95 (m, 2H, C<u>H</u>CON—), 5·76 (q, J = 7 Hz, —CH$_2$O—), 5·75 (m, 1H, C<u>H</u>O—), 6·39 (d.d with additional splittings, large J = 10 Hz, 2H, —C<u>H</u>=C<u>H</u>—), 6·40–8·20 (m, 10H, Ph protons). (Found: C, 68·91; H, 4·81; N, 3·35. Calc. for $C_{24}H_{21}NO_6$: C, 68·73; H, 5·05; N, 3·34%).

An experiment in which 1·247 g diene ester and 1·755 g maleimide were boiled with 25 mg hydroquinone in 10 ml xylene for 20 hr gave 14% recrystallized phthalimide **12** and 1·3% recrystallized **14**, m.p. 283–283·5° (*vide infra*).

1-*Formyl*-3,5,9,11-*tetraoxo*-4,10-*diphenyl*-4,10-*diaza*-2,6,7,8,12-cis-|5.5.2.0^{2,6}. O^{8,12}|*pentacyclotetradec*-13-*ene* (**13**)

A soln of 2·02 g 5-benzoyloxypenta-*trans*-2-*trans*-4-dieneal and 3·46 g N-phenylmaleimide in 10 ml benzene (freshly distilled from NaH), under N_2, was boiled under reflux for 22 hr, during which time a white ppt formed. The ppt was filtered and recrystallized from acetone–water to yield 2·72 g (64%) of **13**, as fine, colorless needles: m.p. 300·5–301·5 (vac): IR spectrum (KBr): 5·65, 5·78, 5·85, 7·20, 13·44 and 14·47 μm; UV spectrum (Dioxan): 219 nm (28,000); (Found: C, 70·54; H, 4·35; N, 6·69. Calc. for $C_{25}H_{18}N_2O_5$: C, 70·42; H, 4·25; N, 6·57%). The benzene filtrate yielded 0·75 g (61%) benzoic acid.

1-*Ethoxycarbonyl*-3,5,9,11-*tetraoxo*-4,10-*diphenyl*-4,10-*diaza*-2,6,7,8,12-cis[5.5.2.0^{2,6}.0^{8,12}]*pentacyclotetradec*-13-*ene* (**14**)

A soln of 1·172 g ethyl 5-chloropenta-*trans*-2-*trans*-4-dienoate and 1·254 g N-phenylmaleimide in 10

ml benzene was boiled for 95 hr. Addition of pet. ether (b.p. 30–60°) to the benzene soln caused the separation of an oil, which was triturated with MeOH. The material (0·332 g, m.p. 260–283°) insoluble in MeOH was recrystallized from acetone to yield 0·243 g (14%) of **14** as colorless needles: m.p. 283–283·5°; IR spectrum ($CHCl_3$): 5·63, 5·74 (shoulder), 5·79, 7·20 μm; UV spectrum (EtOH): 217 nm (17,900); NMR spectrum: see text. (Found: C, 68·50; H, 4·61; N, 6·06. Calc. for $C_{27}H_{22}N_2O_6$: C, 68·93; H, 4·71; N, 5·95%). Attempts to obtain crystals from the MeOH-soluble material were unsuccessful.

N-*phenyl*-3-*carboxy*-6-*hydroxy*-cis,trans,cis-1,2,3,6-*tetrahydrophthalimide lactone* (**15**)

A soln of 5·030 g N-phenylmaleimide and 2·845 g α-pyrone in 15 ml benzene was boiled under reflux for 24 hr. The resulting ppt was filtered, dried and recrystallized from MeOH to afford 5·917 g (76%) of **15** as colorless plates: m.p. 166–170° (dec); IR spectrum ($CHCl_3$): 5·65, 5·80, 7·24 μm; UV spectrum (EtOH): 217 nm (9800); (Found: C, 67·08; H, 4·26; N, 5·48. Calc. for $C_{15}H_{11}NO_4$: C, 66·91; H, 4·12; N, 5·20%).

The NMR spectrum of **15** was strikingly simplified (and its interpretation inversely complicated) by fortuitous magnetic equivalencies and by identities of couplings and long range couplings. Spin decoupling was used to show that H-5 and H-6 are magnetically equivalent, and that $J_{1,6} = J_{1,5} = J_{4,5} = J_{4,6}$.

TABLE 3

H	Multiplicity	δ	Decoupling experiments	
			irradiate at	H collapses to
H-2	d.d	3·43		
H-3	d.d	3·81	H-4: 5·63	d, $J_{2,3}=8·3$
H-1	d.t	4·10	H-5 & 6: 6·62	d, $J_{1,2}=3·5$
H-4	d.t	5·63	H-3: 3·81	t, $J_{4,5}=J_{4,6}=3·5$
			H-5 & 6: 6·62	d, $J_{3,4}=4·5$
H-5 & 6	t	6·62	H-1: 4·10	d, $J_{4,5}=J_{4,6}=3·5$
			H-4: 5·63	d, $J_{1,5}=J_{1,6}=3·5$
C_6H_5	m	7·00–8·60		

1-*Piperonylbut*-3-*enol*-1 (**23**)

Piperonylbutenol was prepared in 88% yield (b.p. 117–120°/0·25 mm) on a 1·0 mole scale as described.[11]

cis-2-*Piperonyl*-1,2,5,6-*tetrahydrobenzoic acid* (**25**)

A soln of 19·2 g allylpiperonylcarbinol, 11·9 g acrylic acid and 5 mg hydroquinone in 50 ml benzene was boiled for 19 hr with azeotropic separation of water. Removal of the benzene *in vacuo* left a viscous oil which was dissolved in 500 ml 1N NaOH and extracted with 300 ml ether. The alkaline soln was acidified with conc HCl and extracted with 300 ml ether. The ether soln was dried over Na_2SO_4 and filtered, and the ether was distilled *in vacuo*. The residual brown oil was dissolved in 50 ml warm benzene. The white crystalline mass which formed upon cooling was filtered, washed with benzene and dried to afford 7·2 g (29%) of crude acid **25**: m.p. 114–135°. Recrystallization from EtOH–water yielded 3·9 g (0·015 mole, 16%) of **25**: m.p. 138·8–140°; IR spectrum ($CHCl_3$): 5·85 μm and piperonyl bands; NMR ($CDCl_3$): 5·50–6·00 (m, 2H, vinyl), 5·88 (s, 2H, —OCH_2O—), 6·72 (m, 3H, piperonyl), 10·50 ppm (s, 1H, —COOH). (Found: C, 68·37; H, 5·74. Calc. for $C_{14}H_{14}O_4$: C, 68·28; H, 5·73%).

Ethyl cis-2-*piperonyl*-1,2,5,6-*tetrahydrobenzoate* (**26**)

To a soln of 0·543 g *cis*-2-piperonyl-1,2,5,6-tetrahydrobenzoic acid in 30 ml anhyd ether was added ethereal diazoethane until the faint yellow color persisted. Removal of the ether *in vacuo* left 0·581 g (100%) *cis*-ester **26** as a colorless liquid. An analytical sample prepared by VPC had the following properties: IR spectrum (CCl_4): 5·76 μm and piperonyl bands; UV spectrum (EtOH): 237 (4800), 286 nm

(4200); NMR (CCl_4): 1·10 (t, J=7·5 Hz), 3·89 (q, J=7·5 Hz), 5·83 (s, —OCH_2O—), 6·58 (m, piperonyl H's), etc. (Found: C, 69·74; H, 6·56. Calc. for $C_{16}H_{18}O_4$: C, 70·06; H, 6·61%).

Ethyl cis- *and* trans-2-*piperonyl*-1,2,5,6-*tetrahydrobenzoate*

Piperonylbutenol (19·2 g), ethyl acrylate (12·0 g), 25 ml xylene, 100 mg hydroquinone and a crystal of *p*-toluenesulfonic acid were boiled under reflux for 94·5 hr, during which time 0·3 ml water was removed by azeotropic distillation. The viscous soln was cooled, dissolved in 200 ml ether and extracted with 200 ml 1N NaOH. The ether soln was dried over Na_2SO_4 and filtered, and the ether and other volatile materials were removed at 100°/15 mm. The remaining yellow oil was distilled: a first fraction of 8·7 g (b.p. 27–130°/0·5 mm) showed negligible CO stretching in its IR spectrum and was discarded; a second fraction (b.p. 130–160°/0·5 mm) of 6·3 g (23%) was a mixture of the *cis*- and *trans*-isomers, not separated by VPC under our conditions. It was shown by NMR to be a 1·4:1 isomer mixture on the basis of two sets uf ethoxyl peaks at 1·02, 1·04, 3·86 and 3·95 ppm.

3,4-*Methylenedioxybiphenyl* (**16**)

A soln of 0·546 g *cis*-2-piperonyl-1,2,5,6-tetrahydrobenzoic acid and 1·052 g 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 5 ml dry benzene was boiled under reflux for 13 hr. The resulting hydroquinone ppt (0·976 g, 96%) was filtered, and discarded. The benzene filtrate was washed through 10 g alumina with 100 ml benzene, to yield 0·252 g (57%) of 3,4-methylenedioxybiphenyl as a colorless liquid. An analytical sample prepared by VPC had the following properties: IR spectrum (CS_2): 3·26, 3·30, 11·30, 12·38, 13·25 and 14·45 μm, and piperonyl bands; UV spectrum (EtOH): 265 (12,000), 288 nm (8600); NMR spectrum (CCl_4): 5·88 (s) and 6·60–7·50 (m) ppm. (Found: C, 79·19; H, 5·30. Calc. for $C_{13}H_{10}O_2$: C, 78·77; H, 5·09%).

Ethyl 2-*piperonylbenzoate* (**18**)

A soln of 2·036 g ethyl 2-piperonyl-1,2,5,6-tetrahydrobenzoate and 3·621 g 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 30 ml dry benzene was boiled under reflux for 4·5 hr, during which time a tan ppt of the hydroquinone formed. The ppt (3·345 g, 98%) was filtered and discarded. The deep red benzene soln was concentrated to 6 ml and washed through alumina with 70 ml benzene. Distillation of the benzene yielded 1·136 g (57%) of crude **18** as a yellow oil. This was distilled in a micro still (pot temp 120–140°/0·25 mm) to afford 0·874 g (44%) ethyl 2-piperonylbenzoate as a colorless liquid: IR spectrum (CCl_4): 5·80 μm and piperonyl bands; UV spectrum (EtOH): 263 (6300), 295 nm (8300); NMR (CCl_4): 1·03 (t, J=7 Hz, 3H, $C\underline{H}_3$—), 4·05 (q, J=7 Hz, 2H, —$OC\underline{H}_2$—) 5·88 (s, 2H, —OCH_2O—), 6·71 (m, 3H, aromatic piperonyl H), 7·10–7·82 (m, 4H, phenyl H). (Found: C, 71·45; H, 5·26. Calc. for $C_{16}H_{14}O_4$: C, 71·10; H, 5·22%).

2-*Piperonylbenzoic acid* (**17**)

Ethyl ester **18** (0·615 g) was saponified by the action of boiling KOH (2·5%) in 1:1 MeOH–water, then isolated in ether. The crude acidic yellow solid (0·426 g, 77% m.p. 125–142°) was recrystallized from *n*-heptane and then from EtOH–water to yield 0·197 g (28%) 2-piperonylbenzoic acid as short, colorless needles: m.p. 143·5–145° (vac); IR spectrum ($CHCl_3$): 5·90 μm and piperonyl bands; UV spectrum (EtOH): 262 (6300), 295 nm (7500); NMR spectrum ($CDCl_3$): 5·96 (s, 2H, —OCH_2O—), 6·80 (m, 3H, piperonyl H), 7·20–8·02 (m, 4H, phenyl H), 11·16 (s, 1H, —$COO\underline{H}$). (Found: C, 69·65; H, 4·45. Calc. for $C_{14}H_{10}O_4$: C, 69·42; H, 4·16%).

4-*Bromo*-3-*hydroxy*-2-*piperonyl*-cis-1,2,3-trans-4-*cyclohexanecarboxylic acid lactone* (**35**)

Method A. To a soln of 0·152 g *cis*-2-piperonyl-1,2,5,6-tetrahydrobenzoic acid in 2 ml warm $CHCl_3$ was added 3 ml 5% Br_2 in CCl_4. After the spontaneous evolution of HBr had ceased, the soln was heated on a steam bath until no solvent or excess Br_2 remained. The residue, which crystallized on cooling, was recrystallized from EtOH–water to yield 0·103 g (51%) of **35** as colorless needles: m.p. 137–138·5° A mixture m.p. with the bromolactone prepared by Method B showed no depression and their IR spectra were identical.

Method B. To 10 ml CCl_4 was added 1·108 g *cis*-2-piperonyl-1,2,5,6-tetrahydrobenzoic acid, 1·474 g N-bromosuccinimide, and 2 mg benzoyl peroxide. The reaction mixture was cautiously brought to boil and maintained at reflux for 4 hr. The insoluble succinimide (0·747 g, m.p. 124–127°) was filtered. The CCl_4 was removed *in vacuo* leaving a yellow gum which was dissolved in 5 ml pyridine and boiled for 1¼

hr. The pyridine soln was poured onto a mixture of 20 ml conc HCl and 100 g crushed ice. This mixture was twice extracted with 100 ml ether and the extract was dried over Na_2SO_4. After filtration the ether was distilled *in vacuo*, and the resulting gum (0·793 g) was dissolved in 2 ml ether. A crystalline material (0·126 g, m.p. 115–136°) separated, was filtered, and recrystallized from EtOH–water to yield 0·074 g (5·5%) of **35** as colorless needles: m.p. 137·8–138·6°; IR spectrum ($CHCl_3$): 5·57 μm and piperonyl bands; UV spectrum (EtOH): 236 (4700), 286 nm (4500); NMR spectrum, Table 1. (Found: C, 51·50; H, 4·12; Br, 24·50. Calc. for $C_{14}H_{13}BrO_4$: C, 51·71; H, 4·03; Br, 24·57%).

3-*Hydroxy*-4-*iodo*-2-*piperonyl*-cis-1,2,3-trans-4-*cyclohexanecarboxylic acid lactone* (**36**)

To a soln of 0·565 g *cis*-2-piperonyl-1,2,5,6-tetrahydrobenzoic acid in 50 ml 5% $NaHCO_3$ soln was added dropwise 5 ml 0·50M KI_3 (2·50 mmole of available I_2). The reaction soln was stirred for 10 min and the excess I_2 was reduced by adding a crystal of $Na_2S_2O_3$. The soln was acidified with 6N HCl. The resulting ppt was filtered and recrystallized from EtOH–water to yield 0·409 g (48%) of **36** as colorless needles: m.p. 141·5–142°; IR spectrum (CCl_4): 5·58 μm and piperonly bands; UV spectrum (EtOH): 237 (4800), 286 nm (4800). (Found: C, 45·07; H, 3·43; I, 34·23. Calc. for $C_{14}H_{13}IO_4$: C, 45·18; H, 3·52; I, 34·10%).

3-*Piperonyl*-cis-1,2,3,6-*tetrahydrophthalic acid* (**27**)

A soln of allylpiperonylcarbinol (60·3 g) and freshly sublimed maleic anhydride (44·4 g) in 100 ml benzene was boiled under reflux for 23 hr. The solid ppt, formed as the soln cooled, was filtered, washed with 300 ml benzene and dried. An IR spectrum demonstrated the presence of a substantial amount of the anhydride adduct. The ppt was added to 1·0 l. of 1N NaOH and stirred for 2 hr at room temp and for 30 min at 100°. The resulting soln was filtered, cooled to 0° and acidified with 100 ml conc HCl. The resulting ppt was filtered, washed with 300 ml water and dried at 90°/15 mm for 1 hr to yield 45·3 g (50%) 3-piperonyl-*cis*-1,2,3,6-tetrahydrophthalic acid. The acid decomposed when heated above 195°.[11]

5-*Bromo*-3-(2′-*bromo*-4′,5′-*methylenedioxyphenyl*)-2-*carboxy*-4-*hydroxy*-cis-1,2,3,4-trans-5-*cyclohexanecarboxylic acid* 2,4-*lactone* (**28**)

To a soln of 4·813 g 3-piperonyl-*cis*-1,2,3,6-tetrahydrophthalic acid in 300 ml 5% $NaHCO_3$aq was added dropwise 200 ml water containing 3·43 g Br_2. After the Br_2 addition was completed the soln was acidified with conc HCl. The ppt which resulted was filtered and recrystallized from acetone–water to yield 1·089 g (15%) of **28** as colorless prisms: m.p. 244·5–245° (vac, dec); IR spectrum (KBr): 5·58, 5·88 μm; UV spectrum (EtOH): 242 (5500), 293 nm (5100); (Found: C, 40·22; H, 2·99; Br, 35·42. Calc. for $C_{15}H_{12}Br_2O_6$: C, 40·21; H, 2·70; Br, 35·68%).

2-*Carboxy*-4-*hydroxy*-5-*iodo*-3-*piperonyl*-cis-1,2,3,4-trans-5-*cyclohexanecarboxylic acid* 2,4-*lactone* (**29**)

3-Piperonyl-*cis*-1,2,3,6-tetrahydrophthalic acid (10·0 g) was dissolved in 300 ml 5% $NaHCO_3$aq. To this was added 70 ml 0·50M KI_3 (35 mmole I_2 available) over 30 min. A yellow ppt formed during the addition. The reaction mixture was stirred for an additional 30 min and acidified with 100 ml 4N HCl. The resulting ppt was filtered, washed with water, and recrystallized from MeOH–water to yield 10·1 g (70%) of **29** as colorless prisms: m.p. 170·5–171° (dec); IR spectrum (KBr): 5·61, 5·84 μm and piperonyl bands; UV spectrum (EtOH): 238 (4700), 287 nm (4700); (Found: C, 43·50; H, 3·23; I, 30·26. Calc. for $C_{15}H_{13}IO_6$: C, 43·29; H, 3·15; I, 30·49%).

Ethyl 2-*carboxy*-4-*hydroxy*-5-*iodo*-3-*piperonyl*-cis-1,2,3,4-trans-5-*cyclohexanecarboxylate*-2,4-*lactone* (**31**)

Method A. A soln of 8·094 g iodolactoneacid **29** in 100 ml dry THF at room temp was treated with ethereal diazoethane until a slight yellow color remained. The solvent was removed at 70°/15 mm and the remaining yellowish gum was recrystallized from MeOH–water to yield 6·300 g (73%) of **31** as colorless needles: m.p. 133·5–135°. The IR and NMR spectra of this substance were identical with those obtained for material prepared by Method B.

Method B. A soln of 2·656 g of **29** in 16·5 g $SOCl_2$ was boiled under reflux 40 min. The excess $SOCl_2$ was removed *in vacuo*; the crude acid chloride solidified on standing. An IR spectrum in $CHCl_3$ showed strong CO absorption at 5·56–5·62 μm. The acid chloride was dissolved in 30 ml abs EtOH and stirred

for 10 min at room temp. The soln was then heated for 25 mn on a steam bath and the excess EtOH removed *in vacuo*. The remaining yellow gum was recrystallized from pet. ether (b.p. 30–60°)–ether to yield 0·992 g of **31** as colorless cubes: m.p. 89·5–90·5°. As the substance was heated above 90·5° needles were observed to grow in the melt and these melted 123–128°. The mother liquor yielded an additional 0·570 g solid (m.p. 128–133°) after standing for 4 days. Recrystallization from MeOH–water afforded 0·422 g colorless needles: m.p. 133–135°. When 50 mg of the cubic crystals was dissolved in warm MeOH and seeded with the needles an almost quantitative yield of the needle crystalline form was obtained: m.p. 133·5–135°. The IR and NMR spectra of the two forms were identical. We concluded that the two substances are different crystalline forms of **31**. The overall yield of this ester was 1·414 g (50%); IR spectrum (CCl_4): 5·57 and 5·76 μm, and piperonyl bands; UV spectrum (EtOH): 237 (4900), 286 nm (5000). (Found: C, 46·10; H, 4·04; I, 28·63. Calc. for $C_{17}H_{17}IO_6$: C, 45·96; H, 3·86; I, 28·57%).

Ethyl 2-*carboxyl*-3-*piperonyl*-cis-1,2,3,6-*tetrahydrobenzoate* (**33**)

Powdered Zn (3·583 g, C.P., 60–200 mesh, J. T. Baker Chemical Co.) was added to a soln of 2·049 g of **31** in 25 ml glacial HOAc and the reaction mixture was rapidly stirred for 12 hr at room temp. The mixture was filtered and the collected Zn salts and excess Zn were washed with 10 ml toluene. The combined HOAc–toluene soln was distilled at 70°/5 mm. The resulting gum was freed of HOAc by two additional distillations of toluene and one of benzene. The residual foam was tentatively identified as ethyl 2-carboxy-3-piperonyl-*cis*-1,2,3,6-tetrahydrobenzoate; IR spectrum ($CHCl_3$): 5·81 μm (broad); NMR spectrum ($CDCl_3$): 1·23 (t, $J=7$ Hz), 4·12 (q, $J=7$ Hz, $-OC\underline{H}_2-$), 5·88 (s, $-OCH_2O-$), 6·68 (m, aromatic H). Complex multiplets of appropriate chemical shift and area were also noted for the vinyl and various aliphatic protons present in the molecule. Attempts to crystallize this material from common organic solvents were without success as was an attempted sublimation. It was used directly in the DDQ oxidation (*vide infra*).

Ethyl 3-*piperonylbenzoate* (**20**)

Method A. To a rapidly stirred mixture of 1·418 g of 3-piperonyl-*cis*-1,2,3,6-tetrahydrophthalic acid in 75 ml $CHCl_3$ (containing 0·75% EtOH as a stabilizer) was added 1·570 g Br_2. The reaction was boiled under reflux for 6 hr during which time all of the acid dissolved and the Br_2 color was discharged. Examination of the IR spectrum of the crude soln showed CO bands at 5·58 and 5·75 μm; the NMR spectrum showed a broadened singlet at 3·98 ppm, thus confirming bromolactonization in the desired manner. The $CHCl_3$ soln was stirred with 2 g Na_2SO_4, filtered and distilled *in vacuo*. To the gummy residue dissolved in 20 ml glacial HOAc was added 2·553 g Zn powder and the reaction mixture was stirred for 9·5 hr at 55–60°. Filtration removed the Zn salts and excess Zn which were washed with 10 ml benzene. The combined HOAc–benzene soln was distilled at 80°/3 mm and the resulting white foam (**33**) (broad absorption at 5·81 μm) was maintained at 1 mm for 12 hr. It was then dissolved in 50 ml dry benzene and 3·028 g DDQ was added. The soln was boiled for 10 hr, cooled and filtered. The filtrate was concentrated to 15 ml and washed through a column containing 25 g activity II alumina with 50 ml benzene. Removal of the benzene *in vacuo* yielded 0·286 g (22%) ethyl 3-piperonylbenzoate as a colorless liquid. The IR spectrum in CCl_4 of this material was identical with that of material prepared by Method B.

Method B. The crude monoester (**33**) prepared from **31** (*vide supra*) was dissolved in 50 ml dry benzene and 2·190 g DDQ was added. The resulting soln was boiled under reflux for 8 hr. The reaction was cooled and filtered and the ppt of hydroquinone was discarded. Distillation of the benzene *in vacuo* gave a residue which was dissolved in 5 ml ether and washed through 20 g alumina with 100 ml benzene. Distillation of the benzene *in vacuo* afforded 0·935 g (75%) from **31** of ethyl 3-piperonylbenzoate as a colorless liquid.

An analytical sample prepared by VPC had the following properties: IR spectrum (neat): 5·80 μm and piperonyl bands; UV spectra (EtOH): 270 (9700), 295 nm (9800); NMR spectrum (CCl_4): 1·36 (t, $J=7$ Hz), 4·33 (q, $J=7$ Hz), 5·90 (s, $-OCH_2O-$), 6·65–7·20 ppm (m, aromatic H). (Found: C, 70·99; H, 5·30. Calc. for $C_{16}H_{14}O_4$: C, 71·10; H, 5·22%).

Method C. Reaction of 1-bromo-3,4-methylenedioxybenzene and ethyl 3-bromobenzoate on a 50 mmol scale with Cu bronze (British Drug Houses Ltd.) at 240° was shown by TLC and comparison with authentic ethyl 3-piperonylbenzoate from Methods A or B to have yielded less than 1% of the desired product.

3-Piperonylbenzoic acid (**19**)

Ethyl 3-piperonylbenzate (0·935 g) was saponified by 24 hrs' boiling with KOH in MeOH–water. Concentration of the soln, then addition of ice and conc HCl yielded a fine white solid which was filtered and recrystallized from EtOH–water to afford 0·713 g (85%) 3-piperonylbenzoic acid as colorless plates: m.p. 227–228° (vac); IR spectrum (KBr): 5·92 μm and piperonyl bands; UV spectrum (EtOH): 269 (10,800), 295 nm (10,300); NMR spectrum (DMSO): 6·09 (s, —OCH_2O—), 6·87–8·27 ppm (m, aromatic H). (Found: C, 69·52; H, 4·16. Calc. for $C_{14}H_{10}O_4$: C, 69·42; H, 4·16%).

Conversion of iodolactoneacid **29** to iodolactone **36**

A soln of **29** (1·450 g) in 15 ml $SOCl_2$ was boiled for 3 hr. The excess $SOCl_2$ was distilled *in vacuo* and the oily acid chloride solidified on standing. It was dissolved in 20 ml dry THF and 0·35 g t-butylhydroperoxide was added. The soln was cooled to 0° and 0·40 g pyridine was added dropwise. The reaction mixture was stirred for 2 hr during which time a ppt formed. The THF was distilled *in vacuo* without heating and the residual gum was partitioned between water and ether. The dried ether layer was washed through 10 g activity II alumina with 200 ml ether. Distillation of the ether *in vacuo* afforded 0·536 g (31%) crude **32** as a colorless solid: m.p. 138–140° (dec); IR spectrum ($CHCl_3$): 5·58, 5·62, 7·24 and 7·32 μm. This substance was dissolved in 10 ml cumene and heated at 110–115° for 12 hr. The resulting soln was examined by TLC in 5 different solvent systems using alumina plates and 50% H_2SO_4 as the developer. A 1% soln of **36** in cumene, prepared by the iodolactonization of *cis*-2-piperonyl-1,2,5,6-tetrahydrobenzoic acid, was used as a standard. In each of the solvent systems studied the cumene reation soln exhibited a spot of the same R_f value as that of the standard. The values varied from 0·18 to 0·97. A minimum of 4 other spots was also noted.

The cumene reaction soln was added to 70 ml pet. ether (b.p. 30–60°). A gummy white ppt formed and an attempted recrystallization from EtOH–water was unsuccessful. The solvent was removed and the material was dissolved in 1 ml ether, then washed through 5 g activity III alumina with 50 ml ether. Removal of the ether left 0·108 g colorless solid: IR absorption: 5·58 μm. The material was thrice recrystallized from MeOH–water to yield 3·8 mg (0·9% based on the crude perester) of **36**: m.p. 141–142°. A mixture m.p. with an authentic sample showed no depression.

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