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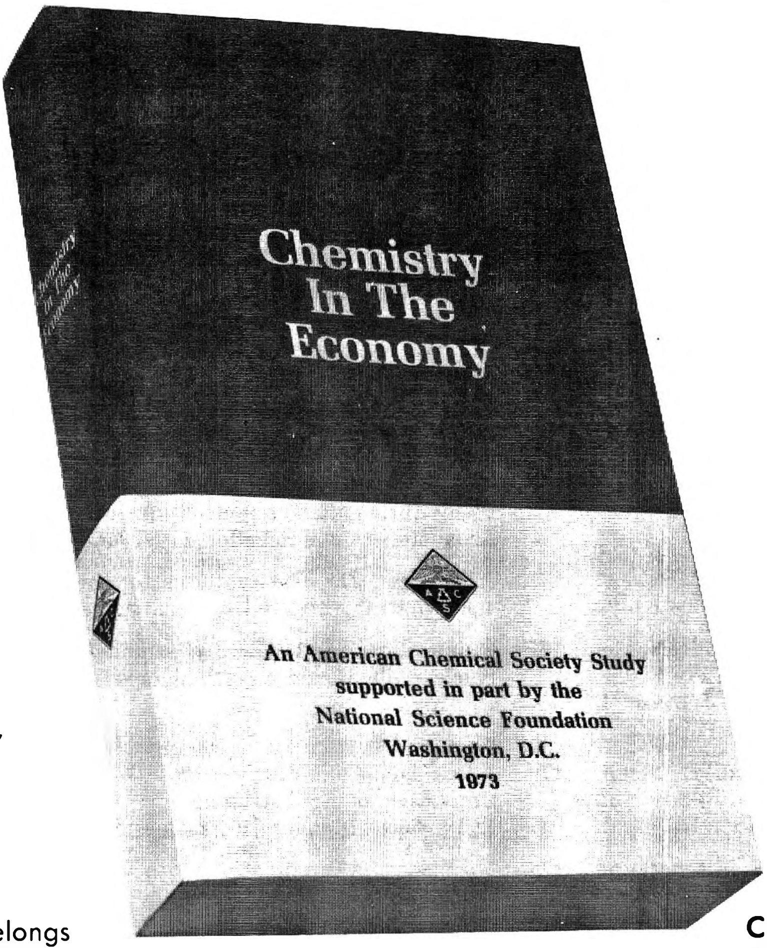
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THE JOURNAL OF Organic Chemistry®

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Estimation by Bond-Additivity Schemes of the Relative Thermodynamic Stabilities of Three-Membered-Ring Systems and Their Open Dipolar Forms

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Some aspects of the chemistry of cyclopropanones, α-lactones, α-lactams, and diaziridinones are discussed in terms of thermodynamic and kinetic stabilities. Semiempirical quantum chemical methods fail for the parent systems, and *ab initio* calculations of substituted systems are limited by practical considerations. Bond-additivity schemes are shown to provide useful estimates of thermal stabilities of the ring systems discussed. Further, they allow formulation of intuitive models which facilitate comparison with experiment. These schemes are used to estimate heats of formation of cyclopropanone, α-lactone, α-lactam, diaziridinone, and related isomers, as well as the open dipolar forms of the first three compounds. The relationships of these structures to methylenecyclopropane, carbon trioxide, and diaziridine imine, and the corresponding open forms are briefly discussed. The heats of decarbonylation of cyclopropanone, α-lactone, α-lactam, and diaziridinone as well as a brief discussion of the role of hyperconjugative stabilization of open forms are included.

Some of the decomposition pathways of α-lactones, α-lactams, and cyclopropanones, the ring systems **1–3**,[1] are explained as proceeding *via* highly reactive, open dipolar intermediates. Difficulty in obtaining these intermediates increases in the above order, namely **1–3**, as will be substantiated in this paper. These compounds are subject to decarbonylation, another contributor to thermal instability, and attack by chemical agents (*e.g.*, nucleophiles and electrophiles) which relates to kinetic stability. The utility of the differentiation of thermodynamic and kinetic stabilities becomes apparent when one considers that a thermodynamically stable, kinetically unstable system may be rendered reasonably unreactive through attachment of substituents which block entry of reagents to reactive sites. The diaziridinone system, **4**, decomposes through radical chain processes and decarbonylation. No reactions invoking the corresponding open forms have been reported to date. The relative propensities of compounds **1–4** to react through the corresponding dipolar forms **5–8** may be explained in the simplified manner depicted in Table I.

While it is possible to compare the above systems to methylenecyclopropanes, diaziridinimines, and carbon trioxide (**14–16**), discussion of these is deferred until the last section. The reason for the separation is that the corresponding open forms (**17–19**) have potential threefold symmetry, which should significantly decrease their dipolar nature relative to **5–8**.

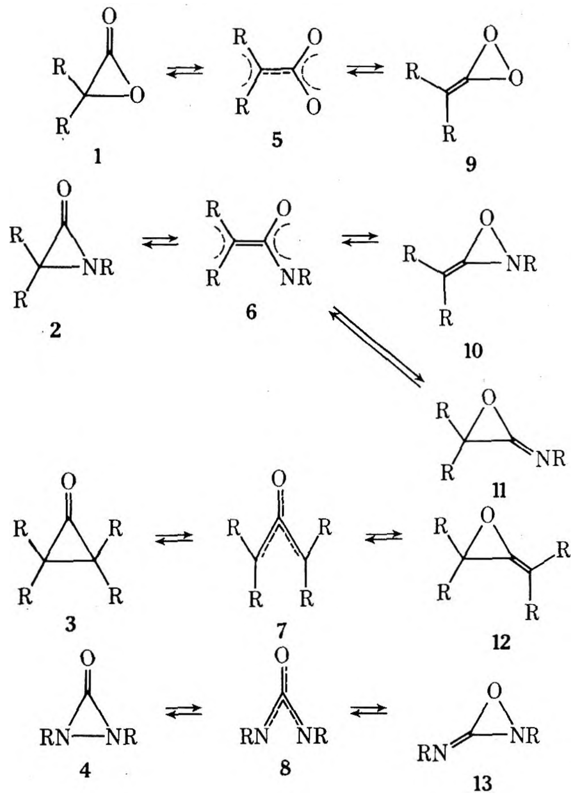
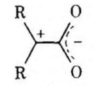
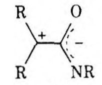
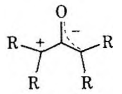
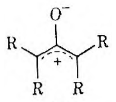
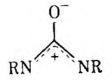
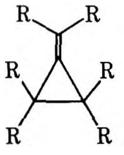


Table I
Factors Determining the Relative Stabilities of the Dipolar Forms Corresponding to Cyclic Compounds 1–4

Dipolar structure	Relative stability	Negative portion	Positive portion
 **5**	Most stable	Strong resonance stabilization	Stabilization by two substituents
 **6**	Moderately stable	Appreciable resonance stabilization	Stabilization by two substituents
 **7a**	Less stable than **6**	Little resonance stabilization	Stabilization by two substituents
 **7b**	Less stable than **7a** More stable than **8**	No stabilization	Allylic system stabilized by four substituents
 **8**	Least stable	No stabilization	1,3-Diazaallylic system less stable than allylic; two substituents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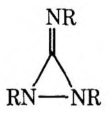
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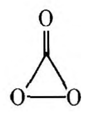
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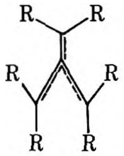
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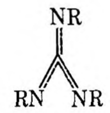
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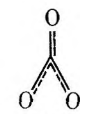
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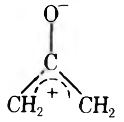
Cyclopropanones and Allene Oxides. While some substituted cyclopropanones undergo cycloaddition reactions, the parent compound has not been induced to react in this manner.[2] These observations are explicable in terms of the barriers to conversion to the corresponding oxyallyl isomers, which are presumably the reacting species. An estimate of the energy difference between cyclopropanone and oxyallyl may be obtained through the use of the bond additivity schemes expressed in eq 1–5 (see ref 3 for the literature source of the heats of formation employed in this paper as well as the rationale for use of this particular source). Such schemes might allow calculation of substituent effects which would otherwise be highly expensive to calculate by computer.[4] They also allow formulation of intuitive models which facilitate comparison with experiment.

Although the assumptions in eq 1 and 2 are quite different, the values are in close agreement, and an average value of −1.5 kcal/mol will be used as the heat of formation of cyclopropanone. Decarbonylation of cyclopropanone is calculated to be exothermic by 12.5 kcal/mol (see Table V).

$$\begin{aligned}\Delta H_f(\mathbf{3}, R = H) &= \Delta H_f(\overset{+}{\Delta}) + \Delta H_f(CH_3COCH_3) - \\ -3\ \text{kcal/mol} &= (239) \quad + (-51.8) \\ &\qquad \Delta H_f[(CH_3)_2CH^+] \quad (1) \\ &\qquad - (190)\end{aligned}$$

$$\begin{aligned}\Delta H_f(\mathbf{3}, R = H) &= \Delta H_f(\mathbf{14}, R = H)^5 + \\ 0\ \text{kcal/mol} &= (48) \\ &\Delta H_f(CH_3COCH_3) - \Delta H_f[CH_2{=}C(CH_3)_2] \quad (2) \\ &+(-51.8) \quad - \quad (-4.04)\end{aligned}$$

Evaluation of oxyallyl requires consideration of dipolar form **20** and diradicals **21** and **22**. Similarities in the effects of methyl substituents in cycloaddition reactions of cyclopropanones and solvolyses of cyclopropyl tosylates are cited[6] as evidence favoring **20** as the structure of oxyallyl. Dipolar form **20** and diradical **21** are of different orbital symmetry and total wave function symmetry, and thus one cannot assume that they are resonance structures of the same species.[7] Equations 3, 4, and 5 estimate heats of formation of **20**, **21**, and **22**, respectively.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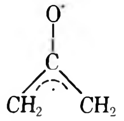
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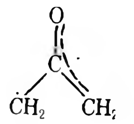
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$$\begin{aligned}\Delta H_f(\mathbf{20}) &= \Delta H_f(\text{allyl cation}) + \Delta H_f(CH_3O^-) + \\ 53\ \text{kcal/mol} &= (216) \quad + \quad (-37.3) \\ &\qquad E_{\text{coul}} - \Delta H_f(CH_4) \quad (3) \\ &\qquad +(-144) - (-17.88)\end{aligned}$$

$$\begin{aligned}\Delta H_f(\mathbf{21}) &= \Delta H_f(\text{allyl radical}) + \Delta H_f(CH_3O\cdot) - \\ 47\ \text{kcal/mol} &= (30) \quad + \quad (-0.5) \\ &\qquad \Delta H_f(CH_4) \quad (4) \\ &\qquad -(-17.88)\end{aligned}$$

$$\begin{aligned}\Delta H_f(\mathbf{22}) &= \Delta H_f(CH_3COCH_2) + \Delta H_f(CH_3\cdot) - \\ 43\ \text{kcal/mol} &= (-7.7) \quad + \quad (33.2) \\ &\qquad \Delta H_f(CH_4) \quad (5) \\ &\qquad -(-17.88)\end{aligned}$$

Estimation of the coulombic energy term (E_{coul}) in (3) is based on the following assumptions.

(a) Assumption of a point charge model with the charges localized on the nuclei. Two unit, but opposite, charges at a distance of 1 Å attract each other with a net stabilization of 14.4 eV = 332.1 kcal/mol.

(b) Charge on oxygen = −1; charges on allylic C_1 and C_3 = +½. No C_1–C_3 repulsion is incorporated in this model since it is implicit in the experimental value of the heat of formation of allyl cation.

(c) Carbon–oxygen bond length = 1.20 Å;[8] carbon–carbon bond length = 1.466 Å.[8]

(d) The value (E_{coul} = −144 kcal/mol) corresponds to the idealized $C_1C_2C_3$ angle of 120°.

The value for the heat of formation of methoxide used in eq 3 has only recently become available. The ion cyclotron resonance determination of equilibrium 6 in the gas phase yields a value for $\Delta G°$ of 1.9 kcal/mol.[9]

$$CH_3O^- + C_2H_5OH \rightleftharpoons CH_3OH + C_2H_5O^- \tag{6}$$

Assuming $\Delta S° \cong 0$ and equal O–H bond dissociation energies for methanol and ethanol, the electron affinity of ethoxy radical is 1.9 kcal/mol greater than that of methoxy radical. The bond dissociation energy assumption is valid in this case, as is apparent from comparison of eq 7 and 8.

$$\begin{array}{lll} \text{Dissociation energy } (CH_3O\text{–}H & = \Delta H_f\ (CH_3OH) - & \\ \quad -99.6\text{ kcal/mol} & = \quad (-47.96) & \\ & \Delta H_f(CH_3O) - \Delta H_f\ (H) & (7) \\ & -(-0.5) \quad - \quad (52.10) & \end{array}$$

$$\begin{array}{lll} \text{Dissociation energy } (C_2H_5O\text{–}H) & = \Delta H_f\ (C_2H_5OH) - & \\ \quad -99.7\text{ kcal/mol} & = \quad (-56.19) & \\ & \Delta H_f\ (C_2H_5O) - \Delta H_f\ (H) & (8) \\ & -(-8.5) \quad - \quad (52.10) & \end{array}$$

A published value[10] of the electron affinity of ethoxy radical (1.68 eV) allows assignment of an electron affinity of 36.8 kcal/mol to methoxy radical and thus the heat of formation of methoxide is −37.3 ± 0.5 kcal/mol.

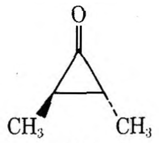
The dipolar oxyallyl intermediate 20 is about 54 kcal/mol higher in energy than cyclopropanone. The intermediates 21 and 22 are, respectively, 49 and 45 kcal/mol higher in energy than cyclopropanone. This is contrary to the expectation that 20 is the structure of the open form. This is a deficiency in the method, probably in large part due to the coulombic term, which appears, at present, to relegate the method to comparison of dipolar forms and the closed rings. In any case, the energy difference between 20 and 22 is not large. Agreement between the above values (*ca.* 50 kcal/mol) and the *ab initio* value of 83 kcal/mol[8] does not appear to be very good. However, the *ab initio* calculation predicts a slightly bonding unoccupied molecular orbital in oxyallyl. A calculation which included partial configuration interaction would lower the energy of oxyallyl and yield an energy difference in closer agreement with the value calculated here. The energy difference between cyclopropanone (unsubstituted) and oxyallyl would appear to preclude cycloaddition reactions unless a concerted mechanism (no intermediacy of oxyallyl) were operative.

Energy differences between open and closed forms of cyclopropanone as well as methyl-substituted cyclopropanones (23–28) are tabulated in Table II. The calculated energy differences between methyl-substituted cyclopropanones and their oxyallyl counterparts are probably underestimated. The reason for this is the fact that the heat of formation of the carbonium ion takes charge delocalization into account implicitly, while the coulombic term employed here assumes charges localized at the atomic centers. Explicit correction of this term would decrease coulomic stabilization of the oxyallyl isomer and increase the energy difference between the open and the closed form.

Table II
Energy Differences between Corresponding Oxyallyls and Cyclopropanones Employing Same E_{coul} as in Eq 3 in All Cases

Species	Energy difference, kcal/mol
Oxyallyl[11] – cyclopropanone	+54
24[a] – **23**	+38
26 – **25**[b]	+35
28[c,d] – **27**[e]	+29

[a] Steric interaction in **24** taken as twice the enthalpy difference between *cis*- and *trans*-2-pentene (1 kcal/mol). [b] Steric interaction in **25** taken as difference in strain energy between *cis*-1,2-dimethylcyclopropane and cyclopropane (2.7 kcal/mol).[12] [c] Steric interaction in **28** is obtained from k_{rel} (150°) of solvolysis of *cis,cis*-2,3-dimethylcyclopropyl tosylate and *trans,trans*-2,3-dimethylcyclopropyl tosylate.[13] The value obtained ($\Delta\Delta H^* \cong \Delta\Delta G^*$ = 7.1 kcal/mol) is due to steric interactions in the transition states. An energy difference (strain in **28**) between allylic cations of 10 kcal/mol is assumed. [d] ΔH_f (1,1,3,3-tetramethylallyl cation) = 160 kcal/mol is obtained by comparison of allyl cation (ΔH_f = 216) with 1,3-dimethylallyl cation (ΔH_f = 182) and 1,1-dimethylallyl cation (ΔH_f = 184). The average difference (−33 kcal/mol) represents the substitution of two methyl groups. Thus, four methyl groups introduce a factor of −66 kcal/mol and an additional 10 kcal/mol steric factor (note c) relative to allyl cation. Addition of ΔH_f (1,1,3,3-tetramethylallyl cation) to ΔH_f (CH_3O^-) and E_{coul} (−144 kcal/mol) and subtraction of ΔH_f (CH_4) yield a value for ΔH_f (**28**) of −3.4 kcal/mol. [e] Steric interaction in **27** taken as 2 × 2.7 = 5.4 kcal/mol.



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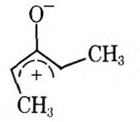

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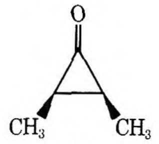

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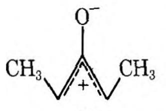

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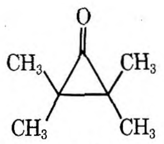

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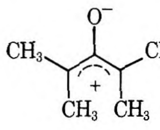

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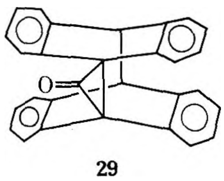
Curiously, the only phenyl-substituted cyclopropanone isolated to date is 29,[14] although diphenyl-substituted cyclopropanones have been generated, for example, as intermediates in syntheses of cyclopropenones.[15-17] Compound 29 does not allow conjugation of phenyl rings in the oxyallyl form and is, therefore, stable to ring opening. Unfortunately, heats of formation of phenyl-substituted allylic cations are presently not available. However, monophenyl- and diphenylcyclopropanones may be isolable. Triphenyl- and tetraphenylcyclopropanones may also be stable in the closed forms, since steric interactions limit the extent of conjugative stabilization of oxyallyl isomers.



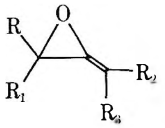
29

Allene oxide (12, R = H) has not been isolated. Its energy relative to cyclopropanone may be calculated through comparison of eq 9 or 10 with eq 2. The average energy

$$\begin{aligned}\Delta H_f(\mathbf{12}, \mathrm{R} = \mathrm{H}) &= \Delta H_f(\mathbf{14}, \mathrm{R} = \mathrm{H})^5 + \Delta H_f(\overset{\mathrm{O}}{\triangle}) - \Delta H_f(\triangle) \quad (9)\\ 23 \text{ kcal/mol} &= (48) + (-12.58) - (12.74)\end{aligned}$$

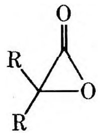
$$\begin{aligned}\Delta H_f(\mathbf{12}, \mathrm{R} = \mathrm{H}) &= \Delta H_f(\mathbf{14}, \mathrm{R} = \mathrm{H})^5 + \Delta H_f(\mathrm{CH_3OCH{=}CH_2}) - \Delta H_f(\text{1-butene}) \quad (10)\\ 20 \text{ kcal/mol} &= (48) + (-27.7) - (-0.03)\end{aligned}$$

difference between cyclopropanone and allene oxide of 23 kcal/mol is in excellent agreement with *ab initio* calculations.[8] Furthermore, comparison with eq 3 suggests that allene oxide is quite stable to ring opening to oxyallyl. Its failure to be isolated must be due to kinetic instability. Allene oxides **30**,[18] **31**,[19] and **32**[20] have been generated but not isolated because of kinetic instability. Highly hindered allene oxides **33**[21] and **34**[22] have been isolated.



30, $\mathrm{R = R_1 = R_2 = R_3 = CH_3}$
31, $\mathrm{R = R_1 = CH_3;\ R_2 = C(CH_3)_3;\ R_3 = H}$
32, $\mathrm{R = R_1 = C(CH_3)_3;\ R_2 = R_3 = H}$
33, $\mathrm{R = R_2 = C(CH_3)_3;\ R_1 = R_3 = H}$
34, $\mathrm{R = R_1 = R_2 = C(CH_3)_3;\ R_3 = H}$

***α*-Lactones.** The α-lactones are in marked contrast to cyclopropanones in their thermal stabilities. To date, only **35** has been isolated.[23] Dialkyl α-lactones **36–41** have been generated at low temperatures ($\leq -78°$) and, with the exception of **36**, react immediately upon formation.[24-26] The α-lactone **36** is stable at −60° and polymerizes at the relatively high temperature of −20° as the result of kinetic stability afforded by the bulky substituents.[24] Diphenyl α-lactone (**42**) appears to exist as the dipolar form at −100°.[24]

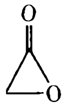


35, $\mathrm{R = CF_3}$
36, $\mathrm{R = C(CH_3)_3}$
37, $\mathrm{R} = n\text{-}\mathrm{C_4H_9}$
38, $\mathrm{R = CH_3}$
39, $\mathrm{R + R = (CH_2)_2}$
40, $\mathrm{R + R = (CH_2)_3}$
41, $\mathrm{R + R = (CH_2)_4}$
42, $\mathrm{R = C_6H_5}$
43, $\mathrm{R = H}$

The heat of formation of α-lactone is calculated in eq 11. The subtraction of the π resonance energy (*RE*) in eq 11 requires comment. The rationale for this approximation will be further substantiated in the sections concerned with α-lactams and diaziridinones.

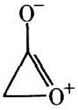
$$\begin{aligned}\Delta H_f(\mathbf{43}) &= \Delta H_f(\mathbf{3}, \mathrm{R} = \mathrm{H}) + \Delta H_f(\mathrm{CH_3COOCH_3}) - \Delta H_f(\mathrm{CH_3COC_2H_5}) - RE^{27} \quad (11)\\ -31 \text{ kcal/mol} &= (-1.5) + (-99.2) - (-58.4) - (-11)\end{aligned}$$

At this point it is worthwhile to note the relative strain energies (in analogy to the hydrocarbons methylenecyclopropane and cyclopropene[12]) in resonance contributors A and B. Thus, the dipolar contribution should be much smaller in α-lactones than in esters or the unstrained δ-lactones.



A

Relative strain = 41 kcal/mol
(methylenecyclopropane[12])

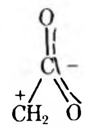


B

Relative strain = 54 kcal/mol
(cyclopropene[12])

Additional evidence may be adduced from the carbonyl stretching frequency of α-lactones (*ca.* 1900 $\mathrm{cm^{-1}}$).[26] The carbonyl frequency of δ-lactone is about 20 $\mathrm{cm^{-1}}$ greater than that of cyclohexanone, following the usual relationship between esters and ketones.[28] However, the carbonyl frequencies of α-lactones are 70–85 $\mathrm{cm^{-1}}$ greater than those of cyclopropanones.[2]

One might consider two open dipolar isomers of α-lactone. The most probable dipolar structure, **44**, is assigned



44

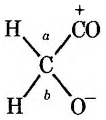
the following geometry: (a) all angles are 120°; (b) carbon–carbon bond length = 1.466 Å;[8] (c) carbon–oxygen bond length = 1.27 Å.

The heat of formation of **44** is calculated in eq 12.

$$\begin{aligned}\Delta H_f(\mathbf{44}) &= \Delta H_f(\mathrm{C_2H_5^+}) + \Delta H_f(\mathrm{CH_3CO_2^-}) + E_{\mathrm{coul}} - \Delta H_f(\mathrm{C_2H_6}) \quad (12)\\ -23 \text{ kcal/mol} &= (219) + (-122) + (-140) - (-20.24)\end{aligned}$$

The coulombic attraction is calculated using the point-charge model and a separation of 2.37 Å. The heat of formation of acetate anion used in eq 12 is obtained from the heat of formation of acetoxy radical (−45 ± 4 kcal/mol)[29] and the electron affinity (3.36 ± 0.05 eV = 77.5 ± 1.2 kcal/mol;[30] 78.2 kcal/mol[31]) of this radical.

The second dipolar form, **45**, might be more stable than **44** in cases where electron-withdrawing substituents are



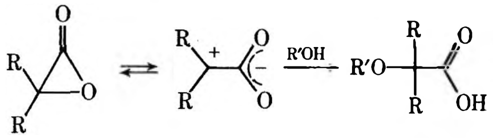
45

attached. It is assigned the following geometry: (a) angle (CO)–C–O = 109.5°; (b) bond length *a* = 1.51 Å (analogy to $\mathrm{CH_3{-}CHO}$); (c) bond length *b* = 1.43 Å (usual C–O bond length).

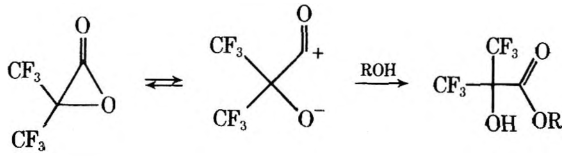
The heat of formation of **45** is calculated in eq 13. Thus, **44** would normally be the lowest energy dipolar form of

$$\begin{aligned}\Delta H_f(\mathbf{45}) &= \Delta H_f(\mathrm{C_2H_5CO^+}) + \Delta H_f(\mathrm{CH_3O^-}) + E_{\mathrm{coul}} - \Delta H_f(\mathrm{C_2H_6}) \quad (13)\\ -12 \text{ kcal/mol} &= (143) + (-37.3) + (-138) - (-20.24)\end{aligned}$$

an α-lactone. This is consistent with the reactions of most α-lactones with alcohol.[24-26]



However, the perfluoroalkyl derivative, **35**, appears to favor open form **45** to **44** as the result of strong electron withdrawal by the substituents, and it reacts with alcohols in the following manner.[23]



Formation of the α-hydroxy ester is also consistent with nucleophilic attack at the carbonyl group of the α-lactone. Facile decarbonylation[23] of **35** may be indicative of the intermediacy of open form **45**.

Table III lists energy differences between open (**44**) and closed forms of α-lactone, dimethyl α-lactone, and diphenyl α-lactone using the format of eq 12 and the same coulombic term in all cases. The parent compound should exist in the closed form but not be much more stable than the open form. Dialkyl α-lactones would appear to be most stable in the open form. The energy differences are not very large and it is easy to envision cases in which steric or strain factors might make the closed form more stable. Diphenyl α-lactone certainly appears to be considerably more stable in the open form, although the energy difference in Table III is probably exaggerated. That is, while the experimental heat of formation of the appropriate substituted carbonium ion contains implicit delocalization of the positive charge, such charge delocalization would have to be accounted for explicitly in calculating a better coulombic energy using the method advanced here. For example, if the charges on the open diphenyl compound were separated by an average distance of 3.0 Å instead of 2.4 Å, as in **44**, then $E_{\text{coul}} = -111$ kcal/mol and the open form of **42** would be 33 kcal/mol more stable than **42** itself.

The isolation[23] of cyclic **35** is not surprising when one considers the strongly dominant destabilizing inductive effect of trifluoromethyl groups on **44** which apparently (*vide infra*) has the effect of making **45** more stable. Data for evaluation of the heats of formation of perfluoro open forms are not yet available. However, if one assumes that the inductive stabilizing and destabilizing effects of trifluoroalkyl groups on **45** are about equal, then **35** is more stable than its open dipolar form by about 19 kcal/mol (compare eq 11 and 13).

The heat of formation of **9** (R = H) is calculated in eq 14. This compound is considerably less stable than the open dipolar forms.

$$\begin{aligned}\Delta H_f(\mathbf{9},\mathrm{R}=\mathrm{H}) &= \Delta H_f(\mathrm{CH_3OOCH_3})^{32} + \Delta H_f[\mathrm{CH_2{=}C(OCH_3)_2}]^{33} - 2\Delta H_f(\mathrm{CH_3OCH_3}) + \text{strain }(\mathbf{14},\mathrm{R}=\mathrm{H})^{12} \quad (14)\\ +36\ \text{kcal/mol} &= (-23) + (-70.4) - 2(-44) + (41)\end{aligned}$$

Decarbonylation of α-lactone is calculated to be exothermic by 23.4 kcal/mol (Table V).

Table III
Energy Differences between Corresponding Open (*i.e.*, 44) and Closed Forms of Some α-Lactones

Closed form	Energy difference, kcal/mol (open − closed)
43	+8
38	−18
42	−62

α-Lactams.[34] The tendency for α-lactams to ring open appears to be intermediate between that of α-lactones and cyclopropanones. The heat of formation of α-lactam (**46**) is estimated in eq 15. In eq 15, as in eq 11, the π resonance energy normally ascribed to amides is excluded.

$$\begin{aligned}\Delta H_f(\mathbf{46}) &= \Delta H_f(\mathbf{3},\mathrm{R}=\mathrm{H}) + \Delta H_f(\mathrm{CH_3CONH_2}) - \Delta H_f(\mathrm{CH_3COC_2H_5}) - RE^{27} \quad (15)\\ +13\ \text{kcal/mol} &= (-1.5) + (-55) - (-58.37) - (-11)\end{aligned}$$

The rationale for this approximation is as follows.

(a) Carbonyl absorption in simple ketones is 20–60 cm^{-1} higher than in the corresponding amides, but that of cyclopropanone is *ca.* 20 cm^{-1} lower than that of α-lactam.[35] This effect is similar to that observed in quinuclidone-2.[35]

(b) X-Ray study of 1,3-diadamantyl α-lactam (**47**) shows that the substituents attached to nitrogen are not coplanar as they are in amides.[36]

(c) As mentioned previously, π resonance in α-lactams would involve an increase in strain energy of about 13 kcal/mol (*i.e.*, cyclopropene *vs.* methylenecyclopropane).[12]

Decarbonylation of **46** is calculated to be exothermic by 13.2 kcal/mol (see Table V).

The heat of formation of the open dipolar form of α-lactam, **56**, is obtained from eq 16 with the following assumptions: (a) all angles are 120°; (b) carbon–carbon bond length = 1.466 Å;[8] (c) carbon–oxygen and carbon–nitrogen bond lengths are similar enough so that E_{coul} remains at −140 kcal/mol as in eq 12.

$$\begin{aligned}\Delta H_f(\mathbf{56}) &= \Delta H_f(\mathrm{C_2H_5^+}) + \Delta H_f(\mathrm{CH_3CONH^-}) + E_{\text{coul}} - \Delta H_f(\mathrm{C_2H_6}) \quad (16)\\ +41\ \text{kcal/mol} &= (219) + (-58) + (-140) - (-20.24)\end{aligned}$$

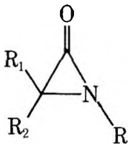
The value for ΔH_f ($\mathrm{CH_3CONH^-}$) used in eq 16 is obtained from pK ($\mathrm{CH_3CONH_2}$) $\cong$ 16,[37] pK ($\mathrm{CH_3CO_2H}$) $\cong$ 5,[37] ΔH_f ($\mathrm{CH_3CONH_2}$) = −54 kcal/mol, ΔH_f ($\mathrm{CH_3CO_2H}$) = −103.31 kcal/mol, and ΔH_f ($\mathrm{CH_3CO_2^-}$) = −122 kcal/mol (*vide infra*). The use of liquid phase pK's in this approach is subject to justified criticism. In the absence of gas-phase values for the heat of formation and electron affinity of $\mathrm{CH_3CONH}$, this crude approximation must suffice. Thus, the energy difference favoring the closed form of α-lactam is predicted to be 28 kcal/mol compared with 54 kcal/mol for cyclopropanone and 8 kcal/mol for α-lactone.

A large number of substituted α-lactams have been synthesized and these exhibit a considerable range of stability.[36,38,39] Sterically hindered 1,3-dialkyl α-lactams such as **47** and **48** are quite stable,[36] while **49** is kinetically unstable.[36] Diaryl and triaryl α-lactams in which an aromatic ring is attached to nitrogen (*e.g.*, **51**–**53**) have not been isolated.[36,38] The compound **50** is quite stable,[39] since it is sterically hindered and matches a substituent which strongly stabilizes the dipolar form with one that strongly

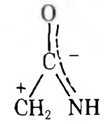
Table IV[a]
Energy Differences between Corresponding Open and Closed Forms of Some α-Lactams

Closed form	Energy difference, kcal/mol (open − closed)
46	+28
49	+2
52[41]	−49
55	−42

[a] The effects of substituents attached to C_3 of α-lactams is assumed to be equal to those in α-lactones (Table III). Steric effects are not included.



46, $R = R_1 = R_2 = H$
47, $R = R_1 =$ adamantyl
48, $R = R_1 = C(CH_3)_3$; $R_2 = H$
49, $R = R_1 = CH_3$; $R_2 = H$
50, $R = C(CH_3)_3$; $R_1 = CF_3$; $R_2 = C_6H_5$
51, $R = R_1 = C_6H_5$; $R_2 = H$
52, $R = R_1 = R_2 = C_6H_5$
53, $R = 2,6\text{-}(CH_3)_2C_6H_3$; $R_1 = C_6H_5$; $R_2 = H$
54, $R = C(CH_3)_3$; $R_1 = R_2 = C_6H_5$
55, $R = H$; $R_1 = R_2 = C_6H_5$



56

destabilizes it. Surprisingly, **54** has been isolated and exists in the cyclic form.[36]

Table IV lists energy differences between open and closed forms of some α-lactams. It is readily apparent that the use of liquid phase pK's has the effect of yielding energies for open dipolar forms that are too low. The thermal stability of **49** is too low and the predicted favoring of the open form of **55** is erroneous. This latter error is also the result of overestimation of the coulombic stabilization of the open form of **55** as stated previously. Conjugative interaction between the α-lactam ring and phenyl substituents[40] is not included.

The heat of formation of **10** (R = H) is estimated in eq 17. The heat of formation of **11** (R = H) is not estimated

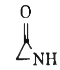
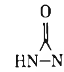
$$\begin{array}{lcl} \Delta H_f(\mathbf{10}, R = H) & = & \Delta H_f(\mathbf{14}, R = H) + \\ +74\ \mathrm{kcal/mol} & = & (48) \end{array}$$

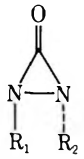
$$\begin{array}{lcr} \Delta H_f(\mathrm{CH_3ONHCH_3})^{42} & - & \Delta H_f(n\text{-}C_4H_{10}) \\ + (-4) & - & (-30.15) \end{array} \quad (17)$$

here since heats of formation of nonresonance-stabilized imines are not experimentally available. It is probably a few kilocalories per mole less stable than **46** (**2**, R = H). Derivatives of **11** have been postulated as intermediates in fragmentation reactions of some α-lactams.[36]

Diaziridinones. The dialkyldiaziridinones **57**–**61** have been prepared and are quite stable.[43-45] No cycloaddition products of these compounds have been observed.[35] This is attributed[35] to either or both steric hindrance to cycloaddition of the open form or negligible presence of the open form.

Table V
Calculated Heats of Decarbonylation of Small-Ring Systems

Compd	Products	ΔH_0, kcal/mol
 →	$CH_2{=}CH_2 + CO$	−12.5
 →	$CH_2O + CO$	−23.4
 →	$CH_2{=}NH^{49} + CO$	−13.2
 →	$HN{=}NH + CO$	−12.6



57, $R_1 = R_2 = C(CH_3)_3$
58, $R_1 = R_2 =$ *tert*-amyl
59, $R_1 = R_2 =$ *tert*-octyl
60, $R_1 = R_2 = C(CH_3)_2CH_2C_6H_5$
61, $R_1 = C(CH_3)_3$; $R_2 =$ *tert*-octyl
62, $R_1 = R_2 = H$

The heat of formation of the unsubstituted ring system, **62**, is calculated in eq 18. Here again, as in the cases of α-lactones and α-lactams, the π resonance energy normally associated with urea is omitted. Evidence supporting this assumption consists of the observation of noncoplanarity of groups attached to nitrogen,[35] and the observation of carbonyl frequencies of diaziridinones which are 15–65 cm^{-1} higher than those of cyclopropanones, while carbonyl bands of ureas are 15–50 cm^{-1} lower than those of the corresponding ketones.[35] Decarbonylation of **62** is estimated to be exothermic by 12.6 kcal/mol (Table V).

$$\begin{array}{lcl} \Delta H_f(\mathbf{62}) & = & \Delta H_f(\mathrm{CH_3NHNHCH_3}) + \Delta H_f(\mathrm{urea})^{46} + \\ +34.9\ \mathrm{kcal} & = & (21.6) \qquad\qquad + \quad (-58.7) \end{array}$$

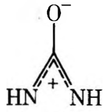
strain ()^{12} $- 2\,\Delta H_f(\mathrm{CH_3NH_2}) - RE^{47}$ (18)

$$+ \ (41) \ - 2(-5.49) - (-20)$$

The poor tendency for cycloaddition of diaziridinones may be accounted for by steric and/or electronic effects. Since the diaziridinones reported in the literature possess bulky substituents, the reluctance for cycloaddition may be steric in origin. An electronic explanation rests upon comparison of dipolar structure **63** and oxyallyl. The negative portions are similar, but the positive part of **63** (1,3-diazaallylic carbonium ion) should be much less stable than the allylic carbonium ion. Unfortunately, the heat of formation of the 1,3-diazaallylic carbonium ion is not available and only extremely crude estimates are possible.

Table VI
Heats of Formation of α-Methyl Substituted Carbonium Ions and Corresponding Alkanes

ΔH_f (Ion), kcal/mol	Registry no.	ΔH_f (Alkane), kcal/mol	Registry no.	(Ion) − (Alkane), kcal/mol
$n\text{-}C_3H_7^+$ (209)	19252-52-9	$n\text{-}C_3H_8$ (−24.82)	74-98-6	234
$i\text{-}C_4H_9^+$ (205)	19252-54-1	$i\text{-}C_4H_{10}$ (−32.15)	75-28-5	237
neo-$C_5H_{11}^+$ (196)	14128-47-3	neo-C_5H_{12} (−39.67)	463-82-1	236



63

It is, therefore, presently impossible to determine whether cyclopropanone or diaziridinone is more stable to ring opening.

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Decarbonylation Reactions and Hyperconjugative Stabilization of Open Dipolar Forms. Table V lists calculated heats of decarbonylation of the ring systems discussed in this paper. Interestingly, omission of resonance energies makes α-lactam and diaziridinone unstable relative to their decarbonylation products. Concerted decarbonylation pathways are prohibited by orbital symmetry.[48]

Hyperconjugative stabilization of open dipolar forms is possible, and the stability conferred onto ring systems by *tert*-butyl groups might be evidence supporting this contention. However, examination of Table VI leads us to conclude that the major effect of the *tert*-butyl groups is steric hindrance to attacking agents, and hyperconjugative stabilization of open forms is relatively minor.

Systems Capable of Threefold Symmetry. Methylenecyclopropane (14, R = H), carbon trioxide (16), and diaziridinimine (15, R = H) are not discussed here since the corresponding acyclic forms (17, 19, 18) have potential D_{3h}, D_{3h}, and C_{3h} symmetries, respectively. Thus, the dipolar structures advanced in this paper are probably less applicable in discussing these systems.

It is worthwhile to point out that the thermal instability of carbon trioxide[50-53] and diaziridinimines[54] relative to methylenecyclopropanes[55-58] is at least in part due to small resonance contributions in the closed forms of the first two as explained in this paper. Additionally, the special instability of carbon trioxide may be due to the fact that stabilization during ring opening is achieved without movement of attached groups, a necessary feature of the other cyclic systems discussed in this paper.

Conclusions

The bond-additivity schemes proposed in this paper reproduce qualitative trends in thermal stability of the ring systems discussed. Refinement of the calculations to the point where they might be used to make reasonably accurate quantitative predictions must await accurate gas-phase determinations of electron affinities and p*K*'s. Calculation of coulombic terms using point-charge assumptions leads to significant errors when phenyl groups, which disperse charge to a large extent, are involved.

We anticipate that the schemes advanced here will provide intuitively satisfying models and hope that further sophistication of the methods as well as additional data will allow more reliable calculations of related systems.

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Registry No. 1 (R = H), 42879-41-4; 2 (R = H), 34734-31-1; 3 (R = H), 5009-27-8; 4 (R = H), 42879-43-6; 9 (R = H), 42879-44-7; 10 (R = H), 42879-45-8; 12 (R = H), 40079-14-9; 14 (R = H), 6142-73-0.

References and Notes

(1) The open forms **5–8** and **17–19** are normally considered 4π systems. Promotion of lone-pair electrons to the π framework permits **5**, **6**, **8**, **18**, and **19** to be "Y-aromatic" [see P. Gund, *J. Chem. Educ.*, **49**, 100 (1972)]. However, this effect need not be invoked to explain these cases (*vide infra*). Compounds **1–4**, **5–8**, and **9–13** also constitute sets of isoelectronic compounds [for applications of the isoelectronic principle see H. A. Bent, *J. Chem. Educ.*, **43**, 171 (1966), and J. F. Liebman, *ibid.*, **48**, 188 (1971)].

(2) For comprehensive reviews of cyclopropanones see (a) N. J. Turro, *Accounts Chem. Res.*, **2**, 25 (1969); (b) N. J. Turro, R. B. Gagosian, S. S. Edelson, T. R. Darling, and W. B. Hammond, *Trans. N. Y. Acad. Sci.*, 33, 396 (1971).

(3) All values of ΔH_f [(g) 298°K] are reported in kcal/mol and are obtained from J. L. Franklin, J. G. Dillard, H. M. Rosenstock, J. T. Herron, K. Draxl, and F. H. Field, "Ionization Potentials, Appearance Potentials, and Heats of Formation of Positive Ions," National Standard Reference Data Series, National Bureau of Standards (U. S.), 26, NSRDS-NBS 26, 1969. We acknowledge that this reference is an unusual, and admittedly perhaps not ideally appropriate, source of information for any species other than a positive ion. However, it does provide a single data compendium for cations such as cyclopropyl, stable and "normal" neutral molecules such as acetone, free radicals such as the methoxy radical, and even some anions such as hydroxide. This uniformity of origin for most of our thermochemical data suggests that the implicit biases in the selection of numerical data from experiment are essentially uniform.

(4) Semiempirical methods to date apparently fail for oxyallyl and predict seemingly erroneous substituent effects in the cyclopropanone series [see A. Liberles, S. Kang, and A. Greenberg, *J. Org. Chem.*, **38**, 1922 (1973)].

(5) K. B. Wiberg and R. A. Fenoglio, *J. Amer. Chem. Soc.*, **90**, 3395 (1968).

(6) S. S. Edelson and N. J. Turro, *J. Amer. Chem. Soc.*, **92**, 2770 (1970).

(7) Resonance structures are governed by both spin and spatial symmetry constraints on a molecule. Normally, this presents no problems. Let us consider the axis colinear with oxygen and carbon and the plane which bisects oxyallyl. The p π orbital of oxygen must be symmetric with respect to this plane. In the zwitterionic structure, **20**, there are two electrons occupying this orbital. The occupied orbital on the allyl cation fragment is symmetric with respect to this plane. Accordingly, all four π electrons are symmetric with regard to this plane. Let us now consider biradical **21**. The single electron on oxygen is again in a symmetric orbital. The allyl radical fragment contains three electrons, of which only two can occupy the previously mentioned symmetric allyl orbital. The remaining electron is presumably in the next higher orbital of the allyl fragment, which, as in the case of the free allyl radical, is antisymmetric with respect to the plane. Accordingly, there are three electrons in symmetric orbitals and one in an antisymmetric orbital and the overall wave function is antisymmetric. Thus, **20**, and **21** are of different wave function as well as orbital symmetry and do not mix.

(8) A. Liberles, A. Greenberg, and A. Lesk, *J. Amer. Chem. Soc.*, **94**, 8685 (1972).

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(11) There is a temptation to use tropone as a model for **20**. However, the heat of formation of tropone may be accurately accounted for without use of dipolar structures; see also M. J. S. Dewar, *Croat. Chem. Acta*, **42**, 1 (1970).

(12) P. v. R. Schleyer, J. E. Williams, Jr., and K. R. Blanchard, *J. Amer. Chem. Soc.*, **92**, 2377 (1970).

(13) (a) P. v. R. Schleyer, G. W. V. Dine, U. Schollkopf, and J. Paust, *J. Amer. Chem. Soc.*, **88**, 2868 (1966); (b) C. H. Depuy, L. G. Schnack, and J. W. Hauser, *ibid.*, **88**, 3343 (1966).

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(18) J. K. Crandall and W. H. Machleder, *J. Amer. Chem. Soc.*, **90**, 7292 (1968).

(19) J. K. Crandall, W. H. Machleder, and M. J. Thomas, *J. Amer. Chem. Soc.*, **90**, 7346 (1968).

(20) J. K. Crandall and W. H. Machleder, *J. Amer. Chem. Soc.*, **90**, 7347 (1968).

(21) R. L. Camp and F. D. Greene, *J. Amer. Chem. Soc.*, **90**, 7349 (1968).

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Base-Promoted Reactions of Bicyclic Mono- and Diquaternary Ammonium Salts[1]

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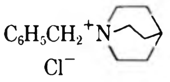
The synthesis and base-promoted reactions of the mono- and diquaternary ammonium salts, 1-benzyl-1-azoniabicyclo[2.2.2]octane chloride (1), 1-benzyl-1-azonia-4-azabiocyclo[2.2.2]octane chloride (2), and 1,4-dibenzyl-1,4-diazoniabicyclo[2.2.2]octane dichloride (3) have been carried out. The acidifying influence of the quaternary nitrogen atom appears to be the controlling factor in determining the reaction pathway. Thus, the most acidic disalt, **3**, leads initially to an elimination product, **11**. Subsequent reaction of **11** leads to both ring expansion and vinyl migration *via* a Stevens rearrangement. Change of a bridgehead carbon atom to a bridgehead nitrogen atom (comparison of 1 and 2) decreases the acidity and removes the elimination pathway while enhancing the Stevens rearrangement product. The novel vinyl Stevens rearrangement was confirmed by the synthesis of benzyldimethylvinylammonium hydroxide (**19**) and its conversion to α-vinylbenzyldimethylamine (**21**).

In recent years a renewed interest has been oriented toward 1,2-anionic rearrangements as new techniques and results have prompted changes in our mechanistic theories.[2] The base-promoted rearrangements of quaternary ammonium salts, the Stevens rearrangement,[3] has received considerable attention in this regard.[4] As a continuation of our interest in this area we have investigated the base-promoted reactions of the bicyclic salts 1-benzyl-1-azoniabicyclo[2.2.2]octane chloride (1) (quinuclidinium salt), 1-benzyl-1-azonia-4-azabicyclo[2.2.2]octane chloride (2) (Dabco monosalt), and 1.4-dibenzyl-1,4-diazoniabicyclo[2.2.2]octane dichloride (3) (Dabco disalt). In contrast to most previous work reported on the Stevens rearrangement, these bicyclic systems introduce stereochemical constraints which could influence the reaction pathways.[5] In addition to the possibility of displacement reactions, the presence of β hydrogen atoms also enables elimination to compete with the rearrangement. Another consideration in the choice of this series of compounds for study was the possibility that intramolecular electronic interactions might be important as one of the bridgehead atoms changes from C to N to N$^+$. Interaction between the nitrogen atoms in Dabco has been observed by esr and uv



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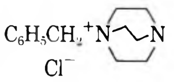

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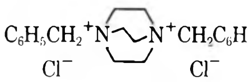

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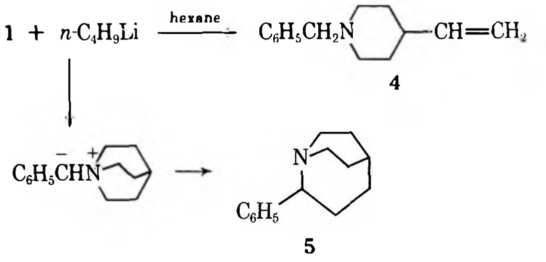
methods.[6a] A theoretical treatment of this for Dabco and related systems has been the basis for consideration of a through bond and through space orbital overlap.[6b,c]

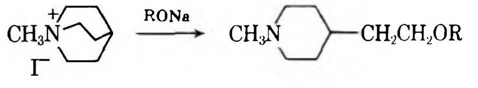
Results and Discussion

The desired quaternary ammonium salts were readily obtained through reaction of the appropriate bicyclic amine and benzyl chloride. Final traces of water were very difficult to remove from the chloride salts and in the case of the monosalts **1** and **2** it was necessary to use the tetrafluoroborate salts for final analytical data. Reactions were carried out on the chloride salts at 50–55° using an excess of strong base, *n*-butyllithium in hexane, as a heterogeneous mixture.

The reaction of the quinuclidinium salt **1** with *n*-butyllithium in hexane provided two major basic products. The major product (37%), 2-phenyl-1-azabicyclo[3.2.2]nonane (**5**), resulted from a ring-expanding Stevens rearrangement proceeding *via* the benzylammonium ylide. The second product (13%), *N*-benzyl-4-vinylpiperidine (**4**), resulted from a ring-opening elimination reaction.



Our results can be compared with the work of Angel, *et al.*,[7] on *N*-methylquinuclidinium iodide (**6**). These workers reported only ring-opening displacement using alkoxides as base. They attributed the absence of elimination to the inability of obtaining an anticoplanar arrangement of a β hydrogen atom and the nitrogen atom in the bicyclic molecule. We did not observe displacement products in this work and it is probable that greater basicity relative to nucleophilicity using *n*-butyllithium in a nonpolar solvent accounts for this. It is clear that formation of the ylide required for the Stevens rearrangement in the system of Angel, *et al.*, would not be expected to be favorable using alkoxide bases.



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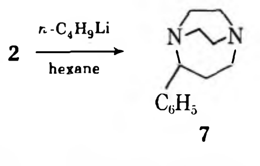
The monosalt of Dabco (**2**) was investigated as a model for the change of a bridgehead atom from carbon to nitrogen. We had anticipated that electronic interaction between the basic nitrogen and the quaternary nitrogen would decrease the activating effect of the positive nitrogen toward reactions with base. This was found, as the observed rate of reaction of **2** with base was slower than that of **1**. It appears, however, that more than electronic effects are acting here, for the distribution of reaction pathways is different from that found with **1**. A ring-expanded Stevens rearrangement product, in this case **7**, was again the major basic material formed. Three minor products can be attributed to displacement reactions. Diazabicyclo[2.2.2]octane (**8**-Dabco) is the result of benzyl displacement. Ring-opening displacement provided 1-benzyl-4-*n*-hexylpiperazine (**9**). The third minor product was not identified but appeared to have incorporated two butyl groups on the piperazine nucleus. In contrast to **1**, no elimination product (**10**) was observed in this system.



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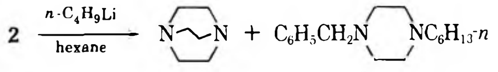
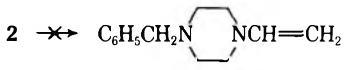


8 **9**



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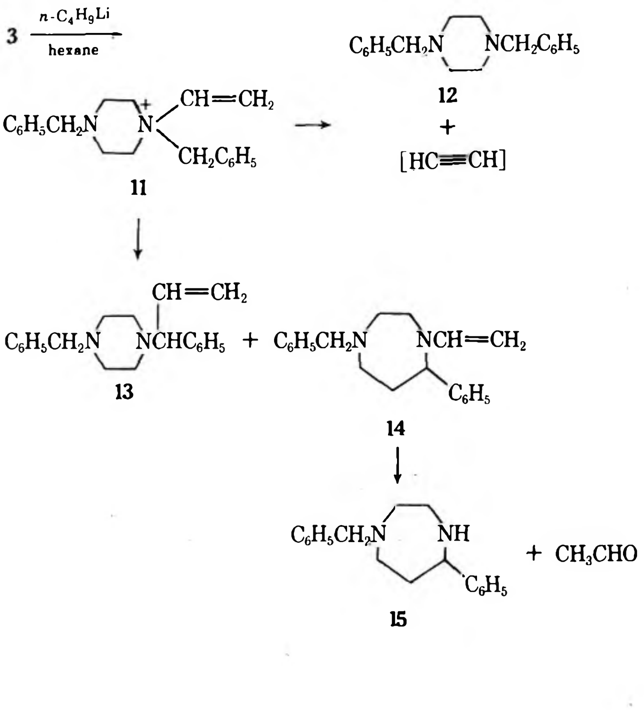
Being an enamine, **10** would have been hydrolyzed during work-up to acetaldehyde and *N*-benzylpiperazine, but neither of these were found.

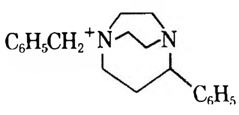
The change in reaction pathways when **2** is compared with **1** could be partly due to small conformational changes as bond lengths and possibly angles are altered. We prefer, however, to attribute the major influence to introduction of the bridgehead nitrogen atom at the 4 position, which reduces the acidity of the molecule. This has the general effect of reducing the reactivity toward base, most notably the elimination. Formation of the benzylic carbanion ylide precursor to the Stevens rearrangement becomes slower while the dispalcement reactions are little influenced by this change and become relatively more important.

The importance of substrate acidity in these reactions is clearly illustrated by the Dabco disalt **3**. Treatment with *n*-butyllithium in hexane results in a rapid, somewhat exothermic reaction. The three basic products were identified as dibenzylpiperazine (**12**), 1-benzyl-4-(α-vinylbenzyl)piperazine (**13**), and 1-benzyl-5-phenylperhydro-1,4-diazepine (**15**). All of these can arise from the vinylammonium salt **11** formed in an initial ring-opening elimination. The major product **12** (60%) then is produced by a second elimination with the loss of acetylene. This same sequence has been observed by Hromatka and Skopalik[8] in the reaction of Dabco dimethyl disalt. The vinylammonium salt intermediate **11** also leads to a novel vinyl Stevens rearrangement product **13** (30%), and a ring-expanded



rearrangement product **14** recovered after enamine hydrolysis as **15** (10%) and acetaldehyde.

Another potential percursor to the Stevens rearrangement products **13** and **14** is **16**, the result of an initial ring-expanding Stevens rearrangement. Ring-opening elimination at either the three-carbon or two-carbon bridge would provide **13** and **14**, respectively. Evidence that **16** is not involved was provided through its independent synthesis (from **7**) and treatment with *n*-butyllithium in hexane. This monosalt (**16**) rapidly reacted to give principally a second ring-expanded Stevens rearrangement product **17** (or **18**). Only a small amount of **13** was found and **14** and **15** were absent.



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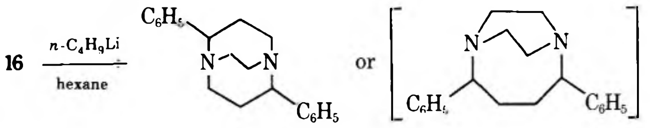
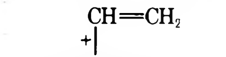


17 **18**

Our assignment of the structure as **17** is based on a more favorable relief of strain in the ring-expansion process and examination of models of **17** and the alternative structure **18** in relation to the spectral data obtained. The rapid reaction of **16** can be attributed to the more flexible [3.2.2] ring system, which allows the necessary migration of a two-carbon chain to the benzylic ylide carbanion. Models show that this should be more facile than in the [2.2.2] bicyclic compounds.

A vinyl rearrangement as exemplified by the conversion of **11** to **13** has never been reported for the Stevens or related 1,2-anionic rearrangements.[4a] We thus chose to investigate the parent benzyldimethylvinylammonium salt (**19**) to determine whether the vinyl rearrangement occurs only in the cyclic case or may be a general reaction.

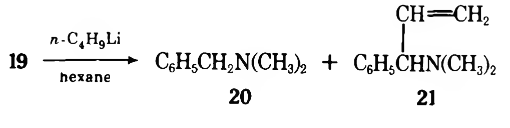


$$C_6H_5CH_2\overset{+}{N}(CH=CH_2)(CH_3)_2\ OH^-$$

19

The desired vinylammonium salt (**19**) was synthesized as outlined below. Treatment of the vinylammonium salt (**19**) with *n*-butyllithium in hexane provided two basic products separable by preparative gas chromatography and identified as benzyldimethylamine (**20**) and α-vinylbenzyldimethylamine (**21**). The product yields (80 and 20%, respectively) were similar to that found with the bicyclic salt **3**. It therefore appears that this hitherto unknown vinyl rearrangement is expected to be general in vinylammonium systems.

$$ClCH_2CH_2N(CH_3)_2 + C_6H_5CH_2Cl \longrightarrow C_6H_5CH_2\overset{+}{N}(CH_2CH_2Cl)(CH_3)_2 \xrightarrow{OH^-} \mathbf{19}$$



$$\mathbf{19} \xrightarrow[\text{hexane}]{n\text{-}C_4H_9Li} C_6H_5CH_2N(CH_3)_2 + C_6H_5CH(CH=CH_2)N(CH_3)_2$$

20 **21**

Conclusions

The bicyclic mono- and diquaternary ammonium salts, when treated with strong base, may follow three reaction pathways: Stevens rearrangement, elimination, or nucleophilic displacement. It appears that relative acidity of the potentially reactive hydrogen atoms within the molecule is the dominant factor in controlling these pathways rather than small conformational changes. Thus the Dabco disalt **3** provides the most acidic β hydrogen atoms and leads initially to an elimination product. Comparison of the quinuclidinium (**1**) and Dabco (**2**) monosalts demonstrates that substitution of a nitrogen atom for a bridgehead carbon atom decreases overall acidity and removes the elimination pathway. A novel vinyl Stevens rearrangement was observed from **3** and confirmed with the parent benzyldimethylvinylammonium system **19**.

Experimental Section

1-Benzyl-1-azoniabicyclo[2.2.2]octane Chloride and Fluoroborate (1). 1-Azabicyclo[2.2.2]octane [formed from 1.0 g (0.007 mol) of the hydrochloride salt] and 1.7 g (0.014 mol) of benzyl chloride were allowed to react in 25 ml of acetone. After 1 hr 1.2 g of solid was recovered. Recrystallization from absolute ethanol–ether gave white crystals, mp 241–242°. Traces of water present could not be removed by numerous methods.

The chloride salt (0.5 g) was dissolved in 10 ml of water and a saturated aqueous solution of silver fluoroborate was added until precipitation ceased. The filtrate was concentrated and cooled to give 0.5 g of solid, which was recrystallized from chloroform–ethyl acetate to give white crystals: mp 131.0–132.0°; nmr ($CDCl_3$) δ 1.7–2.3 (m, 7), 3.3–3.7 (m, 6, $^+NCH_2$), 4.40 (s, 2, $C_6H_5CH_2$), 7.44 (s, 5, C_6H_5).

Anal. Calcd for $C_{14}H_{20}NBF_4$: C, 58.15; H, 6.97; N, 4.84. Found: C, 58.33; H, 6.82; N, 4.84.

1-Benzyl-1-azonia-4-azabicyclo[2.2.2]octane Chloride and Fluoroborate (2). 1,4-Diazabicyclo[2.2.2]octane (5.6 g, 0.05 mol) and 7.5 g of benzyl chloride were allowed to react in 150 ml of acetone. The reaction was slightly exothermic. After 2 hr the precipitate was collected to give 10 g of crude product. Recrystallization from absolute ethanol–ethyl acetate gave 8 g, broad mp *ca.* 147°. Varying amounts of water present could not be removed by numerous drying procedures.

The chloride salt (1.0 g) was mixed with 3.2 g of sodium tetrafluoroborate in 25 ml of water. The solution was evaporated to dryness, and final traces of water were removed under vacuum. The solid was stirred with chloroform and the soluble material was recovered to give 1.2 g of crystalline material. Recrystallization from chloroform–ethyl acetate gave 0.9 g: mp 148.0–149.0°; nmr ($CDCl_3$) δ 3.25 (m, 12, CH_2), 4.50 (s, 2, $C_6H_5CH_2$), 7.4 (s, 5, C_6H_5).

Anal. Calcd for $C_{13}H_{19}N_2BF_4$: C, 53.82; H, 6.60; N, 9.66. Found: C, 53.59; H, 6.28; N, 9.67.

1,4-Dibenzyl-1,4-diazoniabicyclo]2.2.2[octane Dichloride (3). 1,4-Diazabicyclo[2.2.2]octane (1.1 g, 0.01 mol) and 3.7 g (0.03 mol) of benzyl chloride in 15 ml of absolute ethanol were refluxed for 2 hr. After cooling, ether was added to precipitate the product, giving 2.5 g of white solid. Recrystallization from absolute ethanol–ether gave crystals: mp 240° dec; nmr (D_2O) δ (from external TMS) 3.95 (s, 12, $^+NCH_2$), 4.74 (s, 4, $C_6H_5CH_2$), 7.55 (s, 10, C_6H_5).

Anal. Calcd for $C_{20}H_{26}N_2Cl_2$: C, 65.75; H, 7.17; N, 7.67. Found: C, 65.53; H, 7.20; N, 7.35.

Benzyldimethylvinylammonium Hydroxide and Fluoroborate (19). *N*-β-Chloroethyldimethylamine hydrochloride (1.0 g) was dissolved in 5 ml of distilled water and 10 ml of chloroform was added. Sodium hydroxide (6 *N*) solution was added until the aqueous layer gave an alkaline reaction, the mixture was shaken, and the chloroform layer was separated. The aqueous layer was extracted a second time with chloroform (10 ml), and the combined chloroform extracts were dried over magnesium sulfate. Benzyl chloride (1 ml) was added to the chloroform solution and heated to 45° for 16 hr. The solvent and volatile starting material were removed under vacuum to give benzyl(β-chloroethyl)dimethylammonium chloride (1.2 g) as a white, hygroscopic solid: nmr (D_2O) δ (from external TMS) 3.15 [s, 6, $N(CH_3)_2$], 3.77 (t, J = 5.5 Hz, 2, NCH_2), 4.10 (t, J = 5.5 Hz, 2, CH_2Cl), 4.58 (s, 2, $C_6H_5CH_2$), 7.55 (s, 5, C_6H_5).

The chloro salt (0.5 g) was dissolved in water (1 ml) and sodium fluoroborate in water (10 ml, 30%) was added. An oil was precipitated which rapidly crystallized. It was filtered off and recrystallized from acetone–chloroform, mp 96–97°.

Anal. Calcd for $C_{11}H_{17}NClBF_4$: C, 46.27; H, 6.00; N, 4.91. Found: C, 46.22; H, 6.03; N, 4.76.

Benzyl(β-chloroethyl)dimethylammonium chloride (1.0 g) was dissolved in distilled water (10 ml) and introduced onto a column of Amberlite ion exchange resin (IRA 4015) in the hydroxide form (length 135 mm, diameter 0.20 mm). The solution was allowed to remain in contact with the resin for 10 min and was then eluted with water and the column was washed further with water until the eluate was no longer alkaline. The total eluate was then evaporated to give solid **19**: nmr (D_2O) δ 3.25 [s, 6, $N(CH_3)_2$], 5.5 (m, 2, $=CH_2$), 6.5 (m, 1, $=CH$), 6.65 (s, 2, $C_6H_5CH_2$), 7.55 (s, 5, C_6H_5).

The hydroxide salt (**19**) prepared from 0.5 g of chloride was dissolved in a minimum amount of water and 10 ml of 30% sodium fluoroborate was added. The oil which precipitated solidified upon drying and was recrystallized from acetone–chloroform, mp 75.5–77.0°.

Anal. Calcd for $C_{11}H_{16}NBF_4$: C, 53.05; H, 6.48; N, 5.62. Found: C, 52.79; H, 6.46; N, 5.72.

Reaction of 1. The chloride salt (1.0 g, 4×10^{-4} mol) was stirred with 6 ml of 1.6 *M* *n*-butyllithium in hexane (1×10^{-2} mol) under nitrogen at 50° for 20 hr. The reaction mixture was cooled and 15 ml of water was carefully added. Recovery of the basic material using dilute hydrochloric acid and regeneration with dilute sodium hydroxide gave 0.4 g of chloroform-soluble yellow oil. The original aqueous phase gave *ca.* 0.5 g (50%) of unreacted starting material. The basic oil, shown to be two components by tlc, was separated by column chromatography on grade II alumina using 30–60° petroleum ether with increasing concentrations of ether. The minor component (0.1 g) eluted first and was identified as **4**: nmr (CCl_4) δ 1.3–3.0 (m, 9), 3.42 (s, 2, $C_6H_5CH_2$), 4.84, 4.90 (m, 2, $=CH_2$), 5.75 (m, 1, $=CH$), 7.22 (s, 5, C_6H_5).

The slower moving component (0.3 g) was identified as **5**: nmr (CCl_4) δ 1.2–2.3 (m, 9), 2.6–3.3 (m, 4, NCH_2), 3.78 (d of d, J = 5, 10 Hz, 1, C_6H_5CH), 7.0–7.4 (m, 5, C_6H_5).

Anal. Calcd for $C_{14}H_{19}N$: C, 83.59; H, 9.45; N, 6.96. Found: C, 83.78; H, 9.47; N, 7.27.

Reaction of 2. The chloride salt (0.25 g, 1×10^{-3} mol) and 3.2×10^{-3} mol of *n*-butyllithium in 12 ml of hexane was stirred under nitrogen at 50–55° for 3 days. After cooling, water was carefully added and 0.1 g of brown oil was collected from the hexane layer. Partition of this oil between 1 *N* hydrochloric acid and chloroform ultimately yielded 0.05 g of basic materials. Additional rearrangement product **7** could be obtained from the aqueous layer (along with **8**) by partitioning between chloroform and water. The mixed basic materials were purified by column chromatography on grade III alumina using petroleum ether–ether as eluent. The first component eluted was not identified. The second component was identified as **9**: nmr (CCl_4) δ 0.7–1.8 (m, 11, $n\text{-}C_5H_{11}$), 1.9–2.8 (m, 10 NCH_2), 3.42 (s, 2, $C_6H_5CH_2$), 7.2 (m, 5, C_6H_5). The third component was identified as **7**: nmr (CCl_4) δ 1.6–3.7 (m, 4), 2.7 (m, 4), 2.96 (s, 4) 3.89 (d of d, J = 5.5, 11.5 Hz, 1, C_6H_5CH), 7.2 (m, 5, C_6H_5). Methiodide crystallized from absolute ethanol: mp 193–195° dec; nmr (D_2O) δ (external TMS) 3.25 (s, 3, $^+NCH_3$), 2.0–4.1 (m, 12), 4.32 (d of d, J = 5, 12 Hz, 1, C_6H_5CH), 7.45 (s, 5, C_6H_5).

Anal. Calcd for $C_{14}H_{21}N_2I$: C, 48.71; H, 6.42; N, 8.11. Found: C, 48.84; H, 6.14; N, 7.95.

Unreacted starting material and **8** were identified by their nmr spectra.

Reaction of 3. To the dichloride (0.60 g, 1.6×10^{-3} mol) in 15 ml of hexane was added 6 ml (1×10^{-2} mol) of 1.6 *N* *n*-butyllithium in hexane. The mixture spontaneously warmed and after 0.5 hr was further heated at 50° for an additional 1 hr. Work-up as above gave 0.52 g of basic products which could be separated by column chromatography on silica gel. The first component (0.15 g) was eluted using 20% ether in petroleum ether (bp 60–80°) and was identified as **13**: nmr (CCl_4) δ 2.37 (s, 8, CH_2), 3.40 (s, 2, $C_6H_5CH_2$), 3.58 (d, J = 8 Hz, 1, CH), 4.97, 5.10 (m, 2, $=CH_2$), 5.86 (m, 1, $=CH$), 7.18 (s, 5, C_6H_5). The methiodide crystallized from acetone: mp 202–203° dec; nmr ($CDCl_3$) δ 2.0–4.0 (m, 8, CH_2), 3.30 (s, 3, CH_3), 3.98 (d, J = 8 Hz, 1, C_6H_5CH), 5.16 (s, 2, $C_6H_5CH_2$), 5.0–6.2 (m, 3, $CH{=}CH_2$), 7.30 (s), and 7.2–7.8 (m) (total 10).

Anal. Calcd for $C_{21}H_{27}N_2I$: C, 58.07; H, 6.22; N, 6.45. Found: C, 58.27; H, 6.35; N, 6.24.

The second component (0.30 g) was eluted with ether and identified as **12**: mp 89.0–90.0° (reported mp 92°);[9] nmr (CCl_4) δ 2.38 (s, 8, NCH_2), 3.42 (s, 4, $C_6H_5CH_2$), 7.17 (s, 10, C_6H_5).

The third component (0.05 g) was eluted with methanol and identified as **15**: nmr (CCl_4) δ 1.5–3.0 (m, 10, ring H's, NH), 3.44 (s, 2, $C_6H_5CH_2$), 7.0–7.5 (m, 10, C_6H_5). This oil formed a *p*-toluenesulfonamide which was an oil. In a separate run, acetaldehyde was identified as its 2,4-dinitrophenylhydrazone.

Preparation and Reaction of 16. The reaction of **7** and benzyl chloride in acetone overnight gave an insoluble oil which slowly solidified on further washing with acetone. Recrystallization from acetone–chloroform gave **16**, yellow crystals, mp 185°, which was not purified further, nmr (D_2O) δ 2.2–4.3 (m, 13), 5.1 (s, 2, $C_6H_5CH_2$), 7.1–7.9 (m, 10, C_6H_5).

The chloride salt **16** (0.16 g, 0.5×10^{-3} mol) in 10 ml of hexane was stirred with 2.5×10^{-3} mol of *n*-butyllithium under nitrogen at 55° for 2 hr. Work-up gave 0.15 g of colorless oil which was crystallized from cold petroleum ether to give **17** as yellow crystals: mp 109–110°; nmr (CCl_4) δ 1.9–3.4 (m, 12), 4.0 (t, 9, C_6H_5CH), 7.0–7.5 (m, 10, C_6H_5). In addition a small amount of **13** was found, confirming the structural assignment for **16**.

Reaction of 19. Benzydimethylvinylammonium hydroxide (from 1.0 g of chloro salt, 4.6×10^{-3} mol) was suspended in 50 ml of *n*-hexane, and 8 ml of 1.6 *M* *n*-butyllithium solution in hexane (13×10^{-3} mol) was added with stirring. The mixture was heated 45–50° under reflux overnight and after cooling, water (10 ml) was added dropwise. The basic products were recovered as a yellow oil and separated by gas chromatography using 8 ft of Carbowax 20 M on Chromosorb 60–80 WAW at 150°. The two components were identified as benzyldimethylamine (**20**) and α-vinylbenzyldimethylamine (**21**): nmr (CCl_4) δ 2.1 [s, 6, $N(CH_3)_2$], 3.45 (d, J = 8 Hz, 1, C_6H_5CH), 5.0 (d of d, J = 2, 9 Hz), and 5.1 (d of d, J = 2, 17 Hz, 2, $=CH_2$), 5.9 (d of d of d, J = 8, 9, 17 Hz, 1, $=CH$), 7.19 (s, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69. Found: C, 82.10; H, 9.23; N, 8.80.

Registry No. **1**, 42790-41-0; **1** fluoroborate, 42790-20-5; **2**, 42790-42-1; **2** fluoroborate, 42790-21-6; **3**, 42790-43-2; **4**, 42790-44-3; **5**, 42790-45-4; **7**, 42790-46-5; **7** methiodide, 42790-47-6; **9**, 42992-87-0; **12**, 1034-11-3; **13**, 42790-49-8; **13** methiodide, 42790-50-1; **15**, 42790-51-2; **16**, 42790-52-3; **16** chloride salt, 42790-53-4; **17**, 42992-88-1; **19** hydroxide, 42790-54-5; **19** fluoroborate, 42790-22-7; **20**, 103-83-3; **21**, 42790-56-7; 1-azabicyclo[2.2.2]octane, 100-76-5; 1,4-diazabicyclo[2.2.2]octane, 280-57-9; *N*-β-chloroethyldimethylamine hydrochloride, 4584-46-7; benzyl(β-chloroethyl)dimethylammonium chloride, 42790-57-8.

References and Notes

(1) Support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation is gratefully acknowledged.

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Catalysis by Added Salts in the Reaction of Benzenesulfonyl Chloride with *N*-Methylaniline in Chloroform and in Acetone

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The rate of reaction of benzenesulfonyl chloride with *N*-methylaniline in chloroform and in acetone at 24.4 ± 0.1° is strongly accelerated by added salts such as *N*-methylaniline hydrochloride, benzyltriethylammonium chloride, benzyltriethylammonium nitrate, and tetraethylammonium perchlorate. It is proposed that the observed rate increases are due to base catalysis, with the ion pair from the salt actually participating in the rate-determining transition state, rather than to a neutral salt effect.

Reactions in which a proton is transferred somewhere along the reaction path from reactants to products are capable of exhibiting base catalysis under appropriate conditions. Such catalysis has been demonstrated for the reaction of 2,4-dinitrochlorobenzene with *n*-butylamine in chloroform[1] and for the ethanolysis of benzoyl chlorides in acetone and chloroform.[2] In both of these reactions an intermediate addition complex is formed, the rate-determining process involves only bond formation, and the observed catalysis is catalysis of intermediate formation. A reconsideration of presumed salt effects in the reaction of phenacyl bromide with *N*-ethylaniline in chloroform[3] indicates that these results, too, are better explained by invoking base catalysis. This last reaction is of the SN2 type and does not involve an addition intermediate.

The rates of reaction of substituted benzenesulfonyl chlorides with various substituted anilines have been measured in methanol.[4] Substituent effects in the sulfonyl chloride and aniline were correlated by Hammett and Brønsted equations, respectively, and the conclusion was reached that the reaction is a one-step, nucleophilic substitution on sulfur. This interpretation, although further supported by the finding that phenyl benzenesulfonate shows no ^{18}O exchange during either basic[5] or acidic[6] hydrolysis, is arguable.

Ciuffarin, Senatore, and Isola[7] have measured the leaving group mobilities for the reactions of the benzenesulfonyl halides with aniline, *n*-butylamine, and hydroxide ion. The leaving group mobilities of iodide, bromide, and chloride proved to be very similar for each nucleophile, and the authors have buttressed this finding with carefully reasoned arguments in support of a mechanism involving an intermediate complex with bond forming as the rate-limiting step.

In the present study the rates of reaction of benzenesulfonyl chloride with *N*-methylaniline in chloroform and in acetone were determined at 24.4 ± 0.1°. Since the conversion of these reactants to the *N*-methylanilide involves a proton transfer, special attention was given to the possibility of observing base catalysis in this reaction. The study also included measurements of the effect of added salts on the reaction rate.

Results

The reaction of benzenesulfonyl chloride with *N*-methylaniline proved to be autocatalytic, and second-order plots were strongly concave upward. The initial addition of *N*-methylbenzenesulfonylanilide had only a trivial effect on the observed rates, but the initial addition of *N*-methylaniline hydrochloride resulted in a strong acceleration of the reaction rate, and with the initial amine hydrochloride at one-fifth the initial concentration of the benzenesulfonyl chloride or higher, second-order plots were linear to beyond 60% reaction and permitted the determination of apparent second-order rate constants. These have been tabulated in Table I.

In the first four experiments shown in Table I both the initial benzenesulfonyl chloride concentrations and the initial amine hydrochloride concentrations were kept constant, and the initial *N*-methylaniline concentrations were varied. The rate constants that resulted were constant, well within experimental error. The average of the value obtained was 2.44×10^{-2} l. mol^{-1} min^{-1} and the maximum deviation from this average value was only slightly more than 3%.

In the last four experiments in Table I, the amine and acid chloride concentrations were constant and the amounts of added amine hydrochloride were varied. In these experiments the values of the second-order rate constants increase with increasing initial amine hydrochloride concentration. Since a plot of log k_2^* *vs.* $\mu_0^{1/2}$, where μ_0 is the initial ionic strength, is linear, the observed rate accelerations might be attributed to a salt effect. However, a plot of k_2^* *vs.* the initial amine concentration is also linear, as shown in Figure 1. The results presented to this point, can, therefore, be accommodated equally well by assuming that the aminolysis reaction is catalyzed by the amine hydrochloride. The experimental results will be presented on the basis of this latter assumption, and the assertion that a salt effect is not significantly involved will be justified in the subsequent discussion.

Assuming, as we have, that the observed rate increases are due to catalysis and not to a salt effect, the rate expression wil be given by eq 1, where A is the benzenesulfonyl chloride, B is the amine, C is the amine hydrochloride, and X is the product (A, B, C, and X are their concentrations, respectively). Since an increase in the initial amine concentration does not result in an increase in the experimental second order rate constant, k_2 must be equal to zero. The values of k_1 and k_3 can be obtained from the intercept and slope, respectively, of the plot of k_2^* *vs.* C_0 shown in Figure 1, and a least-squares treatment led to a value of 1.83×10^{-2} l. mol^{-1} min^{-1} for k_1 and a value of 0.543 l.^{2} mol^{-2} min^{-1} for k_3.

$$\mathrm{d}x/\mathrm{d}t = k_1AB + k_2AB^2 + k_3ABC \qquad (1)$$

The ratio of k_3 to k_1 above is 29.7 l. mol^{-1}. This is sufficiently large so that at a high initial concentration of the amine hydrochloride the rate of the uncatalyzed reaction will be negligible with respect to that of the catalyzed reaction. The simplified rate expression, eq 2, becomes

$$\frac{\mathrm{d}x}{\mathrm{d}t} \cong k_3(A_0 - X)(B_0 - 2X)(C_0 + X) \qquad (2)$$

appropriate, and this can be integrated to give eq 3.

Table I
Rates of Reaction of Benzenesulfonyl Chloride and N-Methylaniline in the Presence of Initially Added N-Methylaniline Hydrochloride in Chloroform at 24.4 ± 0.1°

$C_6H_5SO_2Cl$, mol l.$^{-1}$	$C_6H_5NHCH_3$, mol l.$^{-1}$	$C_6H_5N^+H_2CH_3$, Cl^-, mol l.$^{-1}$	$k_2^* \times 10^2$, l. mol^{-1} min^{-1}
0.05015	0.1217	0.01026	2.45
0.05026	0.1834	0.01016	2.36
0.05023	0.2754	0.01020	2.52
0.05134	0.3677	0.01022	2.41
0.05026	0.1834	0.01016	2.36
0.05050	0.1833	0.02482	3.22
0.05001	0.1832	0.05019	4.52
0.04993	0.1830	0.07915	6.14

$$k_3t = \frac{(B_0 + 2C_0)\ln\dfrac{A_0 - X}{A_0} - 2(A_0 + C_0)\ln\dfrac{B_0 - 2X}{B_0} + (2A_0 - B_0)\ln\dfrac{C_0 + X}{C_0}}{(2A_0 - B_0)(A_0 + C_0)(B_0 + 2C_0)} \qquad (3)$$

Equation 3 in conjunction with the data for the last run shown in Table I was used to obtain a value for k_3. A plot of t *vs.* the right side of eq 3 was linear, with all eight experimental points on the line, and the slope, equal to k_3, was 0.506 l.^{2} mol^{-2} min^{-1}, in good agreement with the value obtained from the plot of k_2^* *vs.* C_0.

A more general rate expression, containing terms for both the uncatalyzed and the catalyzed reactions, is given by eq 4. Equation 4 can be integrated in a useful form by

$$dx/dt = k_1(A_0 - X)(B_0 - 2X) + k_3(A_0 - X) \times (B_0 - 2X)(C_0 + X) \qquad (4)$$

making the substitution $D_0 = C_0 + k_1/k_3$. The integrated expression that results is eq 5. Using the previously obtained estimates for k_1 and k_3, which gave a value of 0.0337 mol l.$^{-1}$ for the ratio k_1/k_3, eq 5 was used in con-

$$k_3t = \frac{\ln[A_0/(A_0 - X)]}{(B_0 - 2A_0)(D_0 + A_0)} + \frac{2\ln[B_0/(B_0 - 2X)]}{(2A_0 - B_0)(2D_0 + B_0)} - \frac{\ln[D_0/(D_0 + X)]}{(A_0 + D_0)(B_0 + 2D_0)} \qquad (5)$$

junction with the data for the last four experiments in Table I to calculate additional values for k_3. All four of the experiments gave good linear plots, and the k_3's that resulted ranged from 0.44 to 0.50 l.^{2} mol^{-2} min^{-1}, with the average value being 0.48 l.^{2} mol^{-2} min^{-1}. Increasing the ratio k_1/k_3 to 0.0355 mol l.$^{-1}$ led to a lower average value, 0.45 l.^{2} mol^{-1} min^{-1}, for k_3, and decreasing the ratio to a value lower than 0.0337 mol l.$^{-1}$ would presumably result in higher values for k_3. The fit, although not ideal, is still sufficient to provide some confidence in the validity of the treatment.

The presumed catalysis due to N-methylaniline hydrochloride could be either acid catalysis, with hydrogen bonding to the departing chlorine atom of the benzenesulfonyl chloride facilitating reaction, or base catalysis, with chloride ion or the N-methylaniline hydrochloride ion pair assisting in the proton transfer from the N-methylaniline. To permit a choice between these two alternatives, the reaction rates with initially added benzyltriethylammonium chloride and benzyltriethylammonium nitrate were measured. These two salts would be expected to be effective in base catalysis *via* hydrogen bonding to the hydrogen of N-methylaniline but would be ineffective in acid catalysis. The results are shown in Table II.

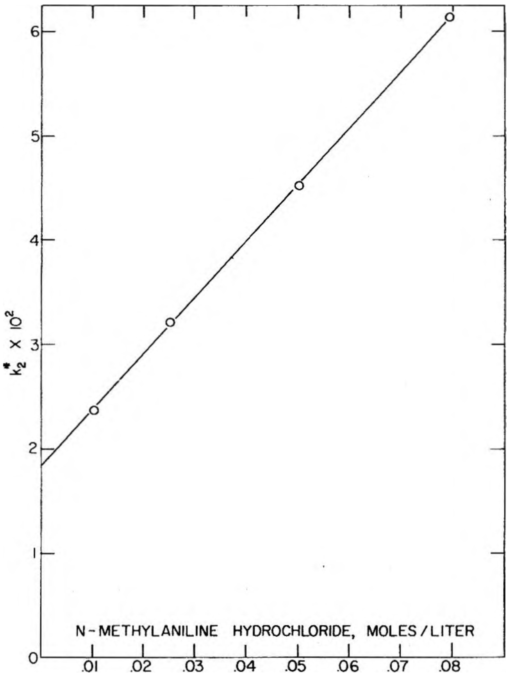


Figure 1. k_2^* *vs.* the initial concentrations of N-methylaniline hydrochloride in chloroform at 24.4 ± 0.1°.

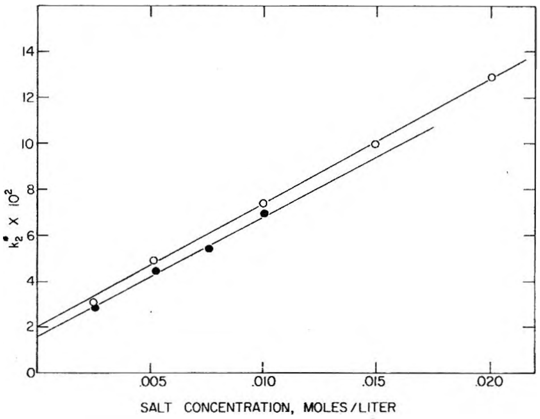


Figure 2. k_2^* *vs.* the initial concentrations of benzyltriethylammonium chloride (lower line) and benzyltriethylammonium nitrate (upper line) in chloroform at 24.4 ± 0.1°.

Both sets of data in Table II gave linear plots of k_2^* *vs.* the salt concentrations, as shown in Figure 2. The intercepts and slopes of these lines result in two additional values for k_1 and the rate constants for the reactions catalyzed by the quaternary ammonium chloride and the nitrate, k_4 and k_5, respectively. The values obtained, using the method of least squares, for k_1 were 1.64 × 10^{-2} l. mol^{-1} min^{-1} from the chloride and 2.00 × 10^{-2} l. mol^{-1} min^{-1} from the nitrate. The k_4 and k_5 obtained from the slopes of the two straight lines were 5.33 and 5.47 l.^{2} mol^{-2} min^{-1}, respectively. Since the quaternary ammonium chloride is ten times more effective in accelerating the reaction rate than the amine hydrochloride, it can be concluded that acid catalysis is not involved.

In acetone as solvent the reaction does not exhibit the strong autocatalytic characteristics observed in chloroform. Individual runs give linear second-order plots to beyond 60% reaction. However, at constant initial concentrations of the sulfonyl chloride, the rate constants obtained increase with increasing initial N-methylaniline concentrations. The observed increases in k_2^* are small

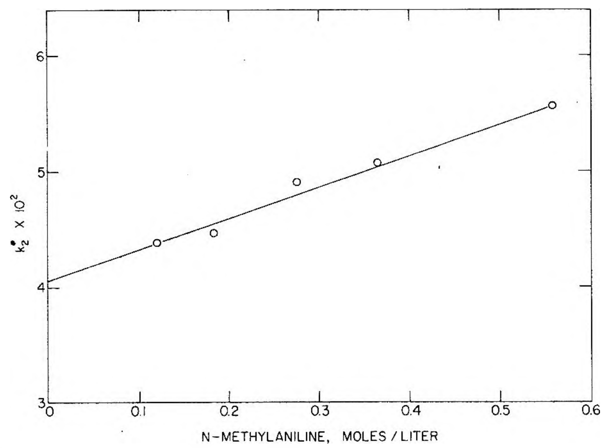


Figure 3. k_2^* *vs.* the initial *N*-methylaniline concentrations in acetone at 24.4 ± 0.1°.

Table II
Rates of Reaction of Benzenesulfonyl Chloride and *N*-Methylaniline in the Presence of Initially Added Benzyltriethylammonium Chloride and Benzyltriethylammonium Nitrate in Chloroform at 24.4 ± 0.1°

$C_6H_5SO_2Cl$, mol l.$^{-1}$	$C_6H_5NHCH_3$, mol l.$^{-1}$	Added salt, mol l.$^{-1}$	$k_2^* \times 10^2$, l. mol^{-1} min^{-1}
A. Benzyltriethylammonium Chloride			
0.05040	0.1821	0.002507	2.88
0.05072	0.1843	0.005115	4.59
0.05069	0.1827	0.007569	5.51
0.05011	0.1847	0.01008	7.04
B. Benzyltriethylammonium Nitrate			
0.05042	0.1843	0.002442	3.18
0.05007	0.1829	0.005108	4.92
0.04985	0.1839	0.009952	7.50
0.05024	0.1829	0.01491	10.1
0.05025	0.1853	0.02010	13.0

Table III
Rates of Reaction of Benzenesulfonyl Chloride and *N*-Methylaniline with and without Added *N*-Methylaniline Hydrochloride and Benzyltriethylammonium Nitrate in Acetone at 24.4 ± 0.1°

$C_6H_5SO_2Cl$, mol l.$^{-1}$	$C_6H_5NHCH_3$, mol l.$^{-1}$	Added salt, mol l.$^{-1}$	$k_2^* \times 10^2$, l. mol^{-1} min^{-1}
0.05074	0.1201		4.39
0.05042	0.1837		4.47
0.05044	0.2757		4.91
0.05087	0.3640		5.08
0.05054	0.5575		5.57
A. *N*-Methylaniline Hydrochloride			
0.05050	0.1831	0.01005	5.09
0.05037	0.1820	0.01759	5.43
0.05040	0.1832	0.02515	5.84
0.05044	0.1829	0.03776	6.49
B. Benzyltriethylammonium Nitrate			
0.05022	0.1819	0.00510	6.28
0.05080	0.1834	0.01010	7.83
0.05057	0.1839	0.02008	11.1
C. Tetraethylammonium Perchlorate			
0.05002	0.1835	0.00498	5.05
0.05055	0.1849	0.01009	5.46
0.05012	0.1831	0.01972	6.06

but beyond possible experimental error. With initially added *N*-methylaniline hydrochloride the observed increases in k_2^* are larger, and with initially added benzyltriethylammonium nitrate the k_2^*'s are larger still. These results are assembled in Table III.

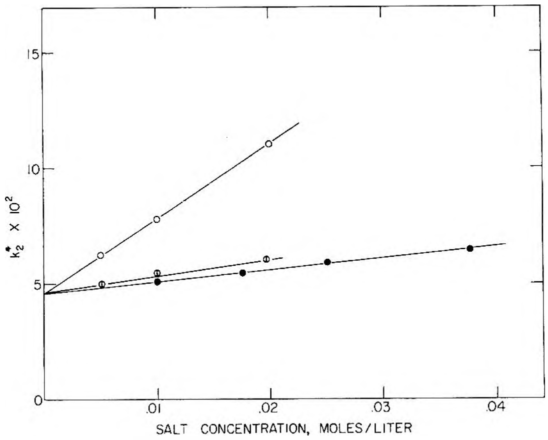


Figure 4. k_2^* *vs.* the initial concentrations of *N*-methylaniline hydrochloride (lower line), tetraethylammonium perchlorate (middle line), and benzyltriethylammonium nitrate (upper line) in acetone at 24.4 ± 0.1°.

Table IV
Rate Constants for the Uncatalyzed and Catalyzed Reactions of Benzenesulfonyl Chloride and *N*-Methylaniline in Chloroform and in Acetone at 24.4 ± 0.1°

	Chloroform	Acetone
$k_1 \times 10^2$, l. mol^{-1} min^{-1} Uncatalyzed reaction	1.83	4.05
$k_2 \times 10^2$, l.^{2} mol^{-2} min^{-1} Catalysis by *N*-methylaniline	0	2.79
k_3, l.^{2} mol^{-2} min^{-1} Catalysis by *N*-methylaniline hydrochloride	0.543	0.529
k_4, l.^{2} mol^{-2} min^{-1} Catalysis by benzyltriethylammonium chloride	5.47	
k_5, l.^{2} mol^{-2} min^{-1} Catalysis by benzyltriethylammonium nitrate	5.33	3.28
k_6, l.^{2} mol^{-2} min^{-1} Catalysis by tetraethylammonium perchlorate		0.677
k_2/k_1, l. mol^{-1}	0	0.69
k_3/k_1, l. mol^{-1}	29.7	13.1
k_4/k_1, l. mol^{-1}	299	
k_5/k_1, l. mol^{-1}	291	81.0
k_6/k_1, l. mol^{-1}		16.7

A plot of k_2^* *vs.* the initial amine concentrations for the first five runs in Table III is linear, as shown in Figure 3. The intercept of this line is equal to k_1, the rate constant for the uncatalyzed reaction in acetone, and the slope is equal to k_2, the rate constant for the reaction catalyzed by *N*-methylaniline. The constants obtained were 4.05 × 10^{-2} l. mol^{-1} min^{-1} for k_1 and 2.79 × 10^{-2} l.^{2} mol^{-2} min^{-1} for k_2.

Plots of k_2^* vs. the initial *N*-methylaniline hydrochloride concentrations (lower line in Figure 4), k_2^* *vs.* the initial tetraethylammonium perchlorate concentrations (middle line in Figure 4), and k_2^* *vs.* the initial benzyltriethylammonium nitrate concentrations (upper line in Figure 4) are also linear. In these three cases the intercepts are equal to k_2^* for the reaction with 0.05 *M* chloride and 0.18 *M* amine, rather than to k_1, because of the slight catalysis by *N*-methylaniline. The slopes, however, do provide estimates of the rate constant, k_3, for the reaction catalyzed by *N*-methylaniline hydrochloride, the rate constant, k_6, for the reaction catalyzed by tetraethylammonium perchlorate, and the rate constant, k_5, for the reaction catalyzed by benzyltriethylammonium nitrate, and the constants obtained were 0.529, 0.677, and 3.28 l.^{2} mol^{-2} min^{-1}, respectively.

To facilitate comparisons between the two solvents, all of the rate constants obtained have been assembled in Table IV. Also included are ratios of each catalyzed rate constant to the uncatalyzed rate constant. These afford a direct indication of the relative importance of the uncatalyzed and catalyzed reactions in product formation and, in general, highlight the fact that catalysis is more important in chloroform than in acetone.

Experimental Section

Materials. Eastman Kodak Co. White Label benzenesulfonyl chloride was distilled at 0.2–0.3 mm and a middle cut, bp 60–62°, was retained.

N-Methylaniline was distilled two times under nitrogen from 20 mesh zinc and a few pieces of mossy zinc, a middle cut being taken each time, bp 84–86° (12 mm). The amine was stored under nitrogen when not in use.

Reagent grade chloroform, containing 0.50% ethanol as stabilizer, from the J. T. Baker Co. was used without purification.

Reagent grade acetone was shaken with calcium chloride and then permitted to stand for several hours over calcium chloride. The drying agent was removed by filtration, and the acetone was distilled, with a sizable forerun and residue being discarded.

N-Methylaniline hydrochloride was prepared by standard methods and crystallized two times from methanol-ether, mp 124–126°.

Anal. Calcd for $C_7H_{10}NCl$: Cl, 24.68. Found: Cl, 24.69.

Benzyltriethylammonium nitrate and benzyltriethylammonium chloride were prepared by methods previously described.[8]

Eastman Kodak Co. White Label tetraethylammonium perchlorate was crystallized from water and dried *in vacuo* at 100°, mp 350–351° dec.

Rate Measurements. Separate, determinate solutions of the benzenesulfonyl chloride and the amine were made up at the temperature of the measurements. When salts were used, these were added to the amine solution rather than to the sulfonyl chloride solution. The solutions were mixed at zero time, and 10-ml aliquots were withdrawn at appropriate time intervals and quenched by shaking with a mixture of 50 ml of benzene and 50 ml of 1:4 nitric acid. The acid layer was separated and the benzene layer was extracted two times with 25-ml portions of water. The water extracts were added to the acid extract, and the combined extracts were analyzed for chloride ion by the Volhard method.

Product Isolation Experiments. *N*-Methylbenzenesulfonanilide. *N*-Methylaniline (9.89 g, 0.0923 mol) was added to a solution of benzenesulfonyl chloride (4.13 g, 0.234 mol) in chloroform (100 ml). The solution was left standing at room temperature for 40 hr and diluted with chloroform (150 ml). The diluted solution was washed with water (50 ml) and two times with 100-ml portions of 1:1 hydrochloric acid and finally with water again. The solution was dried over magnesium sulfate. The solvent was removed with the water pump, and the crude product was crystallized from methanol, yield 5.65 g (97.6%), mp 77–78°. A second crystallization raised the melting point to 78–79°.

When the reaction was run in acetone, the reaction mixture was left standing as above. The acetone was then removed, and benzene (250 ml) was added. The subsequent procedure was as already described. The yield of product was 96.3%. A repetition of the experiment with initially added benzyltriethylammonium nitrate in an amount equivalent to the benzenesulfonyl chloride gave an 80.3% yield of *N*-methylbenzenesulfonanilide.

Discussion

Benzenesulfonyl chloride and *N*-methylaniline react cleanly in both chloroform and acetone to give *N*-methylbenzenesulfonanilide and *N*-methylaniline hydrochloride. The exact mechanism of this reaction is uncertain, since the available evidence does not distinguish fully between an SN2 reaction having a transition state close to reactants and a mechanism involving an intermediate addition complex with bond forming as the rate-limiting step.[4-7] In terms of either possible mechanism the rate constants reported herein reflect the bond-making process and are relatively unperturbed by the bond-breaking process.

Although a salt, *N*-methylaniline hydrochloride, is a product of the reaction, the rate-determining transition state can have only modest dipolar characteristics, since bond breaking is either slight or absent at the transition state. Moreover, the starting reagents are neutral molecules, not ions, and a reaction of this type would be expected to show some increase in rate with an increase in the dielectric constant of the solvent but would also be expected to be insensitive to the ionic strength of the medium.[9]

The two solvents chosen for this study were chloroform and acetone. Chloroform has a dielectric constant of 4.81 at 20°.[10-12] It can function as a donor in hydrogen bonding but not as an acceptor. Acetone has a dielectric constant of 20.7 at 25°.[13-16] It, in contrast, can function as an acceptor in hydrogen bonding but is relatively ineffective as a donor. The overall reaction rates were, as anticipated, somewhat faster in the solvent of higher dielectric constant, acetone, but the observed accelerations in reaction rate on addition of salts greatly exceeded those that might have been expected as a result of increasing the ionic strength of the medium.

Plots of k_2^* *vs.* the square root of the ionic strength, $\mu^{1/2}$, are linear for the experiments with added salts, but the significance of this observation is questionable. The reactants are not ions, and the Brønsted–Bjerrum theory of salt effects,[17,18] which is valid only for dilute solution reactions between ions at small μ (below 0.01 *M* for 1:1 electrolytes), does not properly apply.[19] Moreover, the salts are only very slightly dissociated in the solvents used, whereas the μ's used in the linear plots of k_2^* *vs.* $\mu^{1/2}$ assumed complete dissociation. Fuoss and Kraus[20] have studied ion-pair formation as a function of the dielectric constant by measuring the equilibrium constants for ion-pair dissociation for tetraisoamylammonium nitrate in dioxane–water mixtures at 25°. Using these results, which covered dielectric constants ranging from 2.38 to 53.0, as a guide, it can be estimated that the equilibrium constants for ion-pair dissociation for quaternary ammonium salts in chloroform and in acetone have values of the order of 10^{-8} and 10^{-2}, respectively. In chloroform, therefore, the salts are present almost entirely as ion pairs and higher aggregates, and even in acetone no more than 10% of the salt is dissociated to free ions.

The foregoing considerations make it improbable that the observed accelerations in rate are attributable to a kinetic salt effect. Further support for this contention is afforded by the results in acetone, shown in Table III and Figure 4. Benzyltriethylammonium nitrate and tetraethylammonium perchlorate would be expected to result in very nearly equivalent salt effects, but in the present system, the rate constant for the reaction catalyzed by the nitrate (k_5 in Table IV) is almost five times as large as the rate constant for the reaction catalyzed by the perchlorate (k_6 in Table IV).

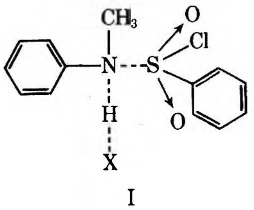
The special case of one or more neutral molecules reacting *via* a strongly dipolar transition state to form oppositely charged ions has also been treated theoretically.[21] A typical case would be the hydrolysis of *tert*-butyl bromide in 90% acetone–10% water, and the treatment leads to a linear relationship between the logarithm of the rate constants and the ionic strength. This treatment is, however, inappropriate for the reactions of present concern, both because the above linear relationship is not observed and because in the absence of extensive bond breaking in the transition state the rate-determining transition state does not have the requisite strong dipolar character.

If the observed rate accelerations due to added salts are not the result of a salt effect, an alternative explanation must be sought. The first suggestion of a possible explanation was provided in an earlier study of rates and salt effects in the reactions of phenacyl bromide with *N*-ethylaniline and triethylamine in chloroform.[3] In the reaction with *N*-ethylaniline the initial addition of 0.057 *M* benzyltriethylammonium nitrate increased k_2^* more than sevenfold, but with triethylamine the addition of the same amount of salt resulted in only a 60% increase in k_2^*. In the first reaction a proton is transferred at some point along the reaction path, and base catalysis is possible. In the reaction with triethylamine, where the product is a quaternary ammonium bromide, this is not the case.

The possibility that a neutral salt can serve as a catalyst, facilitating proton transfer, was explored in greater detail for the reaction of 2,4-dinitrochlorobenzene and *n*-butylamine in chloroform.[1] The initial addition of benzyltriethylammonium nitrate resulted in increases in k_2^* comparable with those observed in the system of present interest. The accelerations in rate were attributed to catalysis of intermediate formation, and the catalysis mode was formulated as involving the formation, in the transition state for intermediate formation, of a hydrogen bond, in which the amine hydrogen acted as the donor and the salt served as the acceptor. Such hydrogen bonding both facilitates the proton transfer and mobilizes the available electrons on the nitrogen, thus making it a more effective nucleophile.

If the rate-determining step in the reaction of benzenesulfonyl chloride with *N*-methylaniline reflects primarily the formation of the new S–N bond, the reaction is analogous for present purposes to the reaction of 2,4-dinitrochlorobenzene with *n*-butylamine, which was studied previously. This is equally the case whether or not an addition intermediate is actually involved. A hydrogen bond, from the amine hydrogen to an appropriate acceptor, in the transition state of this reaction will also promote proton transfer and enhance the nucleophilicity of the amine. It is, therefore, pertinent to explore the possibility that the added salts are functioning as true catalysts and to determine whether or not the available experimental observations are consistent with this hypothesis.

Simply stated, this hypothesis amounts to an assertion to the effect that the salt or some component thereof is actually involved in the rate-determining transition state and more specifically that it is present as the acceptor in hydrogen bonding to the amine nucleophile. Such a possible transition state might be depicted as in I, where X represents the necessary salt component.



I

The formation of this transition state does not necessarily require an intermolecular collision, since the hydrogen bond may be formed in a prior equilibrium between the amine and the salt component. The anion from the salt would be effective as X, and the ion pair, with the negative end of the dipole oriented toward the amine hydrogen, might also be suitable.

Species, other than those derived from the salt, which are capable of functioning as acceptors in hydrogen bonding could also be involved in the transition state of this reaction. The amine nucleophile is a candidate as is the acetone solvent, but not chloroform, which is ineffective as an acceptor. The extent to which acetone is involved in transition states such as I is not directly determined by our experiments. However, to the extent that acetone is so involved the effectiveness of other possible catalytic species would be diminished. The proper measure for the catalytic efficiency of a given species is not the absolute magnitude of the derived rate constant but the ratio of the rate constants for the catalyzed and uncatalyzed reactions. These rate ratios are listed in Table IV, where it is apparent that the observed results are in accord with the above expectations. For catalysis by *N*-methylaniline hydrochloride the rate ratio in chloroform is more than twice the ratio in acetone, and for catalysis by benzyltriethylammonium nitrate the rate ratio in chloroform is almost four times as large as in acetone.

The present results do permit a decision as to the salt species responsible for the observed catalytic effects. As already noted, in the solvents used the salts are present predominantly in the ion-pair form. The concentration of the free anion is proportional not to the concentration of the added salt, but to the square root of the concentration. The ion-pair concentration is, however, directly proportional to the salt concentration. The rates that have been measured are in every case linear with the salt concentrations but not with the square roots of the salt concentrations. The proper species in the transition state is, therefore, the ion pair rather than the anion.

Registry No. Benzenesulfonyl chloride, 98-09-9; *N*-methylaniline, 100-61-8; *N*-methylaniline hydrochloride, 2739-12-0; benzyltriethylammonium chloride, 56-37-1; benzyltriethylammonium nitrate, 2484-08-4; *N*-methylbenzenesulfonanilide, 90-10-8.

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Palladium-Catalyzed Linear Dimerization of Conjugated Dienes

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The dimerization of isoprene in the presence of bis(triphenylphosphine)maleic anhydride palladium(0) occurs in exclusively tail-tail fashion to give 2,7-dimethyl-1,3,7-octatriene (**1**). 2-Ethyl-1,3-butadiene is dimerized similarly to give the corresponding 2,7-diethyl derivative. Codimerization of isoprene and 1,3-butadiene gives a mixture of codimers consisting of 7-methyl-1,3,7-octatriene (70%) and 2-methyl-1,3,7-octatriene (30%). 2,3-Dimethyl-1,3-butadiene is dimerized in low yield to a mixture of 2,3,6,7-tetramethyl-1,3,7-octatriene and an isomeric triene with a branching methylene group. **1** undergoes typical Diels–Alder cycloadditions with common dienophiles and reacts with formaldehyde to give predominantly a dialkyldihydropyran, **16**. Reaction of **1** with catalytic amounts of potassium *tert*-butoxide–dimethyl sulfoxide gives the conjugated triene, 2,7-dimethyl-2,4,6-octatriene (**23**) and with stoichiometric base gives 1,6,6-trimethyl-1,3-cycloheptadiene (**26**). *n*-Butyllithium reacts with **1** *via* an addition-cyclization mechanism to give the anion of a highly alkylated cyclopentane which is protonolyzed or captured with other electrophilic reagents. The isoprene–butadiene codimer is rearranged by catalytic amounts of base to a single conjugated triene, **33**, or cyclized by stoichiometric base to isomeric dimethylcycloheptadienes.

The linear dimerization of 1,3-butadiene to 1,3,7-octatriene in high conversion and yield under catalysis by certain zero-valent palladium complexes has been reported.[1] In a useful variation on this process, palladium-catalyzed dimerization of 1,3-butadiene or isoprene in the presence of compounds with active hydrogen was shown to give a variety of substituted octadienes. In the case of isoprene, dimerization in the presence of phenol was stated to occur in a fashion which placed the branching methyl groups exclusively at the 3,6 and 3,7 positions on the octadienyl chain.[2a] On the other hand, reaction in the presence of active methylene compounds, *e.g.*, ethyl acetoacetate, placed methyl groups in the 2,7 positions of the octadienyl moiety.[2b] The problem of the influence of alkyl substituents on structural selectivity in diene dimerizations carried out in the absence of nucleophiles or other reactive species had not been investigated when these studies began. After their conclusion, there appeared a report[2c] of the dimerization of isoprene with a palladium(II) complex catalyst describing results that are related to aspects of our own findings. In this paper, the dimerization of isoprene and certain of its homologs by a zero-valent palladium catalyst is described, and aspects of the chemistry of the dimers are discussed.

Results and Discussion

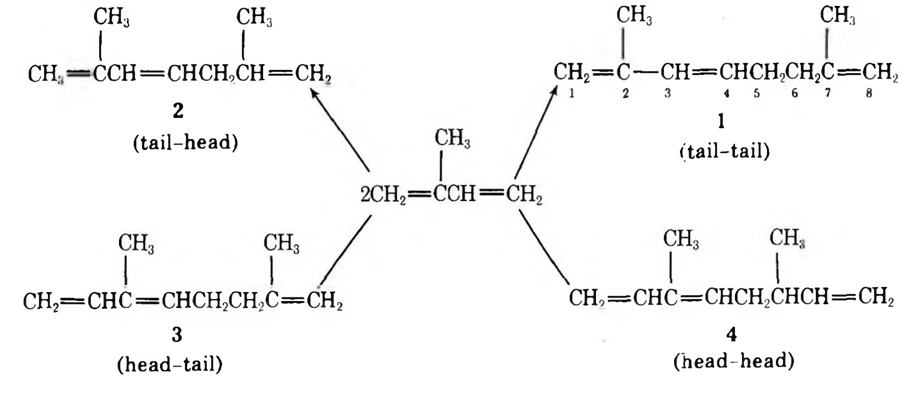
The products of the dimerization of isoprene are especially interesting because of their relationship to naturally occurring diisoprenoid hydrocarbons and other related natural substances. It can be seen that the joining of two isoprene units to give a linear dimer can occur in four distinct ways (Scheme I).

When isoprene was heated in an autoclave under autogenous pressure at 100–110° in acetone solution for 6–8 hr in the presence of bis(triphenylphosphine) maleic anhydride palladium(0),[3] the dimeric product, obtained in 75% yield, was found to consist principally (97–98%) of one isomer along with only trace amounts of other products. From spectroscopic analysis as well as a large body of derivative chemistry, it was shown conclusively that the product was 2,7-dimethyl-1,3,7-octatriene (**1**), the product of tail-to-tail joining of two isoprene units. This finding presents an interesting contrast with processes of nature, where polyisoprenoid materials are formed virtually exclusively by head-to-tail joining. Nmr spectroscopy was uniquely valuable in distinguishing **1** from **3**, which differs only in the location of a methyl group in the diene portion of the molecule. The spectrum of **1** showed singlets at δ 4.80 and 4.69 for the terminal olefinic protons of the diene and monoene group, respectively. The remaining two olefinic protons were seen as an AB multiplet ($J_{\text{trans}} = 16$ Hz) with the lower field component (H_3) appearing as an unsymmetrical doublet and the higher field component (H_4) split further to triplets ($J = 6$ Hz) by two adjacent protons (H_5). The methyl groups were observed as singlets at δ 1.82 (C_2) and 1.73 (C_7).

The ultraviolet spectrum of **1** showed $\lambda_{\max}$ 229 nm (ϵ 24,600). This spectrum is virtually identical with that of 2-methyl-1,3-pentadiene [$\lambda_{\max}$ 228 nm (ϵ 24,600)],[4] which possesses the same chromophore. Mass spectrometry established the molecular weight of **1** (136).

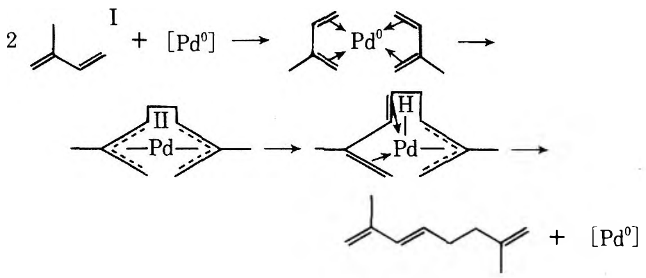
The mechanism of diene dimerization on bis(triphenylphosphine) maleic anhydride palladium(0) is not known with certainty.[1] The remarkable selectivity with isoprene

Scheme I

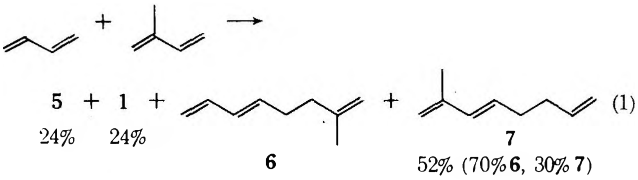


suggests that where alkyl substituents are present, stereochemistry in the catalyst–diene complex may be strongly product determining. It is reasonable that in the first step, two diene units are assembled on the catalyst template through π-complex formation (Scheme II). The ligands maleic anhydride and triphenylphosphine are omitted for clarity, although they are undoubtedly present in the catalyst complex at various stages of reaction. By possibly synchronous processes of oxidative addition of the diene units to palladium and formation of a new carbon–carbon σ bond, the dimer skeleton is formed. Elimination of the elements of a palladium hydride bond from one of the π-allyl units gives a π-alkyl palladium hydride of 3,4-trans stereochemistry. Reductive elimination of the hydrocarbon molecule produces **1** and restores the catalyst for another cycle. The catalyst is quite stable, and after runs involving isoprene:catalyst ratios of *ca.* 700:1, the catalyst residue along with some residual higher diene telomers could be used again with only minor reduction in yield.

Scheme II



The efficient dimerization of both butadiene and isoprene suggested a study of their codimerization. Reaction of equimolar amounts of the dienes under standard conditions gave a dimeric product which was shown by glc to consist of butadiene dimer (1,3,7-octatriene, **5**), **1**, and a codimer in near statistical ratio, 1:1:2.2 (eq 1). The codimer behaved as a single compound on distillation and glc analysis. However, nmr studies revealed that the product was, in fact, a mixture of the isomeric codimers 7-methyl-1,*trans*-3,7-octatriene (**6**) and 2-methyl-1,*trans*-3,7-octatriene (**7**) in the ratio 70:30, respectively. The isomers were differentiated by chemical shifts of the side-chain methyl groups (7-CH_3, δ 1.70; 2-CH_3, δ 1.80) whose subtly different electronic environments had already been observed in the spectrum of **1**. The codimer mixture was further characterized by its uv spectrum [λ_{max} 226 nm (ϵ 23,300)] and mass spectrum (mol wt 122).



24% 24%

6

7

52% (70% **6**, 30% **7**)

The distinct preference for **6** over **7** in codimer formation may be explained plausibly by assuming that the step in which a palladium hydride bond is formed, as in Scheme I, will occur in the manner which produces the more stable remaining π-allyl–metal bond, in this case that in which the π-allyl groups bear the electron-releasing methyl substituent. In this way, the sequence which incorporates butadiene as the dienic part of the codimer (*i.e.*, **6**) is energetically favored over the alternative. This proposal can be tested experimentally by noting the way in which codimer isomer ratios vary as a function of the electronic character of the substituent on the starting diene. Such studies are now in progress.

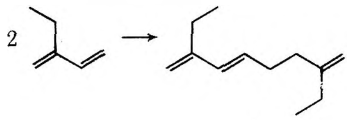
Table I
Effect of Diene Ratio on Dimer Composition

Isoprene: butadiene, mol/mol	Glc peak area 5	6 + 7	1
1:1	1	2.2	1
2:1	1	3.7	2.63
4:1	1	5.15	6.15

A brief study was made of the effect of diene ratio on product composition (Table I).

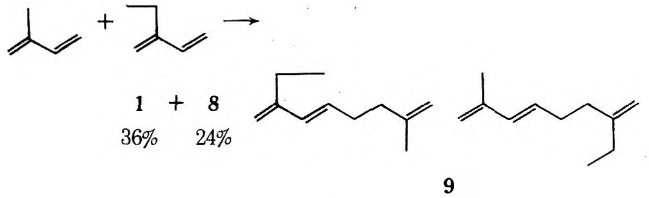
Dimerization reactions were carried out with a variety of readily available dienes.

2-Ethyl-1,3-butadiene. Not surprisingly, this simple diene reacts in the manner of isoprene to give in 75% yield 2,7-diethyl-1,3,7-octatriene (**8**).



8

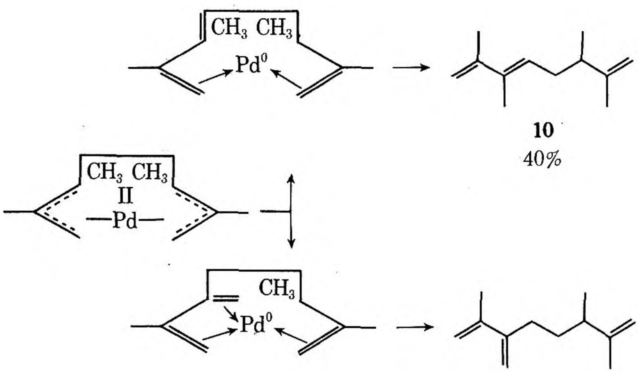
Isoprene and 2-Ethyl-1,3-butadiene. Codimerization of equimolar amounts of these structurally similar dienes gave, in 37% conversion, a product consisting of **1**, **8**, and a new C_{11} codimer, **9**, as shown below. Quantitative analysis by nmr of the isomer distribution in **9** was hindered by severely overlapping resonances, but indications are that neither is markedly preferred.



36% 24%

9
40%

2,3-Dimethyl-1,3-butadiene. The sensitivity of the dimerization reaction to diene structure is well illustrated by the low conversion (*ca.* 10%) noted in this case. In addition, a new type of product bearing a branching methylene group was observed. Both observations may be related to the existence of an intermediate according to Scheme II, *viz.*

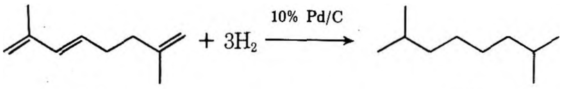


10
40%

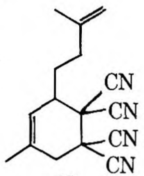
11
60%

Clearly, two methyl groups not only suffer extreme compression, thereby hindering formation of the dimer skeleton, but also offer an alternative path involving a methyl group for β elimination of a palladium hydride bond. The new C-12 trienes **10** and **11** are obtained in 75% yield in the indicated ratio.

Isoprene dimer (**1**) and the butadiene-isoprene codimer (**6** + **7**) were selected for further studies, which have verified the assigned structures and revealed a broad and intriguing derivative chemistry. Catalytic hydrogenation of **1** over 10% Pd/C gave 2,7-dimethyloctane (**12**) as the sole product in high yield, and thereby established the carbon skeleton of the dimer. Reaction of **1** with TCNE gave the expected [2 + 4] cycloadduct **13**. Cycloadditions also occurred readily with acrolein and acrylic acid to yield **14** and **15**, whose structures were assigned from nmr spectra and by analogy with similar reactions described elsewhere.[5]



1 **12**



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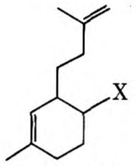
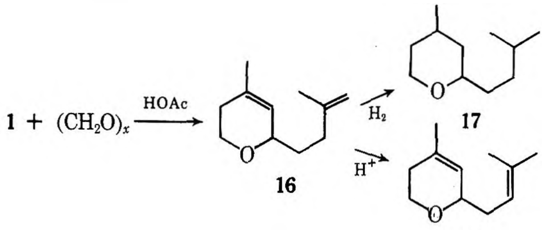


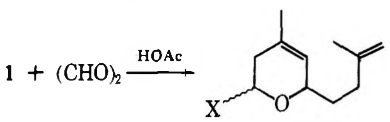
14, X = CHO
15, X = CO_2H

The reaction of **1** with paraformaldehyde in boiling acetic acid took an unexpected course, in that the carbonyl group functioned as the dienophile in a [2 + 4] cycloaddition to give the dihydropyran **16** as the predominant product (49%). A complex, high-boiling fraction appeared to contain the usual array of Prins-type products whose separation was not pursued. **16** was hydrogenated easily to a mixture of cis and trans isomers, **17**. Treatment of **16** with acid failed to cause cyclization, but led instead to the isomeric ether **18**.



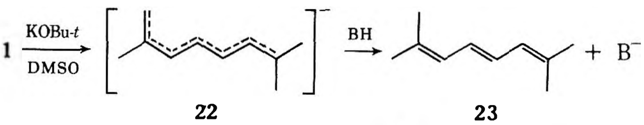
18

In a similar way, **1** reacted with glyoxal to give the formyl dihydropyran **19** as a mixture (60:40) of conformational isomers (32%). Cycloadditions of this type involving highly electrophilic carbonyl compounds (*e.g.*, chloral) have been reported previously.[6] **19** was converted by conventional techniques to the carbinol **20** ($NaBH_4$) and the carboxylic acid **21** (Ag_2O).



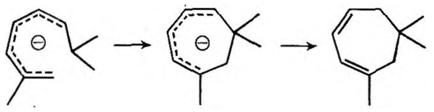
19, X = CHO
20, X = CH_2OH
21, X = CO_2H

Reactions with Strong Bases. The unusual acidities of octatrienes and related hydrocarbons toward typical strong bases have been attributed to stabilization of the resulting carbanions through extensive charge delocalization.[7] In the case of **1**, reaction with a catalytic amount of potassium *tert*-butoxide in dimethyl sulfoxide[8] at 25° for short periods gave 2,7-dimethyl-2,4,6-octatriene (**23**) in 70% yield. It is likely that an intermediate in this isomerization is the heptatrienide anion, **22**, which, under these conditions, is rapidly protonated to give the isomeric, fully conjugated triene. **23** is a crystalline (mp 30°), highly oxygen-sensitive hydrocarbon that has been cursorily mentioned as the product of a laborious synthesis and incompletely characterized.[9] Its unique reactivity is the subject of a separate report.



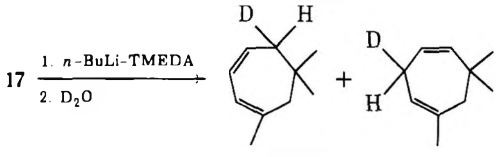
22 **23**

Theoretical studies[10] have indicated that the energetically most favored conformation of an anion such as **22** is the "sickle" form, **24**, which strongly favors cyclization to the new anion, **25**. In fact, treatment of **1** (or **23**) with a stoichiometric amount of potassium *tert*-butoxide in DMSO led, after protonation, to the new hydrocarbon, 1,6,6-trimethyl-1,3-cycloheptadiene (**26**), in 93% yield.

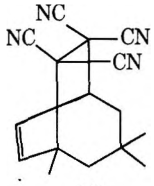


24 **25** **26**

Reaction of **23** with a catalytic amount of metallic sodium also gave **26** (75%) after long reaction times (*ca.* 40 hr) under an argon atmosphere.[11] On the other hand, cyclization of **23** with the *n*-butyllithium-tetramethylethylenediamine (TMEDA) complex followed by hydrolysis with D_2O gave a mixture (75%) consisting principally of the conjugated and nonconjugated monodeuterated dienes **27** and **28** in the ratio 9:1. The structure of **26** was established by its nmr, uv [λ_{max} 251 nm (ϵ 7630)], and mass spectra (mol wt, 136). Diels-Alder cycloaddition of TCNE occurred slowly but gave 94% of the bicyclononene derivative **29**.

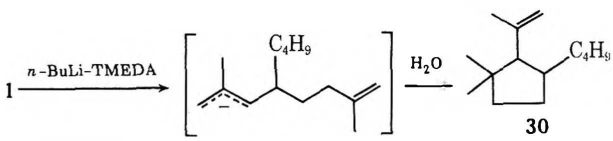


27 (90%) **28** (10%)

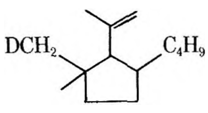


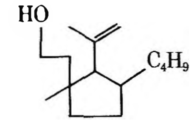
29

An attempt to effect the reaction **1** → **26** with the *n*-butyllithium-TMEDA complex led instead to addition of an *n*-butyl group to the diene chromophore and cyclization of the resulting carbanion to the highly alkylated cyclopentane **30**. The yield is moderately sensitive to temperature (25°, 49%; −30°, 57%). The structure of **30** was clearly established by its 220-MHz nmr and mass spectra (mol wt, 194). Deuterolysis of the reaction mixture led exclusively to **31** and treatment with paraformaldehyde gave the carbinol **32** as a mixture of two conformers of undetermined stereochemistry in the ratio 42:58. The use of al-



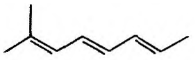
30

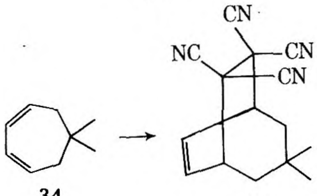

31


32

kyllithium reagents to cause polymerization of conjugated dienes is well known,[11] and the mechanism appears to involve addition of the alkyl carbanion to the diene in the manner shown above.[12] In some instances, 1:1 adducts have been identified in solution by spectroscopic techniques.[12] The transformation **1** → **30** is unique in combining addition and cyclization in a way that is preparatively useful.

The cyclization of butadiene–isoprene codimer (**6** + **7**) with a stoichiometric amount of potassium *tert*-butoxide in DMSO showed surprising structural selectivity. After a lengthy (12 hr) reaction period, the hydrocarbon product was obtained in 67.5% yield as a mixture of three components in the ratio 60:32:8. The minor component (8%) was shown to be 2-methyl-2,4,6-octatriene (**33**), the product of rearrangement of the codimer. The major components were isolated and separately characterized as 6,6-dimethyl-1,3-cycloheptadiene (**34**, 60%) and 1,3-dimethyl-1,3-cycloheptadiene (**35**, 32%) by their uv and nmr spectra as well as their reactions with TCNE to give the isomeric bicyclononene derivatives **36** and **37**, respectively.


33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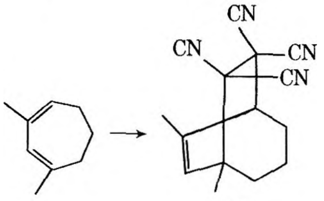
35 37

The conjugated triene **33** could be made the major product (49% yield) by the use of only a catalytic amount of base for a short period (15 min). Even under these mild conditions, appreciable cyclization occurred so that the total hydrocarbon product consisted of **33**, **34**, and **35** in the ratio 60:37:3.

Experimental Section

Nmr spectra were obtained on Varian A-60, HA-100, or HR-220 spectrometers, ultraviolet spectra on a Cary 14 spectrometer, and mass spectra on a Du Pont 21-103C spectrometer. Gas chromatographic analyses were run on a Varian Aerograph 1700 instrument with a 0.25 in. × 12 ft 10% XE-60 on Chromosorb T column (tc detector, helium flow rate 60 ml/min). Boiling points and melting points are uncorrected.

2,7-Dimethyl-1,3,7-octatriene (1). Dimerization of Isoprene. A 2-l., stirred autoclave was charged with 500 g (735 ml) of isoprene, 520 ml of acetone, and 8 g of bis(triphenylphosphine) maleic anhydride palladium(0). The mixture was stirred at 105° for 10 hr, cooled to 25°, and vented, and the product was collected. The pale yellow solution contained a small amount of black palladium metal. Examination by glc (186°) showed significant unreacted isoprene as well as one major new product with a retention time of 1.8 min. Two trace impurities (retention times, 1.6 and 20 min) were noted along with several barely discernible materials of longer retention times.

By water-pump distillation, 45 g (9%) of isoprene was recovered, indicating conversion of *ca.* 90%. After removal of acetone, isoprene dimer was collected at 12–15 mm using a hot-water bath. There was obtained 332 g (75%) of 2,7-dimethyl-1,3,7-octatriene which was 97–98% pure by glc. Redistillation gave an analytical sample: bp 70° (25 mm); nmr ($CDCl_3$) δ 1.70 (s, 3 H, 7-CH_3), 1.78 (s, 3 H, 2-CH_3), 2.12 (broad s, 4 H, -CH_2-), 4.69 (s, 2 H, C_8-vinyl), 4.80 (s, 2 H, C_1-vinyl) AB q (J = 6 Hz) 5.65 center (d of t, J = 6 Hz, 1 H, C_4-vinyl), 6.15 center (1 H, C_3-vinyl); uv max (isooctane) 229 nm (ϵ 24,600), sh 224 nm; mass spectrum mol wt 136 (calcd for $C_{10}H_{26}$, 136).

Anal. Calcd for $C_{10}H_{16}$: C, 88.2; H, 11.9. Found: C, 88.3; H, 11.6.

7-Methyl- and 2-Methyl-1,3,7-octatriene (6 and 7). Codimerization of Butadiene and Isoprene. A. Isoprene:Butadiene Ratio 1:1. A 2-l. stirred autoclave was charged with 136 g (2 mol) of isoprene, 108 g (2 mol) of 1,3-butadiene, 300 ml of reagent grade acetone, and 2.0 g of bis(triphenylphosphine) maleic anhydride palladium(0). The mixture was stirred and heated at 105° for 8 hr under autogenous pressure, cooled, and vented. The light brown solution was stripped of solvent and unreacted dienes at water-pump pressure, and the mixture of dimers was collected in one fraction by rapid distillation using a warm-water bath. Examination of the product by glc showed three peaks in the approximate ratio 1:2.2:1. These are due, respectively, to 1,3,7-octatriene (butadiene dimer), the butadiene–isoprene codimers, and 2,7-dimethyl-1,3,7-octatriene (isoprene dimer).

Separation was accomplished by fractional distillation at 40–50 mm through an 18-in. spinning band column. Thirteen fractions were collected: fractions 1–4, bp 45–54° (47 mm), 13.3 g (butadiene dimer with traces of codimers); fractions 5–6, bp 59–63° (45 mm), 3.76 g (butadiene dimer and codimers, *ca.* 1:1); fractions 7–11, bp 67° (43 mm), 33.84 g (codimers with traces of impurities); fraction 12, bp 80–81° (38 mm), 6.10 g (codimers and isoprene dimer, 1:2); fraction 13, bp 70–75° (25 mm), 16.41 g (isoprene dimer with traces of impurities). Redistillation of fractions 7–11 gave codimers with bp 70° (50 mm). Glc (185°) showed one peak with a retention time of 1.5 min; nmr ($CDCl_3$) δ 1.70 (s, 7-CH_3, 64%), 1.80 (s, 2-CH_3, 36%) (total 3 H), 2.12 (br s, 4 H, -CH_2-), 4.50–5.50 (m, 4 H, terminal vinyl), 5.50–7.00 (m, 3 H, internal vinyl); uv max (isooctane) 226 nm (ϵ 23,300); mass spectrum mol wt 122 (calcd for C_9H_{14}, 122).

Anal. Calcd for C_9H_{14}: C, 88.5; H, 11.5. Found: C, 88.3; H. 11.0.

B. Isoprene:Butadiene Ratio 2:1. In the early stages of the reaction, the ratio of codimers to butadiene dimer was *ca.* 3 and gradually increased as the reaction progressed. Final glc peak area ratios were 1:3.7:2.63 for butadiene dimer:codimers:isoprene dimer.

C. Isoprene:Butadiene Ratio 4:1. Final glc peak area ratios were 1:5.15:6.15 for butadiene dimer:codimers:isoprene dimer.

2,7-Diethyl-1,3,7-octatriene (8). A solution of 41 g (0.5 mol) of 2-ethyl-1,3-butadiene, 1.0 g of bis(triphenylphosphine) maleic anhydride palladium(0), and 40 ml of reagent grade acetone was heated in a 200-ml stainless steel rocker bomb for 9 hr at 110° under autogenous pressure. After cooling to 25°, the product was collected as a pale yellow solution with only a trace of metallic palladium present. Examination of the crude product by glc (186°) showed one major new peak with a retention time of 3.5 min and two trace impurities at 2.9 and 4.0 min. A minor amount of unconverted 2-ethyl-1,3-butadiene was also indicated. The solvent was removed by distillation under water-pump *vacuum, and* the residual hydrocarbon fraction was distilled at reduced pressure. There was obtained 30.3 g (75%) of material: bp 44–46° (0.75 mm); nmr ($CDCl_3$) δ 1.08 (t, J = 7 Hz, 3 H, CH_3 of C_7 C_2H_5), 1.13 (t, J = 7 Hz, 3 H, CH_3 of C_2 C_2H_5), 1.50–2.70 (m, 8 H, -CH_2-), 5.02 (m, 2 H, C_8 vinyl), 5.13 (m, 2 H, C_1 vinyl), 5.40–6.60 (m, 2 H, $C_{3,4}$ vinyl).

Anal. Calcd for $C_{12}H_{20}$: C, 87.7; H, 12.3. Found: C, 87.5; H, 12.0.

Codimerization of Isoprene and 2-Ethyl-1,3-butadiene (9). A 300 ml stainless steel autoclave was charged with 25 g (0.3 mol) of 2-ethyl-1,3-butadiene, 21 g (0.3 mol) of isoprene, 40 ml of reagent acetone, and 1.0 g of bis(triphenylphosphine) maleic anhydride palladium(0). The mixture was stirred rapidly and heated at 105° under autogenous pressure for 7 hr. Periodic monitoring of the reaction mixture by glc (180°) showed that homodimers of isoprene and 2-ethyl-1,3-butadiene (retention times 2.5 and 5.2 min, respectively) were present. In addition, a new component consisting of two poorly resolved peaks was observed at 3.5 min and attributed to the two isomeric codimers. At the end of the reaction period, the reaction product was concentrated to remove acetone, and crude dimeric produce was collected in one fraction by rapid distillation at reduced pressure. On redistillation through a 16-in. spinning band column, there was obtained 5.25 g (0.039 mol) of **1**, 4.90 g (0.03 mol) of **8**, and 6.63 g (0.045 mol) of **9**, bp 75–85° (14 mm); nmr ($CDCl_3$) δ 4.72 (s, 2 H, monoene terminal vinyl), 4.83 (s, 2 H, diene terminal vinyl), 5.20–6.40 (m, 2 H, internal vinyl). Analysis of the aliphatic region δ 0.85–2.50, was hindered by overlapping multiplets but suggested that 2-ethyl-7-methyl- and 2-methyl-7-ethyl-1,3,7-octatriene were present in about equal amounts.

Anal. Calcd for $C_{11}H_{18}$: C, 87.9; H, 12.1. Found: C, 87.6; H, 12.0.

Dimerization of 2,3-Dimethyl-1,3-butadiene (10 + 11). A solution of 51 g (0.62 mol) of 2,3-dimethyl-1,3-butadiene (DMBD) and 1.0 g of bis(triphenylphosphine) maleic anhydride palladium(0) in 75 ml of reagent grade acetone was heated for 8 hr at 105° in a 300-ml stirred autoclave under autogenous pressure. Periodic examination of the reaction mixture by glc (150°) showed the slow growth of two new peaks with retention times of 6.6 and 7.9 min. The ratio of peak areas was *ca.* 3:2, respectively. After 8 hr, much unreacted DMBD remained, and the reaction was terminated. After cooling to 25°, solvent and unreacted DMBD were removed by distillation at water pump pressure, and the residue was fractionally distilled: fraction 1, bp 65–70° (10 mm), 0.83 g; fraction 2, bp 70–72° (10 mm), 0.95 g; fraction 3, bp 73–74° (10 mm), 1.54 g; fraction 4, bp 75–80° (10 mm), 0.52 g.

Fraction 1. Glc peak area ratios 6.6 (77%), 7.9 min (16%); nmr ($CDCl_3$) δ 1.00 (d, J = 7 Hz, 3 H), 1.65 (s, 3 H), 1.85 (s, 3 H), 1.50–2.50 (m, 5 H), 4.68 (s, 2 H), 4.90 (s, 2 H); 5.00 (s, 2 H). Minor resonances due to the presence of another isomer were seen. This spectrum establishes the identity of the major component in this fraction as **11**.

Fraction 4. Glc peak area ratios 6.6 (14%), 7.9 min (86%); nmr ($CDCl_3$) δ 1.04 (d, J = 7 Hz, 3 H), 1.50–2.40 (m, 12 H), 4.60–4.75 (m, 2 H), 4.75–5.10 (m, 2 H), 5.30–5.85 (m, 1 H). Other minor resonances were noted. This spectrum establishes the identity of the major component as **10**.

Hydrogenation of 1. A mixture of 13.6 g (0.1 mol) of **1**, 80 ml of methanol, and 0.5 g of 10% Pd/C was hydrogenated in a Parr apparatus until hydrogen uptake stopped. Glc (180°) showed the complete disappearance of **1** and the appearance of one new component with the retention time (1.2 min) of authentic 2,7-dimethyloctane. On distillation at atmospheric pressure, the hydrocarbon (bp 160°) was removed as an azeotrope (bp 65°) with methanol. The distillate was diluted with water and the hydrocarbon layer was removed to give 11.3 g (83%) of 2,7-dimethyloctane (**12**), nmr ($CDCl_3$) δ 1.86 (d, J = 7 Hz, 12 H, CH_3), 1.10–2.00 (m, 10 H).

Anal. Calcd for $C_{10}H_{22}$: C, 84.4; H, 15.6. Found: C, 84.5; H, 15.2.

On interruption of the hydrogenation at *ca.* 75% completion, it was found that the mixture contained of 60% of **12** along with *ca.* 40% of 2,7-dimethyl-2-octene, indicating that reduction of the 1,3-diene unit is accomplished *via* initial 1,4 addition of hydrogen.

Reaction of 1 with TCNE (13). A solution of 5.73 g (0.045 mol) of TCNE in 35 ml of anhydrous tetrahydrofuran was chilled in an ice bath and 6.2 g (0.045 mol) of isoprene dimer was added in one portion. A deep red color formed but vanished in seconds as the solution became light brown-yellow. The solution was stirred cold for 0.5 hr, then at 25° for 1 hr. Glc analysis indicated complete consumption of isoprene dimer. Removal of the solvent gave a light tan crystalline solid which was recrystallized from hexane to give 8.81 g (79%) of colorless prisms of **13**: mp 81.5–82.5°; nmr ($CDCl_3$) δ 1.70–2.50 (m, 10 H, alkyl), 3.00 (br s, 3 H, singlet H adjacent to CN), 4.82–4.90 (m, 2 H, terminal vinyl), 5.56 (sl br s, 1 H, ring vinyl).

Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.7; H, 6.10; N, 21.2. Found: C, 72.8; H, 6.08; N, 21.5.

Reaction of 1 with Acrolein (14). A solution of 33.3 ml (28 g, 0.5 mol) of freshly distilled acrolein and 68 g (0.5 mol) of isoprene dimer in 125 ml of glacial acetic acid was heated at reflux in a nitrogen atmosphere. After 30 min, glc showed that the starting materials had been consumed and that two new components were present in the ratio 1:1. Acetic acid was removed at reduced pressure, and the residue was fractionally distilled to give 68.7 g (75%) of the unsaturated aldehyde **14** as a 1:1 mixture of isomers: bp 80° (0.05 mm); 100-MHz nmr ($CDCl_3$) δ 1.50–2.70 (m, 16 H), 4.65 (s, 2 H, terminal vinyl), 5.39 and 5.45 (sl br s, ratio 1:1, total 1 H, ring vinyl of epimers), 9.63 and 9.67 (d, J = 2 Hz, ratio 1:1, total 1 H, aldehyde H).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.2; H, 10.5. Found: C, 81.4; H, 10.2.

Reaction of 1 with Acrylic Acid (15). A solution of 71.4 g (0.525 mol) of **1** and 36 g (0.5 mol) of glacial acrylic acid in 100 ml of acetic acid was heated at reflux for 3 hr. The pale yellow solution was cooled and poured into a mixture of ice and water. The mixture was extracted twice with 150 ml of methylene chloride, and the extract was washed twice with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was heated at 70° under vacuum (0.1 mm) for 1 hr to remove traces of acetic acid. The yield of clear, straw-colored carboxylic acid **15** was 87 g (84%): nmr ($CDCl_3$) δ 1.30–3.00 (m, 16 H, alkyl), 4.72 (s, 2 H, terminal vinyl), 5.25 and 5.65 (sl br s, ratio 1:2, total 1 H, ring vinyl of epimers) 11.8 (s, 1 H, CO_2H). The analytical sample distilled at 121° (0.25 mm).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 75.0; H, 9.68. Found: C, 75.3; H, 9.68.

Reaction of 1 with Paraformaldehyde (16). A mixture of 33 g (1.1 mol) of paraformaldehyde, 136 g (1.0 mol) of isoprene dimer, and 250 ml of glacial acetic acid was heated at reflux for 1.5 hr. The clear, light yellow solution was cooled in ice water and poured into a mixture of 200 ml of water and 150 ml of ether. The aqueous layer was drawn off, and the organic layer was washed successively with three portions of 250 ml of water, once with 250 ml of saturated sodium bicarbonate solution, and once with 250 ml of water. After drying over magnesium sulfate and evaporation of the solvent, the residue was fractionally distilled at reduced pressure. After collection of 13.73 g (10%) of unconverted hydrocarbon, there was obtained 72.73 g (48.7%) of colorless, pleasant-smelling dihydropyran **16**: bp 96–100° (18 mm); nmr ($CDCl_3$) 1.20–2.50 (m, 12 H, alkyl), 3.20–4.15 (m, 3 H, ether α H), 4.67 (broad s, 2 H, terminal vinyl), 5.30 (br s, 1 H, internal vinyl).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.5; H, 10.9. Found: C, 79.6; H, 11.0.

Hydrogenation of 16 (17). A mixture of 8.3 g (0.05 mol) of the dihydropyran, 3.5 ml of methanol, and 0.1 g of 10% palladium on carbon was hydrogenated in a Parr hydrogenation apparatus until absorption of hydrogen was complete. Distillation at reduced pressure gave 4.22 g (51%) of material, bp 85–88° (18 mm), which was shown by glc to consist of 85% of 4.9-min and 15% of 6.0-min material. The nmr spectrum shows the absence of any olefinic protons and indicates that the products are probably cis and trans isomers of 2-isoamyl-4-methyltetrahydropyran (**17**), nmr ($CDCl_3$) δ 0.50–2.20 (m, 19 H, alkyl), 2.90–4.30 (m, 3 H, ether α H).

Anal. Calcd for $C_{11}H_{22}O$: C, 77.1; H, 12.9. Found: C, 76.9; H, 12.6.

Acid-Catalyzed Rearrangement of 16 (18). A solution of 8.3 g (0.05 mol) of **16** and 0.1 g of *p*-toluenesulfonic acid in 100 ml of benzene was heated at reflux for 18 hr. During this period the color of the solution became pale yellow and then quite dark, although glc (180°) showed no apparent change in the composition of the solution. An additional 0.1 g of *p*-toluenesulfonic acid was added, and reflux was continued for 7 hr.

The solution was cooled and washed with saturated sodium bicarbonate solution and water before drying over magnesium sulfate. Distillation of the product gave 5.78 g (70%) of material, bp 90–95° (18 mm). Glc analysis of the product showed that its retention time (7.2 min) was identical with that of starting material. However, analysis of the olefinic proton region of the nmr spectrum showed that the product consisted of 87.5% rearranged dihydropyran **18** and 12.5% **16**.

Anal. Found: C, 79.7; H, 10.6.

Reaction of 1 with Glyoxal (19). A mixture of 81.6 g (0.6 mol) of isoprene dimer and 43.5 g (0.6 mol) of glyoxal monohydrate in 300 ml of acetic acid was refluxed for 1.5 hr, cooled, and poured into a mixture of ice water and ether. The aqueous layer was removed, and the organic layer was washed successively with three portions of 250 ml of water, twice with 250 ml of saturated sodium bicarbonate solution, and once with 250 ml of water. After drying over magnesium sulfate and evaporation of the solvent, the residue was fractionally distilled at reduced pressure. After a foreshot (10.77 g, 13.5%) consisting chiefly of unconverted low-boiling [to 6° (0.7 mm)] hydrocarbon, the product was collected at 80–85° (0.15 mm). There was obtained 32.14 g (31.8%) of the aldehyde **19**.

Glc analysis showed that the product consisted of two components, probably cis-trans isomers, in the ratio 60:40 (retention times 11.9 and 13.8 min with a temperature program of 180-225°, 10°/min): nmr (CDCl$_3$) δ 1.50-2.50 (m, 12 H, alkyl), 3.80-4.50 (m, 2 H, ether α H), 4.73 (s, 2 H, terminal vinyl), 5.40 (br s, 1 H, ring vinyl), 9.68 (d, J = 2 Hz, 1 H, aldehyde H).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.2; H, 9.31. Found: C, 74.0; H, 9.65.

Sodium Borohydride Reduction of 19 (20). A solution of 4.05 g (0.11 mol) of sodium borohydride in 150 ml of absolute ethanol was stirred at 25-30° while 41.2 g (0.212 mol) of the aldehyde in 150 ml of absolute ethanol was added dropwise during 1.5 hr. Stirring was continued after the addition for 2 hr, and 10 ml of water was cautiously added. After 0.5 hr, the mixture was concentrated by vacuum distillation, and the residue was added to 250 ml of ether. The ether layer was extracted with three 75-ml portions of water and dried over magnesium sulfate. Removal of solvent and distillation under reduced pressure gave 30.53 g (73.2%) of slightly viscous carbinol, bp 70-80° (0.3 mm). Glc analysis (225°) showed the product to consist of two components with retention times of 13.7 (39%) and 16.8 min (61%). This composition reflects the isomer content of the starting aldehyde which contained two components at 12.3 (40%) and 14.0 min (60%). These are probably cis-trans isomers: nmr (CDCl$_3$) δ 1.30-2.32 (m, 12 H, alkyl), 3.59-3.98 (m, 5 H, -OCH$_2$-, -OH), 4.70 (s, 2 H, terminal vinyl), 5.34 (s, 1 H, internal vinyl).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.4; H, 10.3. Found: C, 73.6; H, 10.3.

Silver Oxide Oxidation of 19 (21). A solution of 35.4 g (0.207 mol) of silver nitrate in 70 ml of distilled water was added to a solution of 16.5 g (0.41 mol) of sodium hydroxide in 70 ml of distilled water. The dark silver oxide was stirred vigorously and chilled in an ice bath while 19.4 g (0.1 mol) of the aldehyde was added in portions during 25 min. The internal temperature was 20-23° throughout the addition. After 30 min, the mixture was filtered through Celite, and the clear, dark brown filtrate was acidified with 12 *N* hydrochloric acid, extracted twice with water, and dried over magnesium sulfate. Exhaustive evaporation of the solvent left a viscous, clear, light brown oil: 18.0 g (86%); nmr (CDCl$_3$) δ 1.75-2.50 (m, 12 H, alkyl), 4.00-4.60 (m, 2 H, ether α H), 4.70 (s, 2 H, terminal vinyl), 5.39 (br s, 1 H, ring vinyl), 11.15 (s, 1 H, CO$_2$H).

2,7-Dimethyl-2,4,6-octatriene (23) from Base-Catalyzed Rearrangement of 1. One liter of reagent grade dimethyl sulfoxide was deaerated with a stream of dry argon for 15 min. 1 (150 g, 1.1 mol) was added and followed with 5 ml of 0.94 *M* potassium *tert*-butoxide in dimethyl sulfoxide under argon. After 15-20 min at 50°, glc showed that a small amount of the conjugated triene was present but that most of 1 remained unchanged. The solution was cooled and 15 ml of the potassium *tert*-butoxide solution was added. The dark solution was stirred for 1 hr, during which glc monitoring showed a dramatic increase in conjugated triene. Five milliliters of water was added, and stirring was continued for an additional 1 hr. A short-path still was attached to the reaction vessel, and distillate was collected at 3-5 mm until the heat temperature was 70°. Water was added to the distillate and the hydrocarbon layer which separated crystallized on cooling in ice. The product was taken up in equal volume of petroleum ether (bp 30-60°), washed once with water, and dried over magnesium sulfate. Distillation at reduced pressure gave 105.4 g (70%) of pure 2,7-dimethyl-2,4,6-octatriene: bp 90-92° (25 mm); mp 30°; nmr (CDCl$_3$) δ 1.80 (br s, 12 H, CH$_3$), 4.50-5.50 (m, 4 H, vinyl), uv max (isooctane) 291 nm (ϵ 36,300), 279 (46,250), 269 (34,300); mass spectrum mol wt, 136 (calcd, 136).

Anal. Calcd for $C_{10}H_{16}$: C, 88.2; H, 11.9. Found: C, 88.3; H, 12.1.

A sample of 23 was readily hydrogenated to give as the sole product 2,7-dimethyloctane (12), with bp 44° (13 mm), in 77% yield.

1,6,6-Trimethyl-1,3-cycloheptadiene (26). A. From Base-Catalyzed Cyclization of 1. A solution of 0.25 lb of potassium *tert*-butoxide in 1 l. of dimethyl sulfoxide was deaerated with a stream of dry argon for 10 min. Isoprene dimer (136 g, 1 mol) was added in one portion under an argon atmosphere. Glc analysis indicated that the dimer was completely consumed in minutes. The dark blue-green solution was heated at 70-75° with stirring for 30 min. A modified Claisen stillhead was then attached, and the pressure was reduced to 6-8 mm with an aspirator. The temperature of the mixture was maintained at 75-80°, and distillate was collected until the head temperature was 70°. Argon was introduced into the system, the stillhead was removed, and water was added to the distillate. The upper hydrocarbon layer was removed and shown by glc to be pure 1,6,6-trimethyl-1,3-cycloheptadiene. The yield was 126 g (93%). A second charge of 68 g of isoprene dimer was added to the distillate residue, and the above process was repeated. A third charge of 36 g of isoprene dimer was treated similarly. Distillation of the product from a total of 240 g (1.76 mol) of isoprene dimer gave 200.5 g (83.5%) of 1,6,6-trimethyl-1,3-cycloheptadiene: bp 64-66° (25 mm); nmr (CDCl$_3$) δ 1.98 (s, 6 H, gem-CH$_3$), 1.81 (s, 3 H, C-1 CH$_3$), 2.00 (s, 4 H, -CH$_2$-), 3.68 (br s, 3 H. vinyl); uv max (isooctane) 251 nm (ϵ 7630); mass spectrum mol wt 136 (calcd, 136).

Anal. Calcd for $C_{10}H_{16}$: C, 88.2; H, 11.8. Found: C, 88.3; H, 11.2.

B. From 23 by Reaction with Potassium *tert* Butoxide. A solution of 5 g of 23 in 25 ml of 0.94 *M* potassium *tert*-butoxide in DMSO was stirred at 60° for 30 min. Glc showed the complete disappearance of 23 and the appearance of 26 at the sole detectable product. After the usual work-up, 1.51 g (30%) of 26 was obtained.

C. From 23 by Reaction with Sodium. A small piece (*ca.* 0.01 g) of clean, dry sodium metal was added to a solution of 13.6 g (0.1 mol) of 2,7-dimethyl-2,4,6-octatriene in 100 ml of dry ethylene glycol dimethyl ether, and the solution was heated to reflux under an argon atmosphere. The sodium dissolved slowly (*ca.* 4 hr) to produce a pale yellow solution. Examination of the mixture by glc showed no cyclization product. Evidently adventitious moisture or oxygen caused consumption of sodium in unprofitable side reactions. A second 0.01-g sample of sodium was added, and refluxing was continued for 11 hr. At this point the solution was deep red in color, and glc showed cyclized product in addition to unconverted starting material in the ratio of 2.3:1.0. A third 0.01-g sample of sodium was added, and refluxing was continued for 24 hr. Isopropyl alcohol (2 ml) was added to decompose metal compounds. The solvent was removed by distillation, and the product was collected at 44-45° (7 mm). There was obtained 10 g (74.5%) of 26.

D. From 23 by Reaction with *n*-Butyllithium-TMEDA Complex. Freshly distilled *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (6.75 g, 0.058 mol) was added to 36.3 ml (0.059 mol) of a 1.6 *M* hexane solution of *n*-butyllithium under argon with water-bath cooling. The complex is ready for further reaction when the addition is complete. A solution of 7.9 g (0.058 mol) of 2,7-dimethyl-2,4,6-octatriene in 20 ml of cyclohexane was added dropwise during 1 hr. The initial pale yellow color changed during the addition to a clear, dark red. The solution was stirred at 25° for 3.25 hr, when analysis of an aliquot by glc showed that the starting triene had disappeared. After hydrolysis with 5 ml of D$_2$O, the organic layer was separated. After TMEDA was removed by washing with 1 *N* HCl solution, the organic layer was washed with saturated sodium bicarbonate solution and dried over magnesium sulfate. The solvent was removed and the residual oil was distilled at reduced pressure to give fractions totaling 5.90 g (74.5%) of isomeric monodeuterated trimethylcycloheptadienes, bp 64-65° (25 mm). The product consisted principally of 1,6,6-trimethyl-1,3-cycloheptadiene-*5-d* (27), which was identified by its nmr spectrum. In addition, the product contained 10-12% of another isomer identified by nmr as 1,6,6-trimethyl-1,4-cycloheptadiene-*3-d* (28), nmr (CDCl$_3$) δ 2.18 (s, C$_3$ H), 5.25 (s, unconjugated vinyl.

Reaction of 26 with TCNE (29). A solution of 2.56 g (0.02 mol) of TCNE in 25 ml of anhydrous tetrahydrofuran was stirred at 25°, and 2.72 g (0.02 mol) of 26 was added in one portion. A deep red color was formed and faded only very slowly over a period of 2 days. The pale tan solution was evaporated to give 5.05 g (95.5%) of light brown, crystalline solid, mp 133-134°. Recrystallization of an analytical sample from ethanol gave thick, colorless prisms of **29:** mp 145°; nmr (CDCl$_3$) δ 1.05, 1.11 (s, 3 H each, gem-CH$_3$), 1.60-2.50 (m, 4 H, ring CH$_2$), 1.68 (s, 3 H, bridgehead CH$_3$), 3.50 (m, 1 H, bridgehead H), 6.00-6.60 (m, 2 H, vinyl H).

Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.7; H, 6.10; N, 21.2. Found: C, 72.9; H, 6.00; N, 21.5.

Reaction of 1 with *n*-Butyllithium-TMEDA Complex (30). A solution of 79 g (0.58 mol) of 1 in 150 ml of dry cyclohexane was added under argon during 2.25 hr to *n*-butyllithium-TMEDA complex prepared from 67.5 g (0.58 mol) of freshly distilled TMEDA and 363 ml (0.58 mol) of 1.6 *M* *n*-butyllithium in hexane. The mixture was initially orange in color, then in the later stages of the addition, bright red. After an additional 1 hr, a sample of the mixture was hydrolyzed and examined by glc (173°). In addition to small amounts of starting material, a large, highly symmetrical new peak at 5.8 min was observed. Smaller peaks appeared at 5.0, 7.4, and 8.1 min. The mixture was stirred for 16 hr and hydrolyzed with H_2O. The organic layer was washed with 1 *N* HCl solution to remove TMEDA, then with saturated sodium bicarbonate solution, and dried over magnesium sulfate. Removal of the solvent left a clear, pale straw liquid shown by glc to consist of 75% 5.8-min material, 12% 7.4- and 8.1-min material, and 13% recovered starting material, 2.0–2.7 min.

Distillation at reduced pressure gave 55.32 g (49.4%) of material: bp 105–115° (25 mm) with major portion boiling at 114–115°; nmr ($CDCl_3$) δ 0.60–2.20 (m, 24 H, alkyl), 4.69 (m, 1 H, terminal vinyl), 4.91 (m, 1 H, terminal vinyl). The 220-MHz spectrum included the following features: δ 175 (s, 3 H, gem-CH_3), 218 (s, 3 H, gem-CH_3), 190 (t, J = 7 Hz, 3 H, CH_3 of *n*-butyl), 372 (s, 3 H, $CH_3C{=}C$), 369 Hz (d, J = 7 Hz, 1 H, allylic H on ring); mass spectrum mol wt 194 (calcd for $C_{14}H_{26}$, 194). The relatively intense (11.3%) molecular ion peak suggests a cyclic structure.

Anal. Calcd for $C_{14}H_{26}$: C, 86.5; H, 13.5. Found: C, 86.2; H, 13.2.

Addition of **1** at −25 to −30° raises the yield of **30** to 57.2%. From the light-colored distillation residue, there could be isolated 6 g of material, bp 60° (0.2 mm), glc retention time (173°) 8.2 min. The mass spectrum of this fraction gave molecular ions at *m/e* 192 and 194, and the fragmentation pattern suggested a branched, acyclic hydrocarbon whose structure has not been determined.

Reaction of Paraformaldehyde with the Adduct of 1 and *n*-Butyllithium (32). A solution of 39.5 g (0.29 mol) in 75 ml of dry cyclohexane was added during 1 hr to a solution of 0.29 mol of *n*-butyllithium–TMEDA complex at −250°. After an additional 15 min at this temperature, the mixture was warmed in an ice water bath for 1 hr. Solid paraformaldehyde, 11 g (0.37 mol), was added to the bright red suspension during 20 min at 0°, and stirring was continued for 0.5 hr. The ice bath was removed, and the mixture was allowed to warm slowly. As the temperature neared 20°, an exothermic reaction occurred, and the mixture became a pale yellow, clear solution. After 30 min, 30 ml of water was added, and after brief stirring, the organic layer was transferred to a separatory funnel, washed several times with water, and dried over magnesium sulfate. After removal of solvent and distillation of the residue, there was obtained 34 g (52%) of the colorless, slightly viscous alcohol, **32**, bp 98° (0.3 mm). Gc analysis with temperature programming (180–225°, 10°/min) showed the presence of two components in the proportion of 42.2 (18.3 min) and 57.8% (20.8 min), which are probably geometrical isomers differing in the conformation of the hydroxyl-bearing side chain.

32 had nmr ($CDCl_3$) δ 0.70–2.50 (n, 23 H, alkyl), 3.25 (s, 1 H, OH, disappears with D_2O), 3.72 (t, J = 7 Hz, 2 H, $-OCH_2-$), 4.85 (s, 1 H, vinyl), 4.99 (s, 1 H, vinyl).

Anal. Calcd for $C_{15}H_{28}O$: C, 80.3; H, 12.6. Found: C, 80.3; H, 12.2.

2-Methyl-2,4,6-octatriene (33) from Base-Catalyzed Rearrangement of 6 and 7. A solution of 20 g (0.164 mol) of butadiene–isoprene codimer in 300 ml of dimethyl sulfoxide was stirred at 25° under a nitrogen atmosphere, and 5 ml of a solution of 0.3 g of potassium *tert*-butoxide in 25 ml of dimethyl sulfoxide was added. The mixture became dark green. After 15 min, glc analysis showed the codimer to be virtually gone, and three new materials were seen with retention times of 2.1 and 2.5 (**34** and **35**, respectively, total 25 area %) and 3.4 min (**33**, 75 area %). An additional 5 ml of potassium tert-butoxide solution was added. The color of the solution was now deep blue. After 15 min, glc showed an increase in 2.1-min material (33 area %), no change in 2.5-min material (7 area %), and a decrease in 3.4-min material (60 area %). Water (50 ml) was added to quench the reaction, a short distillation column was attached to the flask, and distillate was collected in a chilled receiver (−78°) until the stillhead temperature was 60° (9 mm). Water was added to the distillate, and the hydrocarbon layer was taken up in 60–75 ml of petroleum ether. **33** is easily air oxidized, and the work-up was conducted under a nitrogen atmosphere. After drying and removal of the petroleum ether, the crude product was fractionally distilled. The yield of **33**, **34**, and **35**, expressed as per cent of total product, was 60, 37, and 3%, respectively. The net yield of **33** was 49%. A fraction with bp 76° (23 mm) was selected for analysis: nmr ($CDCl_3$) δ 1.72 (s, br, 9 H, $C{=}CCH_3$), 5.20–6.80 (m, 5 H, vinyl); uv max (isooctane) 228 nm (ϵ 37,200), 271 (46,800), 262 (35,600).

Anal. Calcd for C_9H_{14}: C, 88.5; H, 11.5. Found: C, 88.9; H, 11.3.

Cyclization of 6 and 7 with Stoichiometric Potassium *tert*-Butoxide–DMSO. Potassium *tert*-butoxide (300 ml, 0.94 *M*) in dimethyl sulfoxide (0.28 mol) was stirred at 25° under an argon atmosphere, and 25% (0.205 mol) of a 2:1 mixture of 7- and 2-methyl-1,3,7-octatrienes was added in one portion. The reaction was slightly exothermic (35–40°), and a very deep magenta color was produced. After 12 hr, glc analysis (182°) showed three components at 2.0 (60 area %), 2.4 (32 area %), and 3.2 min (8 area %) which are, respectively, **34**, **35**, and **33**. The deep bluish-purple mixture was poured into water and extracted twice with 150-ml portions of petroleum ether. The hydrocarbon layer was washed several times with water and dried over magnesium sulfate. Evaporation of the solvent and distillation of the residue gave 20.83 g (83.5%) of C_9 hydrocarbons.

A fraction with bp 60° (35 mm), 7.49 g, was pure **34**: nmr ($CDCl_3$) δ 0.95 (s, 3 H, gem-CH_3), 1.02 (s, 3 H, gem-CH_3), 1.40–D.50 (m, 4 H, allylic H), 5.40–6.00 (m, 4 H, vinyl); uv max (isooctane) 248 nm (ϵ 8380), 241 (7960).

Anal. Calcd for C_9H_{14}: C, 88.5; H, 11.5. Found: C, 88.8; H, 11.8.

Reaction of 2.44 g (0.02 mol) of **34** with 2.56 g (0.02 mol) of TCNE in dry THF produced a deep red solution. After 16 hr removal of solvent and recrystallization of the adduct from hexane–benzene gave 3.56 g (71%) of **36** as colorless needles: mp 181°; nmr ($CDCl_3$) δ 1.90–2.50 (m, 4 H, ring CH_2), 3.40–3.60 (m, 2 H, bridgehead H), 6.52 (center of AB q, 2 H, vinyl).

Anal. Calcd for $C_{15}H_{14}N_4$: C, 72.0; H, 5.63; N, 22.4. Found: C, 72.0; H, 5.68; N, 22.6.

A fraction with bp 72° (35 mm), 1.06 g, was shown by glc to be **35** of greater than 94% purity: nmr ($CDCl_3$) δ 0.97 (s, 2 H, nonallylic ring CH_2), 1.50–2.50 (m, 10 H, allylic H), 5.30–5.80 (m, 2 H, vinyl); uv max (isooctane) 248 nm (ϵ 7550).

Reaction of 2.44 g (0.02 mol) of **35** with TCNE as described above gave 1.77 g (35%) of pale yellow prisms, mp 180–181°. A sample crystallized twice from ethanol had mp 196°; nmr ($CDCl_3$) δ 1.70–2.20 (m, 9 H, $C{=}CCH_3$, ring CH_2), 3.21 (t, J = 4 Hz, 1 H, bridgehead H), 5.73 (q, J = 1.5 Hz, 1 H, vinyl).

Anal. Calcd for $C_{15}H_{14}N_4$: C, 72.0; H, 5.63; N, 22.4. Found: C, 71.6: H, 5.72; N, 22.4.

Registry No. 1, 36638-38-7; **6**, 36638-61-6; **7**, 36638-62-7; **8**, 36638-39-8; **9** (2-ethyl-7-methyl isomer), 36663-08-8; **9** (2-methyl-7-ethyl isomer), 36638-42-3; **10**, 36638-41-2; **11**, 42915-58-2; **12**, 1072-16-8; **13**, 42915-59-3; *cis*-**14**, 42915-60-6; *trans*-**14**, 42915-61-7; **15**, 42915-62-8; **16**, 42915-63-9; *cis*-**17**, 42915-64-0; *trans*-**17**, 42915-65-1; **18**, 42915-66-2; *cis*-**19**, 42915-67-3; *trans*-**19**, 42915-68-4; *cis*-**20**, 42915-69-5; *trans*-**20**, 42915-70-8; **21**, 42915-71-9; **23**, 38086-92-9; **26**, 42915-72-0; **29**, 42915-73-1; **30**, 42915-74-2; **32**, 42915-75-3; **33**, 42915-76-4; **34**, 25866-61-9; **35**, 40391-65-9; **36**, 42915-79-7; **37**, 42915-80-0; isoprene, 78-79-5; 1,3-butadiene, 106-99-0; 2-ethyl-1,3-butadiene, 3404-63-5; 2,3-dimethyl-1,3-butadiene, 513-81-5; TCNE, 670-54-2; acrolein, 107-02-8; acrylic acid, 79-10-7; paraformaldehyde, 30525-89-4; glyoxal, 107-22-2.

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Alkali Metal and Electrochemical Reductions of Dibenzoylbenzenes[1]

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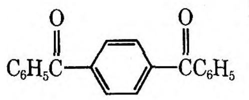
The three isomeric dibenzoylbenzenes **1**, **2**, and **3** have been found to react with 1 equiv of potassium in 1,2-dimethoxyethane (monoglyme) or ammonia to form radical anions **4**, **15**, and **22** as shown by comparison of their esr spectra with those of the radical anions produced from **1**, **2**, and **3** by controlled-potential electrolysis in monoglyme. Treatment of para isomer **1** with 2 equiv of potassium in monoglyme or ammonia affords the diamagnetic dianion **5**, as evidenced by protonation, alkylation, and carboxylation at one of the original carbonyl carbons. The chemical and electrochemical reversibility of this two-electron process has been demonstrated by controlled-potential redox experiments and aerial oxidation to regenerate **1**. Reaction of **1** with 2 equiv of lithium in ammonia produces a mixture of starting ketone **1** and the diastereomeric diols (**7**) resulting from reduction of both carbonyl groups. Treatment of ortho isomer **2** with 2 equiv of potassium in monoglyme or ammonia leads to predominant formation of 10-phenyl-10-hydroxy-9-anthrone (**16**), while similar reductions of **2** with potassium in monoglyme-*tert*-amyl alcohol or with lithium in ammonia afforded mainly 1,3-diphenylisobenzofuran (**17**). Exposure of meta isomer **3** to 2 equiv of potassium in monoglyme produces a paramagnetic intermediate, which appears to be the radical trianion resulting from reduction of a dimer of radical anion **22**.

Alkali metal reductions of ketones continue to be the subject of numerous synthetic and mechanistic studies.[2] In light of this, we have examined a series of alkali metal reductions of dibenzoylbenzenes **1**–**3** using the solvent systems liquid ammonia and 1,2-dimethoxyethane (monoglyme). For comparison purposes, electrochemical reductions of **1**–**3** were also carried out in monoglyme.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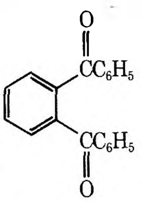
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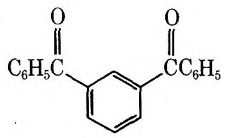
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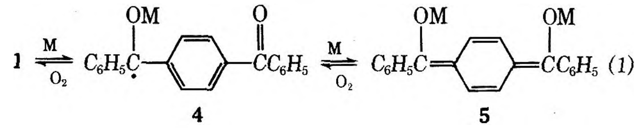
Previous studies dealing with alkali metal and electrochemical reductions of diketones **1**–**3** have been scattered, and no attempts have been made to compare the two processes under similar conditions. For example, Schlenk[3] has reported that para isomer **1** was converted into a dipotassio salt and meta isomer **3** afforded a monopotassio derivative upon treatment with the potassium ketyl of 4-phenylbenzophenone in ether. Using similar reduction conditions, Müller[4] obtained both the mono- and dipotassio salts of **1**. In the same study the monopotassio derivative of **3** was prepared and assigned a pinacolate structure on the basis of its diamagnetism. Further reduction of this material afforded a paramagnetic species, the structure of which was designated as a diketyl of the pinacolate, complexed with two molecules of neutral diketone. Recently, Szwarc and coworkers[5] found that reduction of **3** with sodium or sodium biphenylide in hexamethylphosphoramide (HMPA) afforded mainly the monomeric (paramagnetic) radical anion of **3**, while the dimeric (diamagnetic) radical anion of **3** was formed in tetrahydrofuran (THF). However, the chemistry of these intermediates was not investigated, nor have any reports concerning the chemistry of the presumed radical anion and dianion of **1** appeared to date. In contrast to this, products resulting from alkali metal reductions of ortho isomer **2** have been characterized by Herold,[6] but the spectral and magnetic properties of the intermediates presumably responsible for their formation have not been reported.

Electrochemical reductions of diketones **1**-**3** have been carried out in both protic[7-11] and aprotic solvents,[6,11] but no systematic study of all three isomers has been conducted under aprotic conditions. In a recent investigation,[12] it has been reported that polarographic reduction of para isomer **1** in anhydrous DMF was characterized by three waves, the first and second of which corresponded to reversible, one-electron processes, while the third corresponded to an irreversible two-electron step. Similar reduction of meta isomer **3** resulted in generation of two polarographic waves, the first of which represented a reversible one-electron step. The second was a three-electron wave, the initial portion of which supposedly corresponded to the reversible transfer of one electron. This study was not accompanied by spectral characterization of the postulated intermediates produced during reduction, and products of electrolysis were not identified.

Results and Discussion

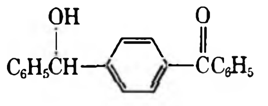
***p*-Dibenzoylbenzene (1).** Brief exposure of a 10^{-2} *M* solution of **1** in monoglyme to a potassium mirror under anaerobic conditions at 25° resulted in formation of an emerald-green solution, which exhibited an esr spectrum consisting of a broad envelope, and had absorption bands at 368, 400, and 790 nm (see paragraph at end of paper regarding supplementary material). Reexposure of this solution to the metallic mirror produced a deep blue solution. Development of the blue color was accompanied by gradual loss of the original esr signal and visible absorption bands, with a new maximum appearing at 575 nm.[13] The intensity of this band varied as the solution was diluted, but no new bands were evident. Slow addition of air to the green solution led to decoloration and regeneration of parent ketone **1**. Similar treatment of the diamagnetic blue solution resulted in initial production of the green species which, on continued admission of air, reverted to **1**. These results are consistent with the steps illustrated in eq 1 involving initial production of radical anion **4** followed by addition of a second electron to **4** to form dianion **5**.[14] Polarographic reduction of **1** in monoglyme revealed two well-defined waves at $E_{1/2} = -2.05$ and -2.50 V, respectively. Cyclic voltammetry indicated that both waves were electrochemically reversible. Controlled-potential electrolysis and coulometry at -2.20 V demonstrated that the first wave corresponded to a one-electron process. The resulting green solution had esr and visible spectra identical with those observed during potassium reduction. Controlled-potential oxidation of this solution


4 **5** (1)

followed by polarographic and thin layer chromatography (tlc) analyses established the chemical reversibility of the initial reduction step. Exhaustive reduction and coulometry at −2.70 V was consistent with a two-electron process. When the resulting diamagnetic blue solution was oxidized at −0.60 V, polarographic and tlc analyses indicated that addition of a second electron to 1 resulted in some loss of chemical reversibility.

Exposure of diketone 1 to 1 molar equiv of potassium in ammonia also produced radical anion 4, the esr spectrum of which was essentially identical with that observed in monoglyme. Radical anion 4 (M = K, Na, or Li) exhibited a low order of basicity toward ammonia as evidenced by persistence of the esr signal and the absence of appreciable amounts of reduced products after 12 hr in this solvent. Radical anion 4 could also be prepared by means of potassium in THF or HMPA, but attempted preparations of dianion 5 in these two solvents were less satisfactory than in monoglyme and ammonia.

Treatment of radical anion 4 (M = K) in monoglyme with anhydrous methanol afforded mainly starting ketone 1, accompanied by ketone alcohol 6 and diastereomeric diols 7. Reaction of 4 with benzyl chloride gave mostly recovered 1 along with traces of benzylation product 8. Diketone 1 was recovered in nearly quantitative yields after treatment of 4 (M = K) with methyl iodide and carbon dioxide. Attempted reactions of 4 (M = K) with methyl iodide and benzyl chloride in liquid ammonia failed to yield isolable amounts of alkylation products.



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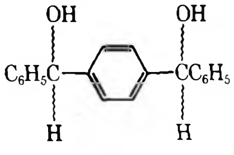

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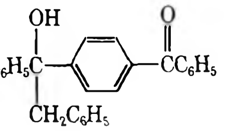

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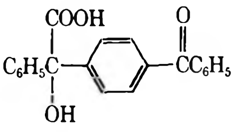

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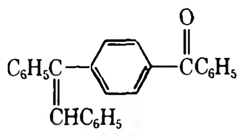
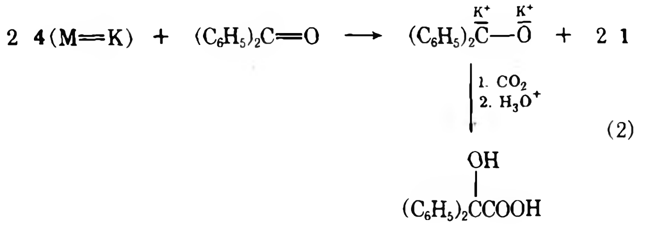


10

Treatment of 4 (M = K) with benzophenone in monoglyme, followed by carbonation of the reaction mixture, afforded a 32% yield of benzilic acid (11) and a 95% recovery of diketone 1. These results are consistent with the electron-transfer reaction shown in eq 2.



$$2\ \mathbf{4}(\mathrm{M{=}K}) + (C_6H_5)_2C{=}O \longrightarrow (C_6H_5)_2\overset{K^+}{\bar{C}}{-}\overset{K^+}{\bar{O}} + 2\ \mathbf{1} \qquad (2)$$

$$\xrightarrow{1.\ CO_2;\ 2.\ H_3O^+} (C_6H_5)_2C(OH)COOH$$

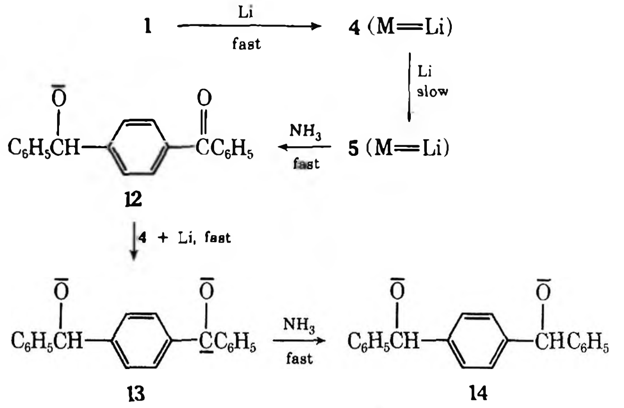
11

Failure of radical anion 4 to undergo significant alkylation with benzyl chloride and methyl iodide may result from its tendency to react with these halides, *via* a similar electron transfer mechanism,[15] which results in reduction of the electrophile and oxidation of 4 to starting diketone.

Although generation of dianion 5 proceeded smoothly with a potassium mirror at low ketone concentrations, more concentrated solutions of 5 were best prepared by refluxing 1 with 2 equiv of potassium or sodium–potassium alloy in monoglyme. Subsequent treatment of 5 with ethanol afforded keto alcohol 6 in 45–52% yield as its 2,4-dinitrophenylhydrazone. Alkylation of 5 with benzyl chloride gave tertiary carbinol 8 (53%), which was dehydrated to unsaturated ketone 10 in 95% yield. Carboxylation of 5 yielded acid 9 (55%). Dianion 5 (M = K) could also be formed by means of 2 molar equiv of potassium in ammonia, as shown by protonation and benzylation to afford 6 (41%) and 8 (57%), respectively. Recovery of starting diketone from the above reactions in yields of 15–25% indicated either that formation of 5 was incomplete or that this intermediate may have reacted to some extent with the added electrophiles by electron transfer.

Exposure of 1 to 2 equiv of lithium in ammonia gave a 44% recovery of 1 and a 47% yield of diols 7. None of the expected keto alcohol 6 could be detected. Treatment of the reaction mixture with methyl iodide or benzyl chloride failed to provide significant amounts of alkylation products; instead 1 and diols 7 were produced in approximately the same yields as in the absence of halide. A possible explanation of these results is presented in Scheme I.

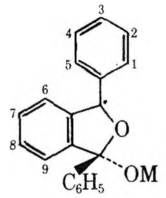
Scheme I



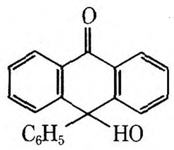
It is proposed that initial, rapid consumption of 1 equiv of lithium to form radical anion 4 is followed by somewhat slower formation of dianion 5. The relatively slow formation of 5, coupled with its rapid ammonolysis,[16] prevents accumulation of significant quantities of this intermediate during the reaction as shown by failure of the attempted alkylation reactions. Preferential reduction of 12 by residual metal and radical anion 4 (*cf.* the reduction of benzophenone by 4) to form trianion 13, ammolysis of this intermediate to yield dianion 14, and neutralization of 14 to give diols 7 completes the reduction process in a manner compatible with the observed stoichiometry. That the solvent does indeed serve as the source of the methine protons of diols 7 was verified by allowing diketone 1 to react with 4 equiv of lithium in ammonia, then removing the solvent, and quenching the residue with deuterium oxide. Pmr analysis of the resulting diols (97%) revealed no incorporation of methinyl deuterium. Although it seems likely that 12 should have a lower reduction potential than radical anion 4, and therefore accept an electron from either lithium or 4, it is not immediately obvious why the resulting radical dianion of 12 would be reduced to trianion 13 in preference to reduction of 4 to dianion 5. However, this appears to be the case; otherwise keto alcohol 6 should have been the major product. In support of this mechanism it was also found that treatment of 1 with potassium in monoglyme containing *tert*-amyl alcohol as a proton source afforded diols 7 and recovered 1, accompanied by only traces of keto alcohol **6**. This indicates that reduction of the remaining carbonyl function of **6** proceeds more rapidly than initial reduction of the equivalent carbonyl groups of **1**.

o-Dibenzoylbenzene (2). Initial contact of a 10^{-2} *M* solution of **2** in monoglyme with potassium gave rise to a burgundy solution which had a complex esr spectrum quite similar to the electrochemically generated spectrum (see supplementary material). The electronic spectrum of this solution was characterized by an intense band at 495 nm. Admission of air followed by quenching with absolute ethanol afforded starting diketone **2** in >90% purity as shown by uv analysis. Prolonged (6 hr) contact of a similar solution with potassium gave a dark blue, weakly paramagnetic solution. During development of the blue color the electronic spectrum gradually assumed the same general features as that obtained on treatment of 10-phenyl-10-hydroxy-9-anthrone (**16**) with potassium in monoglyme (intense bands at 380 and 400 nm). Aerial oxidation of the solution resulting from extended reduction of **2** yielded mainly **16**, along with traces of **2** and anthraquinone.[6b] Reaction of **2** with 1 equiv of potassium in ammonia produced a paramagnetic burgundy solution from which an esr spectrum similar to that observed in monoglyme was obtained.

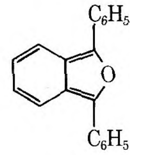
Polarographic reduction of diketone **2** in monoglyme was characterized by two waves at $E_{1/2} = -2.30$ and -2.70 V. Cyclic voltammograms revealed that the first wave corresponded to an electrochemically reversible process, while the second wave exhibited nearly total irreversibility. Controlled potential reduction at -2.40 V gave a pink solution which gradually became burgundy as electrolysis continued. Coulometric analysis was consistent with a one-electron reduction, which proved to be chemically reversible. An esr spectrum of this solution was essentially identical with the spectra observed from potassium reductions.[17] Although the actual structure of the paramagnetic species must still be considered open to further study, we were able to obtain a reasonably good simulated spectrum of the electrochemically generated intermediate by assuming cyclic radical anion structure **15**[6d] with the following coupling constants: a_3^H or $a_8^H = 4.0$ or 3.8, $a_6^H = 3.75$, $a_1^H = a_5^H = 2.35$, and $a_2^H = a_4^H = a_7^H =$ $a_9^H = 0.8$ (all values given in gauss). Controlled-potential reduction of **2** at -2.75 V showed the uptake of nearly four electrons in a chemically irreversible process. The high electron count is attributed to formation and subsequent reduction of anthrone **16** and anthraquinone, both of which exhibit polarographic waves below -2.75 V and were detected as products of exhaustive electrolysis.



15



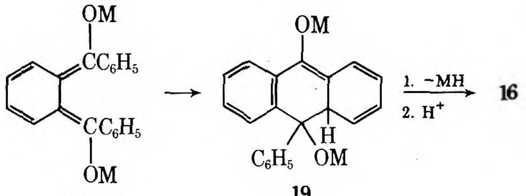
16



17

Reductions of **2** in ammonia were accompanied by an interesting metallic cation effect. Thus, 2 equiv of potassium produced anthrone **16** as the major product, while isobenzofuran **17** was the only product observed with 2 equiv of lithium. Reaction of **2** with 2 equiv of potassium in refluxing monoglyme followed by addition of ethanol produced anthrone **16**, while similar treatment of **2** with potassium in the presence of *tert*-amyl alcohol afforded isobenzofuran **17**. Attempts to trap a possible dianion intermediate by reduction of **2** with potassium or lithium in ammonia followed by addition of benzyl chloride gave **16** and **17**, respectively.

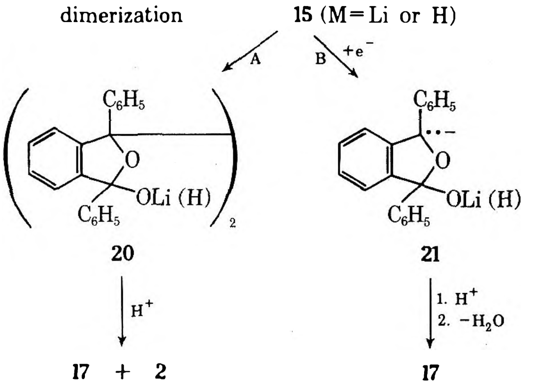
On the basis of the foregoing experiments it is suggested that diketone **2** initially accepts an electron from the reducing metal or mercury cathode to form cyclic radical anion **15**. Addition of a second electron to **15** in the absence of a proton source or lithium ions then yields an acyclic dianion such as **18**, which rapidly cyclizes to form anthrone **16**, possibly by loss of metal hydride from intermediate **19** (eq 3).[18]



18 **19** (3)

Generation of **15** in the presence of a proton donor (*tert*-amyl alcohol) or lithium ions may effectively trap this intermediate in its cyclic form by O-protonation or formation of a highly covalent O–Li bond, respectively. Subsequent production of isobenzofuran **17** might then occur by either or both of the routes illustrated in Scheme II.

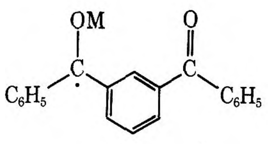
Scheme II



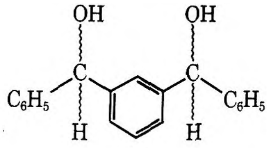
In route A, **15** dimerizes to afford **20**, the protonated form of which is known[6c] to disproportionate to yield equimolar amounts of **17** and **2** in the presence of mineral acid. Alternatively (route B) **15** could accept a second electron to form cyclic dianion **21**, which then undergoes C-*protonation and* subsequent acid-catalyzed, transannular dehydration[19] on work-up to produce **17**. We have now gained evidence that both of these mechanisms may be operating in the lithium–ammonia reductions. Thus, when **2** was subjected to such reduction and the reaction was processed with the careful exclusion of acid, two products, along with some unreacted starting material, were detected by tlc; however, **17** was not present in the crude mixture. The more mobile of these compounds was converted to a mixture of starting diketone **2** and isobenzofuran **17** on brief exposure to acid, while the less mobile component afforded only **17**. From this it is concluded that the first of these is the dimer **20** (H)[6c] and the second is the monomeric alcohol[19] resulting from C- and O-*protonation of* **21**. It was established that neither of these compounds was a diol resulting from reduction of both carbonyl groups of **2**, since independent synthesis of these diols followed by treatment with acid did not product **17**.

***m*-Dibenzoylbenzene (3).** Brief reaction of a 10^{-2} *M* monoglyme solution of **3** with potassium afforded a dark red solution with visible bands at 398 and 510 nm, characteristic of the "diamagnetic dimer" form of radical anion **22** (M = Na) in THF or HMPA.[5] Although the visible band at 760 nm attributed[5] to the monomeric form of **22**

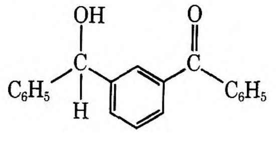
was very weak, the red solution had an esr spectrum in agreement with that reported for the monomeric species in HMPA.[5] Treatment of **3** with 1 equiv of potassium in ammonia produced a red solution, the esr spectrum of which was characteristic of monomeric **22**. This solution could be maintained for 24 hr in the absence of oxygen without appreciable loss of intensity of the original color or esr signal. Exposure of the liquid ammonia or monoglyme solutions of **22** to air resulted in rapid loss of color, and **3** was recovered in excellent yield. When the monoglyme solution of **22** was quenched with methanol prior to opening to the atmosphere, a mixture consisting of **3**, diols **23**, and a minor component possessing spectral properties consistent with keto alcohol structure **24** was obtained.



22



23



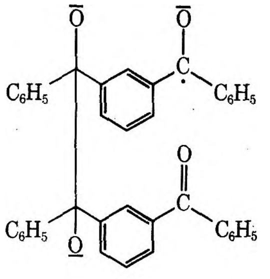
24

Repeated contact of the red solution of **22** in monoglyme with potassium resulted in eventual loss of the bands at 400 and 520 nm accompanied by appearance of an intense new band at 685 nm in the electronic spectrum of the resulting dark blue solution.[20] This solution retained a high degree of paramagnetic character as shown by the presence of a broad, intense esr singlet. Dilution and reconcentration of the solution resulted only in changes in the intensity of the 685-nm band; no new bands could be detected. Gradual admission of air into the blue solution caused it to regain the original red color and finally become colorless; diketone **3** was regenerated in a high state of purity. When the blue solution was quenched with methanol prior to exposure to air, starting ketone **3**, diols **23**, the presumed keto alcohol **24**, and several minor components were produced.

Polarographic reduction of **3** in DME revealed two electrochemically reversible waves at $E_{1/2} = -2.30$ and -2.65 V. Controlled-potential electrolysis and coulometric measurements at -2.40 V were consistent with a one-electron process to form radical anion **22**, the esr spectrum of which was practically the same as that produced by means of potassium in monoglyme or ammonia. A polarogram of the reoxidized solution coupled with tlc analysis demonstrated good chemical reversibility. Controlled-potential electrolyses of **3** at -2.80 V consistently resulted in uptake of *ca.* 1.5 electrons. Reoxidation of this weakly paramagnetic solution showed some loss of chemical reversibility, but **3** was still the major component of such reaction mixtures.

Attempted alkylations of radical anion **22** (M = K) in monoglyme or ammonia with benzyl chloride gave only recovered **3**. Treatment of **3** with 2 equiv of potassium, sodium, or lithium in ammonia followed by ammonium chloride or benzyl chloride also afforded unchanged **3** in yields of >90%. Attempts to generate and trap a possible dianion intermediate by refluxing **3** with 2 equiv of potassium in monoglyme resulted in cleavage of **3** to form benzoic acid, benzhydrol, and several unidentified minor products. However, extended reaction of **3** with 4 equiv of sodium in ammonia afforded diols **23** in 81% yield.

On the basis of our results and those of Szwarc and coworkers,[5] it appears that diketone **3** is reduced by 1 equiv of potassium in monoglyme or liquid ammonia to form radical anion **22**, which exists as a mixture of monomeric and dimeric forms with the latter predominating. However, the fate of **22** in the presence of a second equivalent of metal is less clear. Failure to produce significant amounts of alkylation products or the expected keto alcohol **24**, coupled with the high degree of paramagnetism, appears to preclude the presence of appreciable amounts of a dianion such as that derived from para isomer **1**. The absence of half-field transitions in the low-temperature esr spectra of the blue monoglyme solutions seems to rule out the possibility of triplet (diketyl) species arising from independent reduction of the carbonyl groups of **3**. Since coulometric measurements conducted at -2.75 V ($n = 1.5$) can be rationalized by a one-electron reduction of a dimeric radical anion, we propose that the major species produced on further reaction of **22** may be the dimeric radical anion represented by structure **25**. Although **25** is shown as having a formal C–C bond, the actual bonding may be of the π–π type[5] as evidenced by recovery of starting ketone **3** on exposure of such solutions to oxygen[21] or alkyl halides, and the predominant formation of monomeric reduction products with excess sodium in liquid ammonia.



25

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus in open capillary tubes and are corrected. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich., and in this laboratory by Miss Q. H. Tan using an F & M Model 185 C, H, and N analyzer. Infrared (ir) spectra were recorded on a Beckman IR-5A infrared spectrophotometer and are calibrated with a polystyrene spike at 6.24 μ. Potassium bromide pellets and chloroform solutions were employed for solids and neat samples between sodium chloride plates were used for liquids. Nuclear magnetic resonance (nmr) spectra were obtained on a Varian Associates A-60 spectrometer. Chemical shifts, relative to tetramethylsilane as the internal standard, were measured to the center of a singlet or multiplet. Peak areas were consistent with the assignments given. Mass spectra were obtained on an Hitachi Perkin-Elmer RMU-6E mass spectrometer at 50 eV. Electronic spectra were taken on a Cary 14 spectrophotometer. Thin layer chromatography (tlc) was conducted with an Eastman chromagram apparatus using chromagram sheets type K301R (silica gel) with fluorescent indicator and benzene as the developing solvent. Spots were detected with uv light and iodine.

All electrochemical studies were performed in a Vacuum Atmosphere Dry-Lab Train (argon atmosphere) drybox using 1,2-dimethoxyethane (freshly distilled from lithium aluminum hydride under argon) as solvent and tetrabutylammonium perchlorate as supporting electrolyte at 0.1 *M* concentrations. Substrate concentrations of 1×10^{-3} *M* were employed. Polarographic, cyclic voltammetric, and controlled-potential electrolysis experiments were run in a standard H-type cell employing procedures and circuity described elsewhere.[22] The general procedure used for studying electrochemical behavior is given in the supplementary material.

p-Dibenzoylbenzene (**1**) was prepared according to the procedure of Murray and Trozzolo.[23] *o*-Dibenzoylbenzene (**2**) was prepared as described by Jensen.[24] *m*-Dibenzoylbenzene (**3**) was synthesized by the procedure of Dischendorfer and Verdino.[25]

Simulation of the esr spectrum resulting from electrochemical reduction of 2 was accomplished using a program similar to SESR of Stone and Maki[26] suitably modified to permit its use on the VPI & SU IBM 360/50-40 with an associated Calcomp plotter.

Generation of Radical Anions 4, 15, and 22 and Dianion 5 on a Preparative Scale in Monoglyme and Liquid Ammonia. A. Radical Anions 4, 15, and 22. To a solution of 2.5 g (8.8 mmol) of *the appropriate ketone in 150 ml of monoglyme* contained in a 250-ml three-necked flask equipped with a sealed mechanical stirrer, a nitrogen inlet, and a 10-mm ball and socket stopcock at the bottom was added 0.35 g (9 mg-atoms) of freshly cut potassium. The reaction mixture was stirred at room temperature until metal could no longer be detected (2-3 hr) and the resulting colored solution was filtered through a glass wool plug into a second 250-ml three-necked flask containing a monoglyme solution of the reagent with which the radical anion was to be treated. Preparation of radical anions 4, 15, and 22 (M = K, Na, or Li) in ammonia was conducted similarly except that the ketone was added rapidly as a solid to a solution of the appropriate alkali metal in 150 ml of freshly distilled (from benzophenone potassium ketyl) liquid ammonia, and reagents were then introduced directly into the reaction mixture; a nitrogen atmosphere was maintained throughout.

B. Dianion 5. To a stirred solution of 6.87 g (24 mmol) of diketone 1 in 250 ml of monoglyme under nitrogen was added 1.75 g (49 mmol) of sodium-potassium alloy. The reaction mixture was allowed to reflux for 6 hr, after which time the resulting purple solution of 5 was used in the reactions described below. In the same manner 2.5 g (8.8 mmol) of 1 was refluxed for 6 hr with 0.77 g (19.7 mg-atoms) of potassium metal in 150 ml of anhydrous monoglyme to afford a purple solution of dianion 5. Dianion 5 (M = K or Na) was also prepared by adding 8.8 mmol of solid 1 to a solution of 19.5 mg-atoms of the appropriate alkali metal in 250 ml of anhydrous liquid ammonia. After 1 hr the resulting purple solution was used as described below.

Reactions of Radical Anion 4. A. With Methanol. A monoglyme solution of 4 (8.8 mmol) was added to excess methanol under nitrogen at 25°. The resulting solution was allowed to stir for 18 hr, then concentrated under vacuum, and 50 ml of water was added to the remaining pasty mass. The aqueous suspension was extracted with ether and the extracts were dried (Na_2SO_4). Concentration of the ethereal solution followed by tlc and nmr analysis revealed the presence of diketone 1, keto alcohol 6, and diols 7. Chromatography of the product mixture on silica gel (benzene-$CHCl_3$) afforded 1.75 g (70% recovery) of 1.

B. With Benzyl Chloride. A solution of 4 (8.8 mmol) in monoglyme was added to a solution of 1.11 g (8.8 mmol) of benzyl chloride in monoglyme. The reaction mixture was stirred for 1 hr at 25°, after which time absolute ethanol (5 ml) was added. The solvent was removed under vacuum and replaced with 500 ml of ether. The ethereal solution was washed with water, dried (Na_2SO_4), and concentrated. Analysis of the crude solid by tlc and nmr revealed the presence of starting ketone 1 as the major reaction component along with minor amounts of carbinol 8. Chromatography of the crude product mixture on neutral alumina (benzene) afforded a 73% recovery of 1. Similar treatment of 4 with methyl iodide resulted in nearly quantitative recovery of diketone 1.

C. With Carbon Dioxide. A freshly prepared solution of radical anion 4 in monoglyme was poured onto an excess of Dry Ice. The solvent was evaporated and the residue was diluted with 200 ml of water, after which the mixture was extracted with ether. The extracts was washed with water and dried (Na_2SO_4), and the solvent was removed to give a 90% recovery of starting diketone. After acidification, the aqueous solution was extracted with ether to give <1% of acid 9. Similar results were obtained on adding gaseous carbon dixoide to the reaction mixtures.

D. With Benzophenone. To a stirred monoglyme solution of 8.8 mmol of radical anion 4 was added 0.80 g (4.4 mmol) of benzophenone as a 5% w/v solution in anhydrous monoglyme. After 2 hr the purple reaction mixture was poured onto excess Dry Ice. The solvent was evaporated and the residue was diluted with 200 ml of water. The aqueous solution was extracted with ether and then acidified with 3 *N* HCl. The resulting suspension was extracted with ether, dried (Na_2SO_4), and concentrated to give a viscous yellow oil, which was crystallized from benzene-hexane to afford 0.32 g (32%) of benzilic acid (11), mp 151-153°. A mixture melting point with an authentic sample of 11 showed no depression; the ir spectra of the two samples were identical. The former ethereal extract was processed in the usual manner to afford a 95% recovery of starting diketone 1.

Reactions of Dianion 5. A. Protonation. A monoglyme solution of dianion 5 (24 mmol), prepared utilizing sodium-potassium alloy, was added dropwise to 50 ml of anhydrous ethanol. After 1 hr the solvent was distilled from the reaction mixture under reduced pressure and the residue was diluted with 250 ml of ether and 200 ml of water. The organic layer was separated and the aqueous solution was extracted with ether. The combined ethereal solution was dried (Na_2SO_4) and concentrated to give an oil, which was chromatographed on silica gel [benzene-hexane (1:2)] to give 1.76 g (26%) of starting diketone 1. Further elution with benzene gave 3.84 g of 4-benzoylbenzhydrol (6): nmr (DMSO-d_6) δ 7.93 (m, 14, aromatic), 6.42 (d, 1, OH), and 6.10 ppm (d, 1, CH); ir ($CHCl_3$) 2.77 and 6.93-7.15 (OH) and 6.03 μ (C=O). The 2,4-dinitrophenylhydrazone was prepared under mild conditions to give 5.86 g (52%) of orange crystals: mp 169-172°, and 171.5-172.5° after recrystallization from ethanol; nmr (DMSO-d_6, δ 11.05 (s, 1, NH), 7.99 (m, 17, aromatic), 6.19 (d, 1, OH), and 5.98 ppm (d, 1, CH); ir ($CHCl_3$) 2.76 and 6.92-7.03 (OH), 3.02 and 7.50-7.62 (NH), and 6.63 μ (NO_2); mass spectrum (50 eV) molecular ion peak at *m/e* 468 with abundant fragment peaks at *m/e* 374, 286, 165, 105, and 77.

Anal. Calcd for $C_{26}H_{20}N_4O_5$: C, 66.66; H, 4.30; N, 11.96. Found: C, 66.72; H, 4.58; N, 11.86.

Acidification of the aqueous solution after extraction with ether, followed by the usual work-up, afforded 0.24 g (8%) of benzoic acid, mp 120-122°, mmp 121-122°.

Similar protonation of 8.8 mmol of dianion 5 prepared from 1 and potassium metal in monoglyme afforded 1.86 g (45%) of the 2,4-dinitrophenylhydrazone of 6.

A solution of 8.8 mmol of dianion 5 (M = K) in ammonia was quenched with 2.81 g (0.0525 mol) of solid ammonium chloride. The ammonia was distilled from the reaction mixture as an equal volume of ether was added. Cold 3 *N* HCl was added to the ethereal solution and the layers were separated. After the aqueous solution was extracted with ether, the ethereal solution was washed with water, dried (Na_2SO_4), and concentrated to give a yellow oil, which was chromatographed on silica gel [benzene-hexane (1:2)] to give 1.12 g (45%) of diketone 1. Further elution with benzene afforded 1.28 g of 6; the 2,4-dinitrophenylhydrazone was prepared and gave 1.67 g (41%) of orange crystals, mp 170.5-172.5°, mmp 170-172°.

Similar treatment of 8.8 mmol of dianion 5 prepared by means of sodium in ammonia afforded 23% of 6 as its 2,4-dinitrophenylhydrazone. In this experiment, 1 was recovered in 61% yield.

B. Alkylation with Benzyl Chloride. A monoglyme solution of 24 mmol of dianion 5, prepared by means of sodium-potassium alloy, was added dropwise to a 10% v/v solution of 6.34 g (0.05 mol) of benzyl chloride in anhydrous monoglyme. The resulting mixture was allowed to stir for 2 hr before the dropwise addition of 50 ml of absolute ethanol. The solvent was distilled from the reaction mixture and replaced with an equal volume of ether. Cold water (250 ml) was added to the ethereal solution and the layers were separated. The aqueous solution was extracted with ether. The original ethereal solution and the extracts were combined, washed with water, and dried (Na_2SO_4), and the ether was evaporated to give a dark yellow oil. This oil was absorbed on a column of acid alumina which was eluted with benzene-hexane (1:2) to remove impurities. Further elution with chloroform gave 4.80 g (53%) of 4-benzoyl-α-benzylbenzhydrol (8) as a colorless oil: nmr (DMSO-d_6) δ 7.78 (m, 19, aromatic), 6.25 (s, 1, OH), and 3.87 ppm (s, 2, CH_2); ir (neat) 2.86 and 6.92-7.12 (OH) and 6.02 μ (C=O).

Anal. Calcd for $C_{27}H_{22}O_2$: C, 85.68; H, 5.86. Found: C, 85.77; H, 5.80.

A 2.00-g (53 mmol) sample of 8 was dehydrated by refluxing with a few crystals of *p*-toluenesulfonic acid in 200 ml of benzene. After 3 hr the mixture was cooled, washed with water, dried (Na_2SO_4), and concentrated to afford 1.82 g (95%) of 1,2-diphenyl-1-(4-benzoylphenyl)ethene (10) as a pale yellow oil. An analytical sample of 10, prepared by short-path distillation, had nmr (DMSO-d_6) δ 7.87 ppm (m, aromatic and vinyl CH); ir (neat) 6.00 μ (C=O).

Anal. Calcd for $C_{27}H_{20}O$: C, 89.97; H, 5.59. Found: C, 90.21; H, 5.76.

To a stirred solution of 8.8 mmol of dianion 5 (M = K) in ammonia was added 1.27 g (10 mmol) of benzyl chloride as a 10% v/v solution in anhydrous ether. The resulting mixture was stirred for 1 hr before addition of ammonium chloride. The reaction mixture was processed as in the protonation of dianion 5 to afford a pale yellow oil. Chromatography of this oil on acid alumina with benzene-hexane (1:2) gave a 25% recovery of diketone

1. Further elution with chloroform afforded 1.90 g (57%) of 8. In a similar experiment employing 2 molar equiv of sodium, tlc analysis of the crude product revealed 8 as a minor product with recovered ketone 1 constituting the major component.

C. Carboxylation. Carbon dioxide gas was passed through a solution of 25 mmol of dianion **5**, prepared by means of sodium-potassium alloy in monoglyme. After decolorization had occurred (5 min), 50 ml of absolute ethanol was added. The solvent was evaporated and the residue was diluted with 250 ml of water. The aqueous solution was washed with ether and acidified with 3 *N* HCl. The resulting emulsion was extracted with ether. The ethereal extract was washed with water, dried (Na_2SO_4), and concentrated to give an oil which was passed through a column of silica gel (chloroform) to afford a pale yellow oil, which crystallized from benzene-hexane to give 4.38 g (55%) of 4-benzoylbenzilic acid (**9**), mp 160-161°. After recrystallization from benzene, **9** had mp 161-162°; nmr (DMSO-d_6) δ 7.59 ppm (m, 16, aromatic, OH, and COOH); ir ($CHCl_3$) 2.80-2.95 (OH and COOH), 5.82-5.90 (carboxyl C=O), and 6.04 μ (ketone C=O); mass spectrum (50 eV) molecular ion peak at *m/e* 332. The base peak was at *m/e* 287; abundant fragment peaks were also observed at *m/e* 209, 186, 105, and 77.

Anal. Calcd for $C_{21}H_{16}O_4$: C, 75.89; H, 4.85. Found: C, 76.08; H, 4.98.

Similar treatment of dianion **5**, prepared with potassium metal in monoglyme, afforded acid **9** in yields of 36 and 37%. Formation and carboxylation of dianion **5** were also attempted at room temperature in THF and in HMPA to give **9** in yields of 7 and 5%, respectively. In all reactions the recovery of starting ketone was excellent.

Reaction of 1 with 2 Equiv of Lithium in Liquid Ammonia. To a solution of 0.13 g (18.7 mg-atoms) of lithium in 250 ml of liquid ammonia under nitrogen was added 2.5 g (8.8 mmol) of **1** and the resulting purple solution was stirred for 1 hr. Solid ammonium chloride was added and the ammonia was distilled from the mixture and replaced with an equal volume of ether. Cold 3 *N* HCl was added to the ethereal solution and the layers were separated. The original ethereal solution and extracts were combined, washed with water, dried (Na_2SO_4), and concentrated. The solid residue was fractionally recrystallized from benzene-hexane to give 0.61 g of one diastereoisomer (**7a**) of 4,4′-bis(α-hydroxybenzyl)benzene as white needles: mp 170-172°; nmr (DMSO-d_6) δ 7.42 (m, 14, aromatic) and 5.76 ppm (broad s, OH and CH); ir (KBr) 2.79 and 6.90-7.05 (OH) and 8.94-9.28 μ (COH); mass spectrum (50 eV) molecular ion peak at *m/e* 290 with abundant fragment peaks at *m/e* 211, 183, 105, and 77.

Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.78; H, 6.25. Found: C, 82.84; H, 6.21.

The second diastereomer (**7b**) was obtained as 0.48 g of snowball-like crystals, mp 141-143°. After recrystallization from benzene-hexane, **7b** had mp 142.5-143.5°; nmr (DMSO-d_6) δ 7.28 (m, 14, aromatic), 5.80 (d, 2, OH), and 5.62 ppm (d, 2, CH) ir (KBr) 2.78 and 6.92-7.08 (OH) and 8.97-9.28 μ (COH); mass spectrum (50 eV) molecular ion peak at *m/e* 290 with abundant fragment peaks at *m/e* 211, 183, 105, and 77.

Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.78; H, 6.25. Found: C, 82.74; H, 6.22.

Further crystallization from benzene-hexane afforded a 41% recovery of diketone **1**.

In a similar experiment **1** was reduced with 4 equiv of lithium in ammonia. After the ammonia had been evaporated and replaced with an equal volume of ether, the reaction mixture was quenched with deuterium oxide. An nmr spectrum of a sample of the resulting dialcohol mixture revealed no incorporation of deuterium at the methinyl carbons. Attempted alkylation of a similar reaction mixture with methyl iodide gave only recovered **1** (40%) and diols **7a,b** (42%).

Reduction of 1 in the Presence of *tert*-Amyl Alcohol. A mixture of 8.8 mmol of **1**, 0.11 mol of *tert*-amyl alcohol, and 44 mg-atoms of potassium in 250 ml of monoglyme was refluxed for 4 hr. The reaction was processed in the same manner as when dianion **5** was protonated with ethanol. Tlc analysis of the crude product mixture revealed starting material and diols **7a,b,** but no keto alcohol **6**. Column chromatography afforded 0.74 g of the mixed diols and 0.80 g of **1**.

Reduction of 2 with Potassium in Monoglyme. A mixture of potassium (1.53 g, 38 mg-atoms), o-dibenzoylbenzene (**2**, 5.0 g, 17.5 mmol), and 250 ml of anhydrous monoglyme was stirred for 12 hr at reflux. The reaction mixtrue was then cooled in an ice bath and 25 ml of absolute ethanol was added dropwise. After the excess alkali metal had been destroyed, the solvent was removed and replaced with an equal volume of ether. Water was then added, the layers were separated, and the aqueous solution was extracted with three 150-ml portions of ether. The combined ethereal solution was washed with water and dried (Na_2SO_4), and the solvent was evaporated to give 2.81 g (56%) of 10-hydroxy-10-phenyl-9-anthrone (**16**): mp 212.5-215.5° (lit.[27] mp 207-208°); nmr (DMSO-d_6) δ 8.02 (m, 13, aromatic) and 7.34 ppm (s, 1, OH); ir ($CHCl_3$) 2.79 (OH) and 6.02 μ (C=O).

Reduction of 2 in the Presence of *tert*-Amyl Alcohol. To a mixture of 0.70 g (18 mg-atoms) of potassium, 3.97 g (45 mmol) of *tert*-amyl alcohol, and 200 ml of anhydrous monoglyme at room temperature was added 1.0 g (3.5 mmol) of **2**. The reaction mixture was refluxed for 4 hr and the solvent was removed under reduced pressure. The residue was diluted with 250 ml of ether and 150 ml of cold 3 *N* HCl. The layers were separated and the aqueous solution was extracted with two 100-ml portions of ether. The combined ethereal solution was washed with water, dried (Na_2SO_4), and concentrated to give a yellow oil. Tlc analysis revealed that 1,3-diphenylisobenzofuran (**17**) and the starting diketone were the only components present. The oil was chromatographed on acid alumina (hexane) to give 0.36 g (38%) of **17**, mp 131-132° (lit.[28] mp 127-128°). The ir spectrum of **17** was identical with that of an authentic sample. Further elution with chloroform gave a 39% recovery of diketone **2**.

Reduction of 2 in Liquid Ammonia. A. With Lithium. To a solution of 0.14 g (20 mg-atoms) of lithium in 250 ml of liquid ammonia was added 8.8 mmol of **2**. The resulting purple solution was allowed to stir for 1 hr and then neutralized with ammonium chloride. The ammonia was evaporated as an equal volume of ether was added. To this ethereal suspension was added 150 ml of cold 3 *N* HCl, and the layers were separated. After the aqueous solution was extracted with ether, the combined ethereal solution was washed with water, dried (Na_2SO_4), and concentrated to give a yellow oil, which was chromatographed on neutral alumina (hexane) to give 0.85 g (36%) of **17**. Further elution with chloroform gave a 35% recovery of **2**.

Similarly, diketone **2** was treated with 2 molar equiv of lithium. Following addition of ammonium chloride and removal of the ammonia, the reaction mixture was hydrolyzed with a 5% $NaHCO_3$ solution and extracted with ether. Tlc analysis of the ethereal extracts revealed, in order of decreasing R_f values, starting diketone **2**, two unidentified components, and traces of the diastereomeric diols resulting from reduction of both carbonyl groups of **2**. Chromatography on basic alumina allowed separation of unreacted **2** and the diols from the two unidentified components, but all attempts to separate these from one another failed. Therefore all fractions containing both unknown compounds were combined and an aliquot of their solution in ether was spotted on an analytical tlc sheet, which was developed with benzene. The sheet was turned to 90°, and authentic samples of starting ketone **2** and isobenzofuran **17** were applied. The sheet was exposed to HCl vapors for a few minutes and then developed in a direction perpendicular to the original solvent front. The more mobile of the two components was thus shown to be converted into a mixture of ketone **2** and isobenzofuran **17**, while the less mobile unknown afforded only **17**. Therefore the former is assigned dimeric structure **20** (H) and the latter is presumed to be monomer **21** (H).

B. With Potassium. To a solution of 0.77 g (19.7 mg-atoms) of potassium in 250 ml of liquid ammonia was added 2.5 g (8.8 mmol) of **2**. After stirring for 2 hr, the reaction was processed in the usual manner to afford an oil, which was shown by tlc analysis to consist of starting material, anthrone **16**, and traces of isobenzofuran **17**. Crystallization of the oil from benzene-hexane gave 0..47 g (19%) of anthrone **16**.

Sodium Borohydride Reduction of 2. A solution of sodium borohydride (0.68 g, 18 mmol) and sodium hydroxide (0.10 g, 2.5 mmol) in 50 ml of methanol was added slowly to a cooled suspension of **2** (2.5 g, 8.8 mmol) in 150 ml of methanol at 10-15°. The solution was then allowed to reflux with stirring for 30 min, after which it was stirred overnight at room temperature. The solvent was distilled from the reaction mixture and the residue was diluted with 100 ml of cold 3 *N* H_2SO_4. After this mixture was extracted with ether, the ethereal solution was washed with water, dried (Na_2SO_4), and concentrated. The resulting oil was chromatographed on silica gel to afford 1,2-bis(α-hydroxybenzyl)benzene as an oily mixture of diastereomers: nmr (DMSO-d_6) δ 7.99 (m, 14, aromatic), 6.63 (m, 2, CH), and 6.41 ppm (m, 2, OH); ir (neat) 2.79 and 6.90-7.15 (OH) and 9.10-9.30 μ (COH).

Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.78; H, 6.25. Found: C, 82.90; H, 6.07.

To a solution of the above diols (1.0 g, 3.4 mmol) in 250 ml of ether was added 150 ml of 3 *N* HCl. The reaction mixture was stirred at room temperature for 30 min, after which it was processed in the usual manner to afford a quantitative recovery of diols; no isobenzofuran **17** could be detected.

Protonation of Radical Anion 15. A solution of 0.8 mmol of radical anion **15** (M = K) in 25 ml of monoglyme was quenched with 25 ml of anhydrous methanol under vacuum. The resulting solution was allowed to stir for 12 hr before being opened to the atmosphere. One drop of 6 *N* HCl was added and the resulting yellow solution was subjected to tlc analysis to reveal the presence of starting diketone **2** and isobenzofuran **17**.

Protonation of Radical Anion 22. A methanol quench (under vacuum) of a solution of **22** (M = K) (8.8 mmol) in 150 ml of monoglyme afforded 2.5 g of crude solid. Tlc analysis of this material revealed, in order of decreasing R_f values, diketone **3**, the presumed keto alcohol **24**, and diols **23**. Elution chromatography of the crude product mixture on silica gel (benzene, benzene-chloroform, and chloroform) afforded 1.75 g of **3**, 200 mg of a mixture of diols **23**, and 150 mg of **24** as a colorless oil. This latter material had the following spectral properties: nmr (CDCl$_3$) δ 7.6 (m, aromatic), 5.92, (2, CH), and 2.66 ppm (s, OH); ir (CHCl$_3$) 2.89 (OH) and 6.1 μ (C=O); mass spectrum (50 eV) molecular ion peak at *m/e* 288 with abundant fragment peaks at *m/e* 209, 183, and 105.

Attempts to protonate radical anion **22** in liquid ammonia with ammonium chloride led to recovery of starting ketone **3** in >95% yield. Similarly, treatment of **3** with 2 equiv of sodium or potassium for 1-3 hr in liquid ammonia followed by attempted alkylation of a possible dianion intermediate with benzyl chloride, *p*-chlorobenzyl chloride, or allyl bromide gave nearly quantitative recoveries of **3**.

Reduction of 3 with 4 Equiv of Sodium. Addition of 5.0 g (17.5 mmol) of **3** to 77 mg-atoms of sodium in 250 ml of liquid ammonia was followed by a reaction period of 24 hr. Solid ammonium chloride was added and the reaction mixture was processed in the usual fashion to give a white solid. This residue was fractionally recrystallized from benzene to afford 2.35 g of one diastereomer (**23a**) of 1,3-bis(α-hydroxybenzyl)benzene as white needles: mp 161.5-162.5; nmr (DMSO-d_6) δ 7.46 (m, 14, aromatic), 6.04 (d, 2, OH), and 5.80 ppm (d, 2, CH); ir (KBr) 2.83 and 6.90-7.23 (OH) and 9.14-9.40 μ (COH); mass spectrum (50 eV) molecular ion peak at *m/e* 290 with abundant fragment peaks at *m/e* 211, 183, 105, and 77.

Anal. Calcd for C$_{20}$H$_{18}$O$_2$: C, 82.78; H, 6.25. Found: C, 82.70; H, 6.20.

The second diastereomer (**23b**) of 1,3-bis(α-hydroxybenzyl)benzene was obtained as 1.76 g of white crystals, mp 94.0-96.5°, after chromatography of the mother liquor on silica gel (chloroform). Recrystallization of **23b** from benzene-hexane afforded white crystals: mp 95.0-96.5; nmr (DMSO-d_6) δ 7.51 (m, 14, aromatic), 6.03 (d, 2, OH), and 5.81 ppm (d, 2, CH); ir (KBr) 2.80 and 6.90-7.20 (OH) and 9.15-9.35 μ (COH); mass spectrum (50 eV) molecular ion peak at *m/e* 290 with abundant fragment peaks at *m/e* 211, 183, 105, and 77.

Anal. Calcd for C$_{20}$H$_{18}$O$_2$: C, 82.78; H, 6.25. Found: C, 82.71; H, 6.37.

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Registry No. **1**, 3016-97-5; **2**, 1159-86-0; **3**, 3770-82-9; **4**, 42908-48-5; **5**, 42908-49-6; **6**, 31020-20-9; **6** 2,4-DNP, 42991-62-8; **7a**, 42913-54-2; **7b**, 31024-90-5; **8**, 42908-51-0; **9**, 42908-52-1; **10**, 42908-53-2; **15**, 42908-54-3; **16**, 5146-30-5; **23a**, 42908-56-5; **23b**, 42908-57-6; methanol, 67-56-1; benzyl chloride, 100-44-7; carbon dioxide, 124-38-9; benzophenone, 119-61-9; lithium, 7439-93-2; *tert*-amyl alcohol, 75-84-3; sodium borohydride, 16940-66-2; 1,2-bis(α-hydroxybenzyl)benzene, 42908-58-7.

Supplementary Material Available. Esr spectra of radical anions **4** and **15**, electronic spectra of radical anion **4**, dianion **5**, and radical anion **15**, along with descriptions of procedures used for studying electrochemical behavior and for obtaining esr and electronic spectra, will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N. W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-146.

References and Notes

(1) (a) Presented in part at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, ORGN 138. (b) Abstracted in part from the Ph.D. Dissertation of J. A. C., Virginia Polytechnic Institute and State University, Aug 1970.

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(13) Prolonged (16 hr) treatment of **1** with potassium afforded a diamagnetic, purple-blue solution possessing a weak visible absorption band at 437 nm and an intense band at 650 nm. A complex mixture of products including benzoic acid and benzhydrol was obtained on aerial oxidation of this solution in the presence of anhydrous methanol. Gradual admission of air failed to regenerate radical anion **4**.

(14) Although other resonance forms may contribute to the actual structure of this intermediate, the present representation is used for the sake of convenience.

(15) For examples of related electron-transfer reactions involving hydrocarbon radical anions and alkyl halides see D. F. Lindow, C. N. Cortez, and R. G. Harvey, *J. Amer. Chem. Soc.*, **94**, 5406 (1972), and references cited therein.

(16) Protonation of dianion **5** rather than radical anion **4** appears to be more likely based on our observations that **4** (M = Li) does *not* undergo appreciable ammonolysis in the absence of excess metal and that 1,2-dilithio, but not 1,2-disodio or 1,2-dipotassio salts of related aryl ketones are rapidly protonated by liquid ammonia; see W. S. Murphy and C. R. Hauser, *Chem. Ind.* (*London*), 832 (1969), and references cited therein.

(17) Well-resolved spectra were obtained on solutions taken for analysis just prior to complete reduction. However, some loss of fine structure was observed following exhaustive reduction at −2.40 V.

(18) It has been suggested[6a,b] that this cyclization involves a diradical intermediate, but a suitable rationale for ultimate loss of a hydrogen atom has not been presented. Although a short-lived diradical cannot be ruled out, the present results with para isomer **1** lead us to propose a *dianion intermediate*. The chemical and electrochemical irreversibility associated with electrolysis of **2** at −2.75 V support the hypothesis that addition of a second electron is a necessary prerequisite for cyclization to **16**. Loss of hydride ion from intermediate **19** is precedented in related cyclizations; for example, see G. Levin, J. Jagur-Grodzinski, and M. Szwarc, *J. Amer. Chem. Soc.*, 92, 2269 (1970).

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(20) When this solution was allowed to remain in contact with potassium for 48 hr the band at 685 nm was replaced by a single maximum at 585 nm, which remained unchanged over a period of 48 hr and was unaffected by dilution. A methanol quench of this solution afforded a mixture of products including starting ketone **3**, diols **23**, and benzoic acid.

(21) For examples of similar oxidative cleavages of dimeric dianions, see J. Chaudhuri, S. Kume, J. Jagur-Grodzinski, and M. Szwarc, *J. Amer. Chem. Soc.*, 90, 6421 (1968), and references cited therein.

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Lead Tetraacetate Oxidations of Stereoisomeric 2-Methyl-3-phenylbutyric Acids[1a,b]

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Lead tetraacetate oxidations of carboxylic acids yield products through alkyl radical or alkyl cation intermediates, depending on reaction conditions. We have investigated these reactions in the well-known phenylethyl system by use of *erythro-* and *threo-*2-methyl-3-phenylbutyric acids. Both substitution and elimination products are obtained. Radical and cationic conditions produce different erythro:threo ratios of substitution products, but each kind of product mixture is independent of the configuration of the starting acid. Radical conditions produce mainly a mixture of 2-chloro-3-phenylbutanes (erythro:threo, 1:1.4); cationic conditions produce mainly a mixture of 1-methyl-2-phenyl-1-propyl acetates (erythro:threo, 1.7:1). The cationic product mixtures are different from those obtained from both solvolytic and deamination reactions of 1-methyl-2-phenyl-1-propyl systems.

Studies of various β-phenylethyl systems have provided a wealth of data, interpretation, and controversy about carbocation processes.[2-7] The kind and extent of rearrangement, the stereoselectivity in product formation, and the degree of participation by neighboring phenyl depend upon the method of generation of the carbocation intermediate and have been attributed to differing degrees of association of cation with leaving group and solvent.[2,8,9] We have investigated the oxidative decarboxylation of *threo-* and *erythro-*2-methyl-3-phenylbutyric acids by lead tetraacetate, using conditions which generate intermediate 1-methyl-2-phenyl-1-propyl cations, and have compared the products formed with those from other carbocation processes. The same mixture of diastereomeric acetates is obtained from both diastereomers by oxidative decarboxylation, and migrations of neighboring hydrogen and methyl do not occur. Phenyl participation does not seem to be important enough to influence the ratio of diastereomeric acetate products.

Lead tetraacetate decarboxylations proceed by way of radical and/or cationic intermediates.[10] The course of a particular reaction is dependent on the structure of the carboxylic acid, the solvent, the relative proportions of reactants, and the nature of the catalyst. Copper(II) salts catalyze the reaction and promote the radical pathway;[11] pyridine, on the other hand, causes a shift to a cationic pathway.[11-13]

Separate lead tetraacetate decarboxylations of *cis-* and *trans-*4-*tert-*butylcyclohexanecarboxylic acids in the presence of pyridine gave the same mixture of *cis-* and *trans-*4-*tert-*butyl-1-cyclohexyl acetates, leading to the conclusion that the same carbocation intermediate is formed from the diastereomeric reactants.[14]

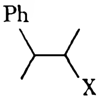
We considered it of interest to investigate whether a β-phenyl substituent would influence the stereochemistry of carbocation product formation in lead tetraacetate decarboxylations. Product formation by solvolysis of 1-methyl-2-phenyl-1-propyl systems is stereospecific,[2,15] but deaminations of the corresponding amines are less stereoselective.[16] Carbocations generated by various means from 1-methyl-2-phenyl-1-propyl systems have been found to give substitution and elimination products resulting from phenyl, methyl, hydrogen, and no rearrangement.[2] Stereochemistry and phenyl rearrangement data have been rationalized in terms of phenyl-bridged cationic intermediates, both symmetrical[15] and unsymmetrical,[7] both providing assistance for the separation of the leaving group and formation after departure of the leaving group. Phenyl-bridged transition states between rapidly equilibrating unbridged cationic intermediates have also been proposed to account for the observed stereochemistry.[5] Recent spectroscopic evidence demonstrates the existence of stable phenyl-bridged cations in superacid solutions.[17]

The acids required for our study were the *erythro-* and *threo-*2-methyl-3-phenylbutyric acids, a mixture of which was synthesized by conventional methods from acetophenone through a sequence of Reformatsky, dehydration, hydrogenation, and saponification reactions and from 2-phenylpropionaldehyde through a Grignard, chlorodehydroxylation, and Grignard carbonation sequence. The mixture of diastereomers (approximately 1:2 theo:erythro) was resolved by fractional crystallization and distillation.

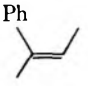
Oxidative decarboxylation was carried out on each isomeric acid separately with pyridine as catalyst and an excess of lead tetraacetate.[12] Product analysis was achieved by comparison of gas chromatographic (gc) data with those of authentic samples; an internal standard was employed for quantitative determinations. The results are summarized in Table I. The only substitution products formed in the oxidation of either isomeric carboxylic acid are acetates obtained without rearrangement due to hydrogen or methyl migration. Rearranged acetates were looked for, but not detected, in the gc chromatogram of the product mixture. Phenyl migration could not be observed under the reaction conditions employed. Such participation, either in generating the intermediate cation or in subsequent reactions of the cation, must be at most a minor factor, however, on the basis of the isomer distribution of the acetates. Phenyl participation is expected to favor erythro acetate considerably more substantially than is found (It-OAc/Ie-OAc ~ 0.20).[18]

The formation of identical (within experimental error) erythro:threo ratios of acetates from both isomeric acids demonstrates the existence of a single cationic intermediate in the oxidation. This observation is supported by the results of the separate halodecarboxylation, a reaction proceeding by a radical pathway,[20] of the isomeric acids. The results are given in Table II. Since the same ratio of erythro:threo chlorides results from the isomeric reactants, a common radical intermediate must be formed after loss of carbon dioxide. The ligand transfer step[21] which follows is then the same for the two isomers and identical product distributions result. It follows that the cation resulting from an electron transfer step[22] must likewise be independent of the stereochemistry of the parent compound, resulting in identical product distributions from the isomeric acids, as found. The specific values of

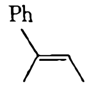
Table I
Product Distribution from Oxidative Decarboxylation of Isomeric 2-Methyl-3-phenylbutyric Acids



I-X



II-Z

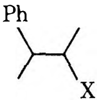


II-E

Starting acid, mmol	Reaction time, hr	Recovered acid, mol %	Product distribution, mol %[a]					It-OAc/Ie-OAc
			I-H	II-Z	II-E	It-OAc	Ie-OAc	
				A. Erythro				
3.16	9	17	1			38	61	0.62
3.70	9	12		16	2	32	50	0.64
3.03	30	2	0.1	10	0.7	33	56	0.58
3.04	17		0.4	17	3.6	30	49	0.60
4.46	22		0.5	17	4.2	29	49	0.59
								av 0.61 ±0.02
				B. Threo				
2.86	22	31	2.8			33	64	0.52
3.08	21	Trace	0.6	14	3.1	31	52	0.60
2.50	48	3	0.6	17	3.9	30	49	0.61
								av 0.58 ±0.04

[a] It = threo; Ie = erythro.

Table II
Product Distribution of Halodecarboxylation of *erythro*- and *threo*-2-Methyl-3-phenylbutyric Acids



I-X

Configuration of starting acid	Time, hr	Product distribution, mol %[a]		Ratio It-Cl:Ie-Cl
		Ie-Cl	It-Cl	
Erythro	3	41.5	58.5	1.43:1
Threo	4	42.2	57.8	1.37:1

[a] It = threo; Ie = erythro.

the erythro:threo ratios must be determined by the direction of attack on either the radical or cationic intermediate. Several pairs of diastereomeric carboxylic acids which do not have a β-phenyl substituent have previously been found also to give the same proportion of diastereomeric products.[12-14,23,24]

Tables III and IV give summaries of substitution and elimination product distributions from reactions involving 1-methyl-2-phenyl-1-propyl cationic intermediates. Solvolyses occur with high stereoselectivity and little or no methyl and hydrogen migration. Amine deaminations occur with lower stereoselectivity and substantial methyl and hydrogen rearrangements. The pyridine-catalyzed oxidative decarboxylations, which take place with only moderate stereoselectivity but without hydrogen or methyl rearrangements, appear to proceed through a cationic intermediate different from either solvolytic or deamination intermediates.

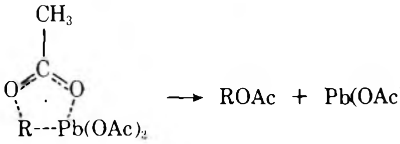
The elimination products likewise illustrate this difference in character of the intermediate cations. The sterically less favored *Z* isomer (steric interaction between the phenyl and methyl groups) is formed from each isomeric parent acid in preference to the thermodynamically more stable *E* isomer.[25]

A small amount of radical product, 2-phenylbutane, is present in the decarboxylation product mixture. The much smaller proportion (2-3% of the hydrocarbon mixtures) of alkane formed from the 2-methyl-3-phenylbutyric acids compared to the amount (~25% of hydrocarbon product) obtained from a similar reaction with 2-methylbutyric acid[11] strongly indicates that conversion of the phenyl-substituted radical to substitution and elimination products (oxidative processes) is easier than it is with the less substituted radical intermediates.

The apparent absence of any significant stabilization of one conformation of an intermediate 1-methyl-2-phenyl-1-propyl cation by neighboring phenyl participation causes one to consider seriously an alternative to an alkyl cation intermediate in the processes leading to alkyl acetate products. A ligand-transfer reaction, parallel to that in halodecarboxylation and involving transfer of AcO· to R·, is, at first thought, an attractive alternative. However, we presume that the stereochemical influences for Cl· and AcO· transfer from Pb(IV) species to R· will be quite similar. The reversed ratios of threo:erythro products for the RCl and ROAc mixtures strongly argues for different mechanisms in the two processes.

It is also conceivable that the alkyl acetates are formed by an SNi-type reaction from an alkyllead intermediate.

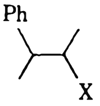
$$R\cdot + Pb(OAc)_4 \longrightarrow RPb(OAc)_4$$

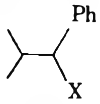


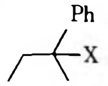
Again, however, there is no apparent reason for one stereochemical pathway (threo product) being preferred for alkyl chloride formation [ligand transfer from Pb(IV) to R·] and the other (erythro product) for alkyllead bond formation [between Pb(IV) and R·] in the intermediate. One would expect the SNi reaction, as illustrated above, to occur with retention of configuration at the carbon bound to lead.

Finally, the alkyllead intermediate, formed with the same stereochemical preference as is RCl in the ligand-transfer step and pictured above, may undergo SN2-type displacement by acetate. Although this process would be consistent with the stereochemical results in the present study, it cannot be a general pathway for the formation of alkyl acetates from those systems, such as norbornyl,[12,24] which yield rearranged products extensively or exclusively, and the composition of the hydrocarbon fraction of the

Table III
Summary of Substitution Products from the 1-Methyl-2-phenyl-1-propyl System


I-X


III-X


IV-X

Configuration of starting material	Reagent	X	Product distribution,[a] mol % Ie-X	It-X	III-X	IV-X	Ref
Ie-OTs	HOAc	OAc	94	5			27
Ie-OTs	HCOOH	OCHO	100	9			27
Ie-OH	$SOCl_2$	Cl	90				28
Ie-NH_2	HOAc, HONO	OAc	68	6	6	20	16a
Ie-COOH	$Pb(OAc)_4$, py	OAc	63	37			
Ie-COOH	$Pb(OAc)_4$, Cl^-	Cl	42	58			
It-OTs	HOAc	OAc	4	96			27
It-OTs	HCOOH	OCHO	0	100			27
It-OH	$SOCl_2$	Cl		95			28
It-NH_2	HOAc, HONO	OAc	19	25	32	24	16a
It-COOH	$Pb(OAc)_4$, py	OAc	63	37			
It-COOH	$Pb(OAc)_4$, Cl^-	Cl	42	58			

[a] Ie-X = erythro; It-X = threo.

Table IV
Summary of Elimination Products from the 1-Methyl-2-phenyl-1-propyl System

Configuration of starting material	Reagent	Temp, °C	Yield of olefin, %	Product distribution, mol % II-E[a]	II-Z[a]	V[b]	VI[c]	Ref
Ie-OTs[d,f]	HOAc	75	23	56	8	23	13	29
Ie-OBs[e]	HOAc	30	6	59	13	13	15	29
Ie-OTs	CH_3CN	82	50	45	22	12	21	29
Ie-OCS_2CH_3		180	91	5	50	38		26
Ie-OTs	$LiAlH_4$	25	22	22				30
Ie-$NO(CH_3)_2$	THF	25	g	0	95	5		31
Ie-COOH	$Pb(OAc)_4$, py	80	9	18	82			
It-OTs[d]	HOAc	75	35	42	28	24	6	29
It-OBs	HOAc	30	12	24	55	13	10	29
It-OTs	CH_3CN	82	67	34	34	9	23	29
It-OCS_2CH_3		180	76	36	12	38		26
It-OTs	$LiAlH_4$	25	21		21			30
It-$NO(CH_3)_2$	THF	25	80	95	0	5		31
It-COOH	$Pb(OAc)_4$, py	80	6	18	82			
IV-OAc[h]	HOAc	75	90	54	3	43		29
IIZ, IIE or V	HOTs	75	100	79	18	3		32

[a] II-Z = (*Z*)-2-phenyl-2-butene; II-E = (*E*)-2-phenyl-2-butene. [b] V = 2-phenyl-1-butene. [c] VI = 3-phenyl-1-butene. [d] I = 1-methyl-2-phenyl-1-propyl; Ie = erythro; It = threo. [e] OBs = *p*-bromobenzenesulfonate. [f] OTs = *p*-toluenesulfonate. [g] Yield of olefin was not determined. [h] IV-OAc = 1-methyl-1-phenyl-1-propyl acetate.

present product mixture appears to require cationic intermediates.

Experimental Section

The reagents used in all syntheses were reagent commercial chemicals; unless otherwise indicated, these chemicals were used as received. The solvents used were dried by storage over calcium hydride. Pyridine was stored over potassium hydroxide.

Infrared (ir) spectra of thin films on sodium chloride plates or of solid solutions in potassium bromide disks were obtained with a Perkin-Elmer Infracord Model 137 spectrometer. Proton nuclear magnetic resonance (nmr) spectra of carbon tetrachloride or chloroform-*d* solutions (10-20%) were obtained with a Varian Associates Model A-60A spectrometer or, with the assistance of D. Latour, with a Varian Associates Model HA100 spectrometer; tetramethylsilane (TMS) was used as internal reference. Gas chromatographic (gc) data were obtained with a Hewlett-Packard Model 700 instrument equipped with a hydrogen flame ionization detector and 0.125-in. aluminum columns.

Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. Spinning band distillations were performed on a 24-in. Nester/Faust Annular Teflon Spinning Band Distillation Column.

Synthesis of the 2-Methyl-3-phenylbutyric Acids. A. A 3:1 mixture of the diastereoisomeric ethyl 3-hydroxy-2-methyl-3-phenylbutyrates[33] was prepared[34] in 56% yield (68.6 g) from zinc, acetophenone (0.57 mol), and ethyl 2-bromopropionate (0.55 mol) in benzene (125 ml) solution: bp 109-111° (2.4 mm); nmr (CCl_4) major isomer δ 0.90 (m, 3, OCH_2CH_3), 1.27 (d, J = 7.0 Hz, 3, CH_3CH), 1.36 (s, 3, CH_3COH), 2.91 (q, J = 7.0 Hz, 1, $CHCH_3$), 3.25 (s b, 1, OH), 3.84 (q, J = 7.0 Hz, 2, OCH_2CH_3), 7.30 (m b, 5, C_6H_5); minor isomer δ 0.90 (m, 3, OCH_2CH_3), 1.20 (d, J = 7.0 Hz, 3, CH_3CH), 1.49 (s, 3, CH_3COH), 2.75 (q, J = 7.0 Hz, 1, $CHCH_3$), 4.16 (q, J = 7.0 Hz, 2, OCH_2CH_3), 7.30 (m b, 5, C_6H_5).

The mixture of hydroxy esters (0.31 mol) was dehydrated[33] with potassium hydrogen sulfate (0.32 mol) to **ethyl 2-methyl-3-phenyl-3-butenoate**[35] in 71% yield (44.5 g): bp 109-113° (2.2 mm); nmr (neat) δ 1.11 (t, J = 7.2 Hz, 3, CH_2CH_3), 1.36 (d, J = 7.0 Hz, 3, CH_3CHCO_2Et), 3.67 (q, J = 7.0 Hz, 1, $CHCO_2Et$), 4.08 (q, J = 7.2 Hz, 2, CH_2CH_3), 5.27 (b s, 1, cis HC=CPh), 5.37 (s, 1, trans HC=CPh), 7.33 (m, 5, C_6H_5).

The unsaturated ester (0.22 mol) was hydrogenated in ethanol solution over Pd/C in a Parr apparatus at an initial hydrogen pressure of 40 psig. After removal of solvent by distillation at reduced pressure, nmr analysis [relative intensities of δ 4.12 (OCH_2CH_3, erythro isomer) and 3.87 (OCH_2CH_3, threo isomer) absorptions] of the residue (43.7 g, 98% yield) showed it to be a mixture of **ethyl 2-methyl-3-phenylbutyrates**,[36] *ca.* 2:1 erythro: threo. Pure erythro isomer (gc analysis, 8-ft Carbowax column at 130°) was obtained as the higher boiling fraction from a reduced pressure, spinning-band distillation, bp 101-102° (3.0 mm).

The *erythro*-**2-methyl-3-phenylbutyric acid**[37] was obtained (67% yield after recrystallization from cyclohexane) by saponification of the distilled erythro ester: mp 130–131°; ir (KBr) 1672 $\mathrm{cm^{-1}}$ (s, C═O); nmr (CCl_4) δ 0.99 (d, J = 6.9 Hz, 3, $\mathbf{CH_3}CHCO_2H$), 1.34 (d, J = 6.6 Hz, 3, $\mathbf{CH_3}(CHPh)$, 2.56 (dq, $J_{2,3}$ = 10.0, $J_{2,\mathrm{Me}}$ = 6.9 Hz, 1, $\mathbf{CH}CO_2H$), 2.90 (dq, $J_{2,3}$ = 10.0, $J_{3,4}$ = 6.6 Hz, 1, $\mathbf{CH}Ph$), 7.20 (m, 5, C_6H_5), 12.2 (s, 1, $CO_2\mathbf{H}$).

Saponification of the lower boiling ester distillate led to a mixture of crystalline (erythro isomer) and oily acids. The oily material, ***threo*-2-methyl-3-phenylbutyric acid,**[38] was separated by filtration and was distilled: bp 109–110° (0.4 mm); ir (neat, film) 1710 $\mathrm{cm^{-1}}$ (s, C═O); nmr (CCl_4) δ 1.08 (d, J = 7.0 Hz, 3, $\mathbf{CH_3}CHCO_2H$), 1.22 (d, J = 7.0 Hz, 3, $\mathbf{CH_3}CHPh$), 2.64 (p, J = 7.0 Hz, 1, $CH_3\mathbf{CH}COOH$), 3.15 (p, J = 7.0 Hz, 1, $CH_3\mathbf{CH}Ph$), 7.12 (s, 5, C_6H_5), 10.9 (s, 1, $CO_2\mathbf{H}$).

B. When a 1:1.9 threo:erythro mixture of 2-chloro-3-phenylbutanes was converted through a Grignard reagent to the carboxylic acids, the two diastereomeric 2-methyl-3-phenylbutyric acids were isolated in a 1:1.9 threo:erythro ratio (combined yield, 41%).

2-Chloro-3-phenylbutanes. While the temperature of the mixture was kept below 30°, 3-phenyl-2-butanol (45.9 g, 0.31 mol, 1:1.8 threo:erythro mixture prepared by a Grignard synthesis from 2-phenylpropionaldehyde[39] was added slowly to thionyl chloride (40.1 g, 0.90 mol). This mixture was stirred for 2 hr at room temperature and for 1 hr at reflux temperature, concentrated by distillation, and poured over ice. The alkyl chloride was extracted into pentane, and the pentane solution was washed thoroughly, dried, and concentrated by rotary evaporation. Distillation of the residue gave 43 g (85%) of **2-chloro-3-phenylbutane,**[28] bp 69–69.5° (2 mm). Gc analysis of the distillate (8-ft Carbowax column at 140°) showed it to be a 1:1.9 threo:erythro mixture.[40] The diastereomers were satisfactorily separated by a spinning band distillation. For the lower boiling threo isomer, the nmr absorptions (CCl_4) were δ 0.99 (d, J = 6.6 Hz, 3, $\mathbf{CH_3}CPh$), 1.34 (d, J = 6.9 Hz, 3, $\mathbf{CH_3}CCl$), 2.56 (dq, $J_{2,3}$ = 10.0, $J_{1,2}$ = 6.9 Hz, 1, $\mathbf{CH}Cl$), 2.90 (dq, $J_{2,3}$ = 10.0, $J_{3,4}$ = 6.6 Hz, 1, $\mathbf{CH}Ph$), 7.20 (m, 5, C_6H_5). For the higher boiling erythro isomer, the nmr absorptions (CCl_4) were δ 1.33 (d, J = 6.8 Hz, 3, $\mathbf{CH_3}CCl$), 1.33 (d, J = 7.2 Hz, 3, $\mathbf{CH_3}CPh$), 3.02 (dq, $J_{2,3}$ = 5.2, $J_{3,4}$ = 7.2 Hz, 1, $\mathbf{CH}Ph$), 4.15 (dq, $J_{1,2}$ = 6.8, $J_{2,3}$ = 5.2 Hz, 1, $\mathbf{CH}Cl$), 7.13 (m, 5, C_6H_5).

Preparation of Isomeric Phenylbutenes. 2-Phenyl-2-butenes and 2-Phenyl-1-butene. An ether solution of 2-phenyl-2-butanol obtained by a Grignard synthesis from butanone (0.20 mol) was dehydrated with a warm mixture of sulfuric and acetic acids[41] to a mixture of alkenes from which **(*E*)-2-phenyl-2-butene**[26] (pure by gc) was isolated by repeated distillation: 12.6 g (48%); bp 90–93.5° (22 mm); nmr (CCl_4) δ 1.74 (dq, $J_{1,3}$ = 7.0, $J_{1,4}$ = 1.1 Hz, 3, $\mathbf{CH_3}CH$), 1.95 (m, 3, $\mathbf{CH_3}CPh$), 5.83 (qq, $J_{3,4}$ = 7.0, $J_{1,3}$ = 1.1 Hz, 1, C═CH), 7.25 (m, 5, C_6H_5).

The mixture of alkenes above was equilibrated with *p*-toluenesulfonic acid and distilled.[41] From the lower boiling fraction, **(*Z*)-2-phenyl-2-butene**[26] was obtained by a spinning-band distillation: bp 57–60° (10 mm); nmr (CCl_4) δ 1.56 (dq, $J_{1,3}$ = 6.9, $J_{1,4}$ = 1.5 Hz, 3, $\mathbf{CH_3}CH$), 1.99 (m, 3, $\mathbf{CH_3}CPh$), 5.51 (qq, $J_{1,3}$ = 6.9, $J_{3,4}$ = 1.5, 1, C═CH), 7.17 (m, 5, C_6H_5). In the higher boiling fraction, **2-phenyl-1-butene**[29] was identified [mixed with (*E*)-2-phenyl-2-butene] by gc and nmr data: nmr (CCl_4) δ 1.04 (t, J = 7.0 Hz, 3, $\mathbf{CH_3}CH_2$), 2.45 (m, 2, $CH_3\mathbf{CH_2}$), 5.01 (m, 1, trans **HC**═CPh), 5.24 (m, 1, cis **HC**═CPh), 7.3 (m, 5, C_6H_5).

3-Phenyl-1-butene[29] was prepared in 13% yield by a Wittig synthesis[42] from 2-phenylpropionaldehyde (0.11 mol): bp 29.1° (1.2 mm); $n^{24}\mathrm{D}$ 1.5108; nmr (CCl_4) δ 1.32 (d, J = 7.0 Hz, 3, $\mathbf{CH_3}CH$), 1.75 (m, 1, $CH_3\mathbf{CH}$), 4.87, m, cis **HC**═CR), 5.09 (m, 1, trans **HC**═CR), 5.99 (ddd, $J_{1,2\text{-}cis}$ = 9.3, $J_{1,2\text{-}trans}$ = 17.6, $J_{2,4}$ = 6.1 Hz, 1, C═CHR), 7.14 (s, 5, C_6H_5).

1-Phenyl-2-methyl-1-propene. An ether solution of 2-methyl-1-phenyl-1-propanol, prepared by a Grignard synthesis from benzaldehyde (0.14 mol), was dehydrated by a warm mixture of sulfuric and acetic acids.[41] The alkene[43] was obtained in 26% yield: bp 40–42° (1.8 mm); $n^{24}\mathrm{D}$ 1.5371; nmr (CCl_4) δ 1.80 (m, 6, CH_3), 6.40 (m, 1, C═CH), 7.14 (s, 5, C_6H_5).

Synthesis of Isomeric Acetates. A portion of (*E*)-2-phenyl-2-butene was converted by hydroboration[44] to threo alcohol, which was esterified with acetic anhydride and pyridine. Conventional work-up of the pyridine solution gave *threo*-1-methyl-2-phenyl-1-propyl acetate:[16a] bp 97.5–99.6° (3.7 mm); $n^{24}\mathrm{D}$ 1.4877; ir (neat, film) 1739 $\mathrm{cm^{-1}}$ (s, C═O); nmr (CCl_4) δ 1.10 (d, J = 6.0 Hz, 3, $\mathbf{CH_3}CHOAc$), 1.19 (d, J = 7.0 Hz, 1, $\mathbf{CH_3}CHPh$), 1.80 (s, 3, $\mathbf{CH_3}CO_2$), 2.92 (m, 1, $\mathbf{CH}Ph$), 5.05 (m, almost p with separation of 6 Hz, 1, $\mathbf{CH}OAc$), 7.17 (s, 5, C_6H_5).

In the same manner, (*Z*)-2-phenyl-2-butene was converted into ***erythro*-1-methyl-2-phenyl-1-propyl acetate:**[16a] bp 76–77° (1.5 mm); ir (neat, film) 1730 $\mathrm{cm^{-1}}$ (s, C═O); nmr (CCl_4) δ 0.95 (d, J = 6.3 Hz, 3, $\mathbf{CH_3}CHOAc$), 1.24 (d, J = 6.8 Hz, 3, $\mathbf{CH_3}CHPh$), 1.87 (s, 3, $\mathbf{CH_3}CO_2$), 2.80 (m, 1, $\mathbf{CH}Ph$), 4.97 (m, 1, $\mathbf{CH}OAc$), 7.17 (s, 5, C_6H_5).

1-Methyl-1-phenyl-1-propyl acetate was prepared by esterification of 2-phenyl-2-butanol with acetic anhydride and pyridine. The pure ester[16a] was isolated in 67% yield after chromatography of a pentane–ethyl ether (97:3, v/v) solution on a 35-cm alumina column: bp 61.0–61.4° (0.5 mm); ir (neat, film) 1710 $\mathrm{cm^{-1}}$ (s, C═O); nmr (CCl_4) δ 0.72 (t, J = 7.0 Hz, 3, $\mathbf{CH_3}CH_2$), 1.76 (s, 3, $\mathbf{CH_3}CPh$), 1.94 (s, 3, $\mathbf{CH_3}CO_2$), 2.0 (m, 2, $CH_3\mathbf{CH_2}$), 7.21 (s, 5, C_6H_5).

Esterification of 2-methyl-1-phenyl-1-propanol with acetic anhydride and pyridine gave **2-methyl-1-phenyl-1-propyl acetate:**[16a] bp 68–73° (0.8 mm); $n^{24}\mathrm{n}$ 1.4890; ir (neat, film) 1742 (s, C═O), 1385 and 1370 $\mathrm{cm^{-1}}$ (s, isopropyl); nmr (CCl_4) δ 0.77 (d, J = 6.6 Hz, 3, $\mathbf{CH_3}CHCH_3$), 0.93 (d, J = 6.6 Hz, 3, $CH_3CH\mathbf{CH_3}$), 1.93 (s, 3, $\mathbf{CH_3}CO_2$), 2.02 (m, 1, $Me_2\mathbf{CH}$), 5.47 (d, J = 7.5 Hz, 1, $\mathbf{CH}Ph$), 7.22 (s, 5, C_6H_5).

A sample of 2-benzyl-2-propanol, prepared by a Grignard synthesis from benzyl chloride and acetone, was partly esterified by acetic anhydride and pyridine. Pure ester (1-benzyl-1-methylethyl acetate)[43] was isolated by chromatography of a pentane–ethyl ether (90:10, v/v) solution through a 40-cm silica gel column: $n^{23.5}\mathrm{D}$ 1.4911; ir (neat, film) 1730 (s, C═O), 1380 and 1365 $\mathrm{cm^{-1}}$ (s, Me_2C); nmr (CCl_4) δ 1.40 [s, 6, $(\mathbf{CH_3})_2C$], 1.88 (s, 3, $\mathbf{CH_3}CO_2$), 3.03 (s, 2, $\mathbf{CH_2}Ph$), 7.17 (s, 5, C_6H_5).

Decarboxylation Procedures. A. Oxidative Decarboxylation.[12] To an ice-cooled, stirred solution of benzene, pyridine, carboxylic acid, and *tert*-butylbenzene (internal standard for gc analysis) (typical quantities, 10 ml, 3.5, 3.0, and 0.5 mmol, respectively), lead tetraacetate (typical, 4.0 mmol) was added all at once. The reaction flask was then placed in a preheated oil bath, and the mixture was refluxed until completeness of reaction was indicated by formation of a white precipitate in a yellow solution. The cooled mixture was filtered, the precipitate was washed with benzene, and the combined benzene solution was washed sequentially with dilute perchloric acid–sodium chloride solution and with saturated aqueous solutions of sodium chloride, sodium bicarbonate, and sodium chloride. The benzene solution was dried and analyzed by gc methods; internal standards were used for quantitative determination of the product distributions, which are summarized in Table I. Unconsumed carboxylic acid was recovered from the bicarbonate wash solution by acidification with 3 *M* hydrochloric acid.

B. Halodecarboxylation.[20] Lithium chloride was added to a solution of benzene (10 ml), carboxylic acid, lead tetraacetate, and *tert*-butylbenzene (gc internal standard). (See Table II for exact quantities.) The mixture was refluxed for 3–4 hr, cooled, and filtered to remove the white precipitate. The benzene solution was treated and analyzed as described for oxidative decarboxylation. The product distributions are summarized in Table II.

Product Stability Experiments. A benzene solution of a mixture of diastereomeric 1-methyl-2-phenyl-1-propyl acetates was washed, dried, and analyzed as described above for the oxidative decarboxylation product mixture. There was no change in composition of the mixture.

In separate experiments, *erythro*- and *threo*-1-methyl-2-phenyl-1-propyl acetates, 1-methyl-1-phenyl-1-propyl acetate, 2-methyl-1-phenyl-1-propyl acetate, and 2-methyl-1-phenyl-1-propene were substituted for carboxylic acid in the oxidative decarboxylation, and each was unchanged by the procedure.

Registry No. Ethyl 3-hydroxy-2-methyl-3-phenylbutyrate isomer A, 17226-97-0; ethyl 3-hydroxy-2-methyl-3-phenylbutyrate isomer B, 17226-96-9; acetophenone, 98-86-2; ethyl 2-bromopropionate, 535-11-5; ethyl 2-methyl-3-phenyl-3-butenoate, 25289-62-7; ethyl *erythro*-2-methyl-3-phenylbutyrate, 42879-13-0; ethyl *threo*-2-methyl-3-phenylbutyrate, 42879-14-1; *erythro*-2-methyl-3-phenylbutyric acid, 42971-03-9; *threo*-2-methyl-3-phenylbutyric acid, 42879-15-2; *threo*-3-phenyl-2-butanol, 1502-80-3; *erythro*-3-phenyl-2-butanol, 1502-79-0; *threo*-2-chloro-3-phenylbutane, 5706-90-1; *erythro*-2-chloro-3-phenylbutane, 5706-91-2; 2-phenyl-2-butanol, 1565-75-9; (*E*)-2-phenyl-2-butene, 768-00-3; (*Z*)-2-phenyl-2-butene, 767-99-7; 2-phenyl-1-butene, 2039-93-2; 3-phenyl-1-butene, 934-10-1; 2-phenylpropionaldehyde, 93-53-8; 1-phenyl-2-methyl-1-propene, 768-49-0; 2-methyl-1-phenyl-1-propanol, 611-69-8; *threo*-1-methyl-2-phenyl-1-propyl acetate, 42879-20-9; *erythro*-1-methyl-2-phenyl-1-propyl acetate, 42879-21-0; 1-methyl-1-phenyl-1-propyl acetate, 10042-36-1; 2-methyl-1-phenyl-1-propyl acetate, 5706-87-6; 2-benzyl-2-propanol, 100-86-7; 1-benzyl-1-methylethyl acetate, 151-05-3.

References and Notes

(1) (a) Based on the Ph.D. Dissertation of Sister Alice Theine, Louisiana State University (Baton Rouge), Dec 1972. Grateful acknowledgment is made to the Dr. Charles E. Coates Memorial Fund of the LSU Foundation donated by George H. Coates for financial aid toward the preparation of that dissertation. (b) Presented in part at the Southwest Regional Meeting of the American Chemical Society, Baton Rouge, La., Dec 7, 1972, Paper ORGN 213. (c) Participant in National Science Foundation Summer Institutes for College Teachers of Chemistry, Louisiana State University (Baton Rouge), 1968–1970.

(2) C. J. Lancelot, D. J. Cram, and P. v. R. Schleyer in "Carbonium Ions," Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1972.

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$$\mathrm{R}\cdot + (\mathrm{RCO_2})_4\mathrm{Pb^{IV}X} \longrightarrow \mathrm{RX} + \mathrm{Pb^{III}(O_2CR)_4}\quad \textbf{(ligand transfer)}$$

$$\mathrm{X}\cdot + (\mathrm{RCO_2})_4\mathrm{Pb^{IV}X} \longrightarrow \mathrm{X_2} + \mathrm{Pb^{III}(O_2CR)_4}$$

$$\mathrm{Pb^{III}(O_2CR)_4} \longrightarrow \mathrm{R}\cdot + \mathrm{CO_2} + \mathrm{Pb^{II}}$$

$$\mathrm{R}\cdot + \mathrm{X_2} \longrightarrow \mathrm{RX} + \mathrm{X}\cdot$$

(22) Oxidative decarboxylation[11] involves initial formation of a radical.

$$\mathrm{Pb^{IV}(O_2CR)_4} \longrightarrow \mathrm{Pb^{III}(O_2CR)_3} + \mathrm{R}\cdot + \mathrm{CO_2}$$

The propagation steps which follow are

$$\mathrm{Pb^{III}} \longrightarrow \mathrm{Pb^{II}} + \mathrm{R}\cdot + \mathrm{CO_2}$$

$$\mathrm{R}\cdot + \mathrm{Pb^{IV}} \longrightarrow \underset{\substack{\downarrow\\ \textbf{alkene, ester}}}{\mathrm{R}^{+}} + \mathrm{Pb^{III}}\quad \textbf{(electron transfer)}$$

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Halomethyl Metal Compounds. LXVI. Preparation of *C*-Tetrachloroaziridines by Reaction of Carbonimidoyl Dichlorides with Phenyl(bromodichloromethyl)mercury. Fragmentation of Azo- and Azoxyarenes upon Reaction with Phenyl(bromodichloromethyl)mercury[1,2]

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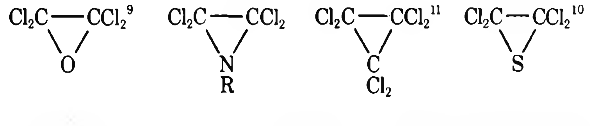
Phenyl(bromodichloromethyl)mercury has been found to transfer CCl_2 to alkyl- and arylcarbonimidoyl dichlorides to give 1-alkyl- and 1-aryl-2,2,3,3-tetrachloroaziridines in fair yield. These C-tetrachloroaziridines are much more stable thermally than monochloro- or *gem*-dichloroaziridines but do rearrange to give the $RN{=}C(Cl)CCl_3$ compound (R = Ph and c-C_6H_{11}, but not *i*-C_3H_7) when heated at 180° for 3 hr. Similar CCl_2 addition to the C=N bond of $PhN{=}C(Cl)Ph$ was observed. Azoarenes reacted with $PhHgCCl_2Br$ with cleavage of the N=N bond; giving $ArN{=}CCl_2$ when an excess of the azoarene is used and a 1-aryl-2,2,3,3-tetrachloroaziridine when an excess of the mercurial is used. Azoxyarenes react similarly after an initial deoxygenation by CCl_2 to give the azoarene.

The addition of a dihalocarbene to the C=N bond of imines of type $ArN{=}CHAr'$ to give 1,2-diaryl-3,3-dihaloaziridines was reported first by Fields and Sandri in 1959,[4] and this reaction was utilized subsequently by others.[5] In these reactions, the dihalocarbene was generated by the haloform-base or the hexachloroacetone-base procedures. However, all of our earlier attempts[2,6] to add dichlorocarbene to the N=C bond of imines of types $PhCH{=}NPh$,[2,6] $PhCH{=}NCH_3$,[6] and $Me_2C{=}NPh$[2] using $PhHgCCl_2Br$[7] as the potential CCl_2 source were unsuccessful. In all cases, tarry reaction products rather than the expected aziridines were obtained. Other workers have recorded a similar lack of success in the attempted reaction of $PhHgCBr_3$ with $Me_3CCH{=}NCMe_3$.[5c] In more recent studies, we have found that a reaction of $PhCH{=}NPh$ with a twofold excess of phenyl(bromodichloromethyl)mercury for 18 hr at 50° did indeed give the expected 1,2-diphenyl-3,3-dichloroaziridine, but only in low yield. Again, the major reaction which occurred in this system was one which produced much tar.

Tar formation of the type encountered in these $PhHgCCl_2Br$-imine reactions is characteristic of the reactions of such mercurials with tertiary amines.[8] It thus may be that in the case of these imines, as with trialkylamines, the main reaction involves initial attack by the nucleophilic nitrogen center at the electrophilic mercury atom of the $PhHgCX_3$ compound, with subsequent reactions producing the observed tarry products. Dihalocarbene extrusion from $PhHgCX_2Br$ (X = Cl and Br) would appear to be too slow to be competitive with this rapid nucleophilic substitution reaction.

In order to achieve successful CX_2 addition to the C=N bond of an imine *via* a phenyl(trihalomethyl)mercury reagent, one must, on the basis of the above considerations, decrease the nucleophilicity of the nitrogen atom.

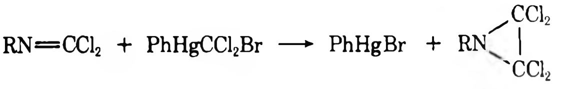
The carbonimidoyl dihalides (or isonitrile dihalides), $RN{=}CX_2$, are such a class of imines in which the nitrogen atom of the C=N bond should be decidedly less nucleophilic as a result of the electron-withdrawing effect of the two halogen substituents on the carbon atom of the C=N bond. This decrease in the availability of the lone electron pair on nitrogen might be sufficient to allow successful CX_2 extrusion from $PhHgCX_2Br$ and subsequent CX_2 addition to the C=N bond. Should such addition be successful, a new and interesting class of compounds, the *C*-tetrachloroaziridines, would be in hand, to add to the *C*-perhalo series of three-membered rings. The *C*-perchloro analogs are the following.



Accordingly, we have investigated reactions of *N*-alkyl- and *N*-arylcarbonimidoyl dichlorides, which are readily prepared from aryl isothiocyanates or *N*-arylformamides, with phenyl(bromodichloromethyl)mercury.

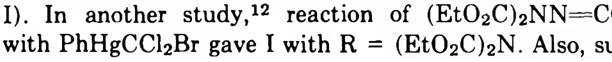
Results and Discussion

We have found that the carbonimidoyl dichlorides as a class react readily with phenyl(bromodichloromethyl)mercury in benzene at 70-80° as shown in eq 1. The isolated


(1)

I

yields of the 2,2,3,3-tetrachloroaziridines obtained ranged from about 30 to 55%, and glc yields tended to be higher. Prepared in this manner were compounds of type I with R = Ph, *p*-MeC_6H_4, *p*-ClC_6H_4, c-C_6H_{11}, and *i*-C_3H_7 (Table I). In another study,[12] reaction of $(EtO_2C)_2NN{=}CCl_2$ with $PhHgCCl_2Br$ gave I with R = $(EtO_2C)_2N$. Also, such dihalocarbene addition has been effected using $PhHgCCl_2F$ as CClF source (eq 2).[13]

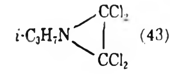
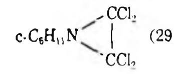
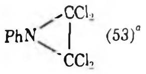
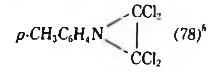
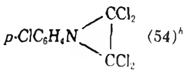

(2)

74%

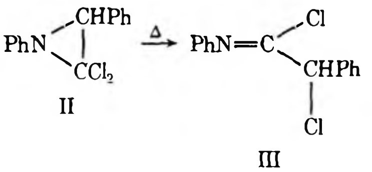
It thus appears that the chlorine substitution on carbon does indeed reduce the nucleophilicity of the nitrogen atom in $RN{=}CCl_2$ compounds to an extent sufficient to allow the CX_2 chemistry of phenyl(trihalomethyl)mercurials to come into play.

Compounds of type I are very stable and survive both distillation and glc at temperatures around 150°. They are significantly more stable than monochloroaziridines, which must be stored at 0° to prevent their decomposition,[14] and dichloroaziridines, *e.g.*, II, whose thermal rearrangement (eq 3) can be accomplished by heating its toluene solution at reflux for a few hours.[15,16] In the case of compounds of type I, the *N*-isopropyl derivative was recovered unchanged after it had been heated for 6 hr at 180°. The *N*-phenyl and *N*-cyclohexyl derivatives, on the

Table I
Reactions of Carbonimidoyl Dichlorides with Phenyl(bromodichloromethyl)mercury

RN=CCl$_2$ (mmol)	Registry no.	PhHgCCl$_2$Br, mmol	C$_6$H$_6$, ml	Reaction conditions	Product (% yield)	Registry no.	PhHgBr, %
i-C$_3$H$_7$N=CCl$_2$ (50)	29119-58-2	50	80	3 hr, 80°		25252-60-2	80
c-C$_6$H$_{11}$N=CCl$_2$ (30)	2666-80-0	30	70	12 hr, 60°		25252-59-9	84
PhN=CCl$_2$ (40)	622-44-6	30	70	12 hr, 60°		25252-58-8	84
p-CH$_3$C$_6$H$_4$N=CCl$_2$ (16)	16001-28-8	10	15	3 hr, 80°		42880-62-6	90
p-ClC$_6$H$_4$N=CCl$_2$ (12)	2771-67-7	10	20	3 hr, 80°		42880-63-7	99

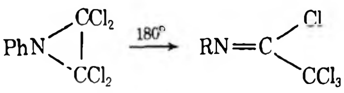
[a] Isolated (by distillation) yield. [b] Glc yield.


(3)

II

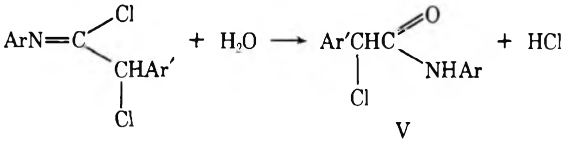
III

other hand, underwent such rearrangement when they were heated at 180° for 3 hr (eq 4).


(4)

IV

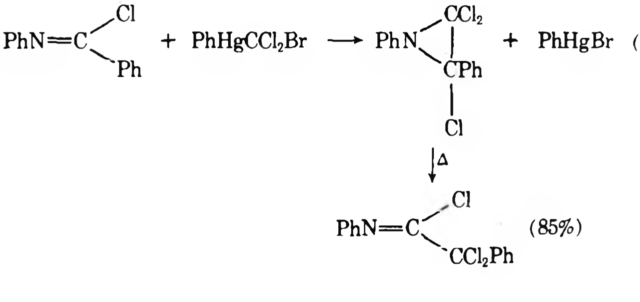
Compounds of type III are known to hydrolyze as shown in eq 5, and thus the hydrolysis product IV (R = Ph), tri-


(5)

V

chloroacetanilide, CCl$_3$C(O)NHPh, obtained in 95% yield, provided good confirmation of the structure of IV. The thermal rearrangement-hydrolysis sequence of 1,2-diaryl-3,3-dichloroaziridines (II) to give anilides (V) may be accomplished simply by heating them in boiling water for 30 min, but as a result of their greater thermal stability, C-tetrachloroaziridines are not affected when heated in 2 *N* hydrochloric acid for 12 hr at 100°.

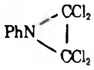
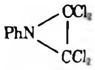
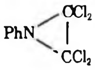
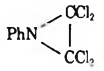
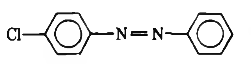
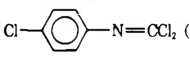
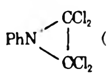
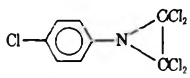
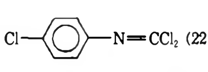
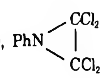
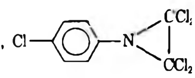
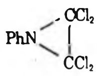
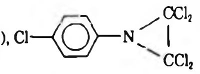
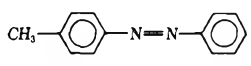
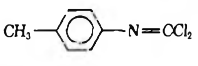
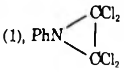
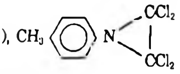
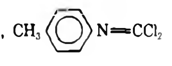
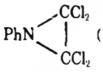
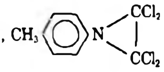
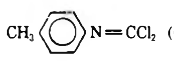
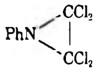
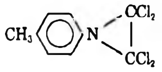
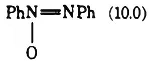
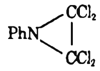
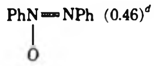
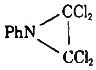
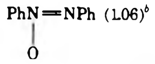
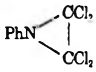
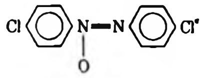
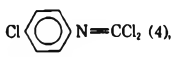
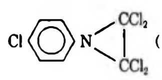
This study was extended to an investigation of possible CCl$_2$ addition to compounds of type PhN=C(Cl)R (R = Ph, CCl$_3$). Phenylbenzimidoyl chloride did react with phenyl(bromodichloromethyl)mercury to give the expected aziridine, as shown by infrared spectroscopic examination of the reaction mixture, but attempted isolation of the aziridine by distillation resulted in its partial rearrangement (eq 6). On the other hand, PhN=C(Cl)CCl$_3$ did not react with phenyl(bromodichloromethyl)mercury, even under forcing conditions. Presumably, this lack of reactivity is a consequence of the steric bulk of the trichloromethyl substituent on carbon.


(6)

More complicated reactions of other organonitrogen compounds with phenyl(trihalomethyl)mercurials have been found to give *C*-tetrachloroaziridines, in all cases *via* intermediate carbonimidoyl dichlorides. We have reported previously[17] that phenyl isocyanate reacts with PhHgCCl$_2$Br to give 1-phenyl-2,2,3,3-tetrachloroaziridine in low yield. The reaction of carbodiimides with this mercurial was found to result in formation of RN=CCl$_2$ compounds,[17] and, given sufficient starting mercurial, these could be converted *in situ* to the *C*-tetrachloroaziridine. Gibson, *et al.*,[18] reported the reaction of phenyl(trichloromethyl)mercury with phenyl azide in 1,2-dimethoxyethane at 80°, which gives first phenylcarbonimidoyl dichloride and then 1-phenyl-2,2,3,3-tetrachloroaziridine. Their rate studies indicated that dichlorocarbene was an intermediate in both steps. Other classes of compounds which react with phenyl(bromodichloromethyl)mercury to give first ArN=CCl$_2$ and then 1-aryl-2,2,3,3-tetrachloroaziridines are, as we have found, the azoarenes and azoxyarenes.

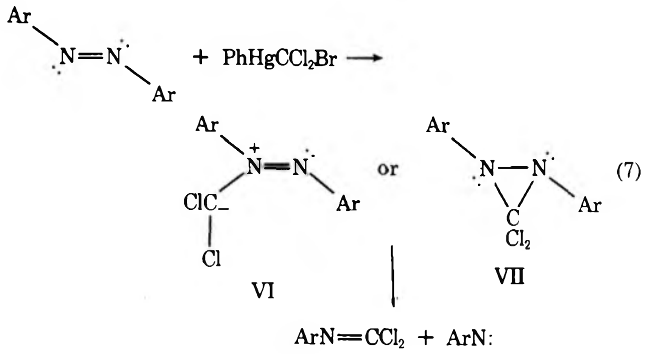
Depending on the reactant stoichiometry, the major product of the azoarene-PhHgCCl$_2$Br reactions is either the arylcarbonimidoyl dichloride (azoarene in excess) or the *C*-tetrachloroaziridine (mercurial in excess). Such reactions, however, do not proceed without complications, and product yields did not exceed 40-50% and often were lower (Table II). Information concerning these reactions was sought by allowing PhHgCCl$_2$Br to react with two unsymmetrically substituted azoarenes. In the case of 4-chloroazobenzene there appeared to be no significant difference in the effect of the substituted and the unsubstituted benzene rings, as far as product yields indicated (Table II). With 4-methylazobenzene, products containing the unsubstituted phenyl group appeared to be favored. However, in view of the poor product yields and material balances in these experiments, we hesitate to read any great significance into these results. These systems, unfortunately, do not appear to be amenable to mechanistic

Table II
Reactions of Azo- and Azoxybenzenes with Phenyl(bromodichloromethyl)mercury

Azoarene (mmol)	Registry no.	$PhHgCCl_2Br$, mmol	Products (% yield)
PhN=NPh (2.00)[a]	103-33-3	10.00	 (12)
PhN=NPh (0.48)[b]		4.50	 (28)
PhN=NPh (0.46)[c]		4.50	 (28)
PhN=NPh (10.0)[a]		5.0	$PhN{=}CCl_2$ (12),  (2)
 (5.0)[a]	4340-77-6	5.0	$PhN{=}CCl_2$ (19),  (19),  (9),  (5)
(5.0)[a]		2.3	$PhN{=}CCl_2$ (25),  (22),  (6),  (0)
(0.46)[c]		4.5	 (11),  (9)
 (5.0)[e]	949-87-1	5.0	$PhN{=}CCl_2$ (4),  (1),  (1.3),  (0)
(5.0)[a]		2.3	$PhN{=}CCl_2$ (11),  (1),  (1.2),  (0)
(2.3)[a]		5.0	$PhN{=}CCl_2$ (1),  (0),  (8),  (4)
 $\mathrm{Ph}\underset{\mathrm{O}}{\underset{\vert}{\mathrm{N}}}{=}\mathrm{NPh}$ (10.0)	495-48-7	10.0	$PhN{=}CCl_2$ (3),  (12), PhN=NPh (6)
 $\mathrm{Ph}\underset{\mathrm{O}}{\underset{\vert}{\mathrm{N}}}{=}\mathrm{NPh}$ (0.46)[d]		4.50	 (34)
 $\mathrm{Ph}\underset{\mathrm{O}}{\underset{\vert}{\mathrm{N}}}{=}\mathrm{NPh}$ (1.06)[b]		5.00	 (35)
 (3.0)	614-26-6	11.0	 (4),  (15)

[a] In 10 ml of benzene at 80° for 3 hr. [b] In 3 ml of benzene at 80° for 3 hr; mercurial added in portions. [c] In 3 ml of benzene at room temperature for 9 days. [d] In 10 ml of benzene at room temperature for 15 days. [e] In 10 ml of benzene at 50° for 12 hr.

study. The formation of the initial product, the carbonimidoyl dichloride, may be pictured as occurring *via* an open (VI) or a cyclic (VII) intermediate, which then decomposes to give the observed $ArN{=}CCl_2$ and an arylnitrene.



(7)

The latter, in principle, could react with $PhHgCCl_2Br$ or with CCl_2 derived from it to give more $ArN{=}CCl_2$.[19] However, further speculation is not justified in view of the limited information available.

The reaction of phenyl(bromodichloromethyl)mercury with *1* molar equiv of azoxybenzene in benzene solution at 80° for 3 hr gave three products: azobenzene, 6% yield; phenylcarbonimidoyl dichloride, 3% yield; and 1-phenyl-2,2,3,3-tetrachloroaziridine, 12% yield. The use of an excess of the mercurial in such a reaction increased the yield of the aziridine to 35%, and in such reactions no $PhN{=}CCl_2$ was obtained. A similar reaction occurred with 4,4′-dichloroazoxybenzene. The course of these reactions is the same as those of azobenzene after an initial deoxygenation of the azoxyarene by $PhHgCCl_2Br$ to give the corresponding azoarene. Such an initial step is made plausible by a report[21] that $PhHgCCl_3$-derived dichlorocarbene can deoxygenate pyridine *N*-oxide. In view of the generally poor product yields in these reactions of phenyl(bromodichloromethyl)mercury with azo- and azoxyarenes, further investigation of their scope and mechanism was not worthwhile.

Experimental Section

General Comments. All reactions were carried out under an atmosphere of dry nitrogen using flame-dried glassware. Carefully dried solvents were used in all reactions. Nmr spectra were recorded using a Varian A60 or T60 spectrometer. Chemical shifts are given in δ units, parts per million downfield from internal tetramethylsilane. Unless otherwise specified, the solvent used was carbon tetrachloride. Infrared spectra were recorded using Perkin-Elmer 337, 257, or 457A infrared spectrophotometers. Gas-liquid chromatography (glc) was used for yield determinations and for collection of liquid samples. Commercial stainless steel columns were employed with an F & M (Hewlett-Packard) Model 700, 720, or 5754 gas chromatograph. Yields were determined using the internal standard procedure. The standard apparatus used in these reactions of phenyl(bromodichloromethyl)mercury consisted of a three-necked flask of appropriate size equipped with a reflux condenser (topped with a gas inlet tube), a thermometer, and a magnetic stirring assembly. Phenyl(bromodichloromethyl)mercury was prepared as described in a previous paper of this series.[22] The progress of the reactions involving this mercurial was followed using thin layer chromatography.[11]

Preparation of Organonitrogen Starting Materials. The carbonimidoyl dichlorides used in this study are all known compounds and were prepared by standard literature procedures.[23] Isopropyl- and cyclohexylcarbonimidoyl dichlorides, in particular, have been characterized in a previous paper of this series.[11] Phenylbenzimidoyl chloride was prepared using the method of von Braun and Pinkernelle.[24]

The reaction of nitrosobenzene with the respective 4-substituted aniline in glacial acetic acid was used to prepare 4-methyl- and 4-chloroazobenzene. Both are known compounds.[25,26]

Reactions of Phenyl(bromodichloromethyl)mercury with Carbonimidoyl Dichlorides. The reaction of phenylcarbonimidoyl dichloride with $PhHgCCl_2Br$ is described in detail. The other reactions are summarized in Table I. Table III presents physical and spectroscopic properties for the *C*-tetrachloroaziridines prepared.

A solution of 13.2 g (30 mmol) of the mercurial and 7.0 g (40 mmol) of $PhN{=}CCl_2$ in 70 ml of dry benzene was prepared in the standard apparatus under nitrogen and was stirred and heated at 60° for 12 hr. The reaction mixture was filtered to remove 9.0 g (84%) of crude phenylmercuric bromide, mp 265–268°. The filtrate was concentrated at 50° (rotary evaporator) to leave a red-brown, liquid residue. Distillation of the latter gave, after initial fractions containing benzene and $PhN{=}CCl_2$, 4.1 g (53% yield, based on the mercurial) of 1-phenyl-2,2,3,3-tetrachloroaziridine, bp 70–72° (0.02 mm), as a colorless liquid which crystallized on standing to give large crystals, mp 38–40°.

In some other reactions, *e.g.*, that of $PhHgCCl_2Br$ with *p*-tolylcarbonimidoyl dichloride, the reaction mixture was heated at 80° for 3 hr. The yield of 1-*p*-tolyl-2,2,3,3-tetrachloroaziridine was determined by glc (4 ft × 0.25 in. 10% UC W-98 silicone column at 140°) and analytical and spectroscopic samples also were isolated by glc.

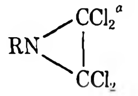
Reaction of Phenyl(bromodichloromethyl)mercury with Phenylbenzimidoyl Chloride. The imidoyl chloride (2.16 g, 10.0 mmol), $PhHgCCl_2Br$ (5.00 g, 11.2 mmol), and 10 ml of benzene were stirred and heated at 80° for 3 hr. The reaction mixture was filtered from 3.60 g (98%) of PhHgBr, mp 265–267°. Evaporation of the solvent *in vacuo* gave an oily residue (2.56 g, 86%). The ir spectrum of the residue showed the presence of the expected 1,3-diphenyl-2,2,3-trichloroaziridine by strong bands at 1370 and 835 cm^{-1}. Attempted purification of the product by distillation at 120° (0.01 mm) resulted in partial rearrangement of the initial product to the imidoyl chloride as indicated by a new ir band at 1670 cm^{-1}.

When the crude product (1.0 g, 3.36 mmol) was distilled at 160° (1.0 mm), pure rearranged product, $PhN{=}C(CCl_2Ph)Cl$, was obtained in 85% yield (0.85 g): $n^{25}{}_{D}$ 1.6088; ir (neat) 3060 m, 3030 w, 1940 w, 1880 w, 1670 s, 1590 s, 1520 w, 1480 s, 1443 s, 1380 w, 1310 w, 1280 w, 1210 m, 1180 m, 1070 w, 1050 s, 1025 w, 1000 w, 870 m, 830 w, 800 s, 755 s, 710 s, 690 s, 660 w, 600 cm^{-1} w, nmr (CCl_4) δ 7.30 ppm (m, aromatic protons).

Anal. Calcd for $C_{14}H_{10}NCl_3$: C, 56.31; H, 3.38; N, 4.69; Cl, 35.62. Found: C, 56.09; H, 3.43; N, 4.71; Cl, 35.06.

Reaction of $PhHgCCl_2Br$ with Phenyltrichloroacetimidoyl Chloride. The imidoyl chloride (2.56 g, 10.0 mmol), $PhHgCCl_2Br$ (8.80 g, 20.0 mmol), and 20 ml of benzene were stirred and heated at 80° for 4 hr. The reaction mixture was filtered from 7.0 g (97%) of PhHgBr, mp 250–256°. The solvent was evaporated with a rotary evaporator. The high-boiling residue (2.49 g) showed an identical ir spectrum with that of the starting material. No ir band at 1370 cm^{-1}, a characteristic band for the aziridine ring, was observed. Glc (4 ft × 0.25 in., 10% UC W-98, 130–180°) and tlc showed no sign of the expected aziridine product.

Table III
***C*-Tetrachloroaziridines**[c]



R	Bp, °C (mm)	Mp, °C	$n^{25}{}_{D}$
i-C_3H_7	60–62 (6.0)		1.4810
c-C_6H_{11}	61–62 (0.02)	47–50[b]	1.5130
C_6H_5	70–72 (0.02)	38–40[b]	1.5740
p-$CH_3C_6H_4$			1.5698
p-ClC_6H_4			1.5870

[a] The ir and nmr spectra of these compounds were in agreement with the presence of the groups on nitrogen indicated. [b] The oily product crystallized upon prolonged standing. [c] Satisfactory analytical data were reported for all compounds listed in the table.

Another experiment was carried out in the absence of solvent. The mercurial (2.20 g, 5.0 mmol) was dropped into preheated (100°) phenyltrichloroacetimidoyl chloride (2.53 g, 10.0 mmol) by portions. After the reaction mixture was heated at 100° for 2 hr, it was worked up as in the previous experiment. The imidoyl chloride was recovered quantitatively.

Reaction of Phenyl(bromodichloromethyl)mercury with *N*-Benzylideneaniline. The mercurial (9.0 g, 20 mmol) and $PhN{=}CHPh$ (1.80 g, 10 mmol) in 15 ml of carbon tetrachloride were stirred and heated at 50° under nitrogen for 18 hr. The resulting red-brown solution was filtered from crude (brown) phenylmercuric bromide (6.40 g, 90%, mp 257–265°). The nmr spectrum of the filtrate showed a singlet at 3.58 ppm and the ir spectrum showed bands at 1400 and 760 cm^{-1}, which indicated the presence of the expected 1,2-diphenyl-3,3-dichloroaziridine. An authentic sample of the latter had been prepared by reaction of *N*-benzylideneaniline with 50% aqueous $NaOH$-$CHCl_3$ in the presence of a catalytic amount of benzyltriethylammonium chloride, and it was found to have identical spectroscopic properties.

Attempted isolation of the aziridine product from the reaction mixture by distillation (to 130° at 0.35 mm) gave only a trace amount of this product (identified by its nmr spectrum) and left a tarry residue.

Thermal Rearrangement of the *C*-Tetrachloroaziridines. 1-Phenyl-2,2,3,3-tetrachloroaziridine (3.7 g, 14 mmol) was sealed under nitrogen in a heavy-walled tube and heated for 3.5 hr at 180°. The tube contents quickly turned dark brown. The disappearance of the aziridine is indicated by the disappearance of a strong, broad absorption in the ir spectrum characteristic of these aziridines and by the appearance of a new, strong band at around 1680 cm^{-1} (ν C=N). The oily reaction mixture was distilled at reduced pressure to give 2.6 g (76%) of phenyltrichloroacetimidoyl chloride [$PhN{=}C(Cl)CCl_3$], bp 69–70° (0.02 mm), $n^{25}{}_{D}$ 1.5773, as a colorless oil which crystallized after prolonged standing to give a solid with mp 35–37°.

Anal. Calcd for $C_8H_5NCl_4$: C, 37.39; H, 1.96; N, 5.46; Cl, 55.19. Found: C, 37.72; H, 2.15; N, 5.52; Cl, 54.86.

Ir (neat liquid) 3105 w, 3095 w, 3080 m, 3040 m, 3030 w, 1965 w, 1945 w, 1870 w, 1790 w, 1740 w, 1690 s (broad), 1670 s, 1600 s, 1585 s, 1495 s, 1455 s, 1360 w, 1290 w, 1260 w, 1235 sh, 1215 s, 1175 m, 1160 w, 1105 w, 1080 s, 1060 s, 1030 m, 1005 m, 910 m, 880 s, 810 s, 780 s, 770 s, 730 s, 710 s, 640 cm^{-1} m.

Similar treatment of 6.7 mmol of 1-cyclohexyl-2,2,3,3-tetrachloroaziridine gave cyclohexyltrichloroacetimidoyl chloride c-$C_6H_{11}N{=}C(Cl)CCl_3$ (75%), bp 64–65° (0.02 mm), $n^{25}{}_{D}$ 1.5137.

Anal. Calcd for $C_8H_{11}NCl_4$: C, 36.52; H, 4.22; Cl, 53.94. Found: C, 36.93; H, 4.15; Cl, 53.77.

In the ir spectrum (liquid film) strong bands at 1690, 1685, and 1670 cm^{-1} were present.

Similar heating of 1-isopropyl-2,2,3,3-tetrachloroaziridine failed to cause any change.

An 0.8-g (31 mmol) sample of $PhN{=}C(Cl)CCl_3$ and 5 ml of 2 *N*

HCl were charged into a 25-ml round-bottomed flask equipped with a reflux condenser and a magnetic stirring unit. The mixture was stirred and heated at 100° for 2 hr. The bottom organic layer crystallized after the two-phase mixture had cooled to give 0.7 g (95%) of trichloroacetanilide, mp 93–94° after two recrystallizations from ethanol (lit.[27] mp 94–95°).

1-Phenyl-2,2,3,3-tetrachloroaziridine was not hydrolyzed under these conditions and was recovered unchanged.

Reactions of Phenyl(bromodichloromethyl)mercury with Azobenzene and Azoxybenzene. A 50-ml flask equipped with a thermometer, magnetic stir bar, and a condenser topped with a nitrogen inlet tube was charged with the azobenzene or azoxybenzene and the mercurial. The reaction was carried out either at room temperature in benzene solution or in refluxing benzene solution. The resulting reaction mixture was dark red-brown in color. The crude PhHgBr, obtained as a brown solid in 80–90% yield, decomposed at 230° to give a black tar. The filtrate was directly analyzed with an MIT isothermal unit or was trap-to-trap distilled at 0.02 mm (pot temperature to 100°). The distillate was examined by glc (F & M Model 700 gas chromatograph using a 4 ft × 0.25 in. column, 10% UC W-98 at 130–150°, *n*-hexadecane as internal standard). Products were isolated by glc and identified by the comparison of their ir spectrum and glc retention time with those of the authentic samples synthesized independently. The results are summarized in Table II.

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Registry No. Phenyl(bromodichloromethyl)mercury, 3294-58-4; phenylbenzimidoyl chloride, 4903-36-0; 1,3-diphenyl-2,2,3-trichloroaziridine, 42880-67-1; diphenyldichloroacetimidoyl chloride, 42880-68-2; phenyltrichloroacetimidoyl chloride, 25252-86-2; *N*-benzylideneaniline, 538-51-2; 1,2-diphenyl-3,3-dichloroaziridine, 3543-98-4; cyclohexyltrichloroacetimidoyl chloride, 25252-87-3.

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Aziridines. 27. The Synthesis and Reactions of 4-Aroyltetrahydro-2*H*-1,2,4-oxadiazines

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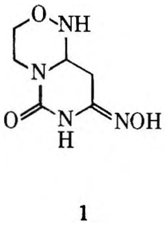
2-Aryl- or 2-alkyl-4-aroyltetrahydro-2*H*-1,2,4-oxadiazines have been prepared by heating 1-aroylaziridines and nitrones in toluene or *m*-xylene. In hot acetic acid 2-(*p*-tolyl)-3-phenyl-4-(3,5-dinitrobenzoyl)tetrahydro-2*H*-1,2,4-oxadiazine (**6**) is converted into a mixture of *p*-azotoluene, *p*-azoxytoluene, benzaldehyde and *N*-(β-hydroxyethyl)-3,5-dinitrobenzamide. **6** reacts with *p*-nitrotoluene in concentrated sulfuric acid to give 2-methyl-5-nitro-4′-aminodiphenylmethane, *N*-(β-hydroxyethyl)-3,5-dinitrobenzamide, and benzaldehyde. In hot basic solution 2-(*p*-tolyl)-3-phenyl-4-(*p*-nitrobenzoyl)tetrahydro-2*H*-1,2,4-oxadiazine (**5**) isomerizes into *N*-(*p*-tolyl)-β-(*p*-nitrobenzamido)ethylbenzimidate (**17**). Reduction of **6** leads to *N*-benzyl-*p*-toluidine and thermolysis of **6** at 200° causes vigorous decomposition and formation of *N*-benzal-*p*-toluidine.

Only a limited number of saturated 1,2,4-oxadiazines are known. Those that have been reported include the dihydrocytosine derivative **1**[1] and the 1,2,4-oxadiazinium salts **2**. The salts **2** were prepared by treating aziridinium perchlorates with cyclic nitrones.[2,3] In view of this reaction and the known ring-opening reactions of 1-carbethoxy- and 1-aroylaziridines by dipolar species such as enamines,[4] phosphonium and arsonium ylides,[5,6] and dimethyl sulfoxide,[7] it seemed likely that nitrones would interact with 1-aroylaziridines to produce 4-aroyltetrahydro-2*H*-1,2,4-oxadiazines (**3**). The purpose of this paper is to describe the synthesis of **3** and to delineate the reactions of **3** with glacial acetic acid, sulfuric acid, reducing reagents, and potassium hydroxide in dimethylformamide (DMF).



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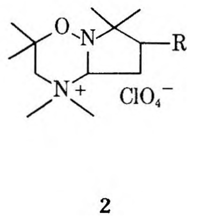

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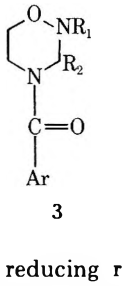

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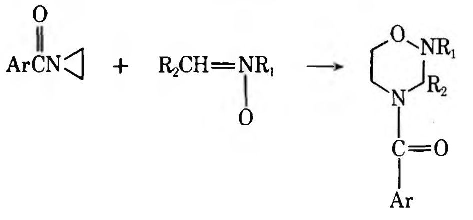
Results and Discussion

4-Aroyltetrahydro-2*H*-1,2,4-oxadiazines (3) were usually obtained when a mixture of a nitrone and an 1-aroylaziridine was refluxed in toluene or *m*-xylene (Scheme I, Table I).

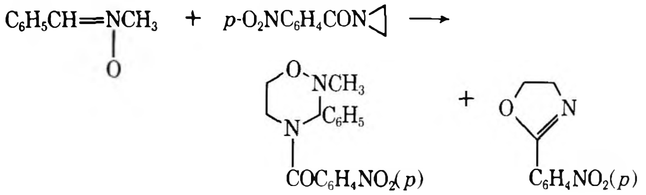
Scheme I



3

In a few instances heating a mixture of a nitrone and an 1-aroylaziridine produced little or no **3**. In these cases, an isomer of the 1-aroylaziridine, namely an 2-aryl-2-oxazoline, was formed. For example, heating α-phenyl-*N*-methylnitrone with 1-(3,4-dichlorobenzoyl)aziridine or with 1-(*p*-nitrobenzoyl)aziridine gave 2-(3,4-dichlorophenyl)-2-oxazoline (45%) and 2-(*p*-nitrophenyl)-2-oxazoline (80%), respectively. In the former case no 1,2,4-oxadiazine was isolated and in the latter case only 7% of 2-methyl-3-phenyl-4-(*p*-nitrobenzoyl)-tetrahydro-2*H*-1,2,4-oxadiazine (13) was obtained (Scheme II). In sharp contrast, the same nitrone reacted with 1-(3,5-dinitrobenzoyl)-aziridine to give only 2-methyl-3-phenyl-4-(3,5-dinitrobenzoyl)tetrahydro-2*H*-1,2,4-oxadiazine (7) in 73% yield.

Scheme II



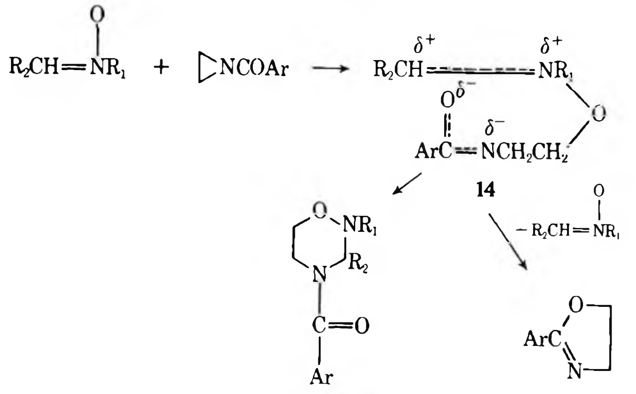
13

The mass spectra of the 4-aroyltetrahydro-2*H*-1,2,4-oxadiazines (3) were consistent with the structural assignments. Thus, the mass spectrum of 2,3-diphenyl-4-(*p*-nitrobenzoyl)tetrahydro-2*H*-1,2,4-oxadiazine (4) exhibited peaks at *m*/*e* 389 (molecular ion, $C_{22}H_{19}N_3O_4$), 359 ($M^+ - H_2CO$), 181 ($C_6H_5N{=}CHC_6H_5$), 180 ($C_6H_5N{\equiv}CC_6H_5$), and 150 ($O_2NC_6H_4CO$). Corresponding fragments were obtained for compounds **7** and **10**.

The nmr spectra of **3** usually showed the methylene groups as a broad multiplet extending (in the case of **4**) from δ 3.2 to 4.4. The proton at C-3 appeared in the aromatic region for all of the 1,2,4-oxadiazines substituted with aryl groups in the 2 and 3 positions of the ring. For those 1,2,4-oxadiazines substituted with a methyl group at position 2 the C-3 proton appeared further upfield.

A mechanism that could account for both the formation of the 1,2,4-oxadiazines and the 2-aryl-2-oxazolines involves a nucleophilic attack of the nitrone oxygen on the aziridinyl carbon to form the dipolar intermediate **14** which then could either ring close to **3** or expel nitrone to give the isomeric 2-oxazoline (Scheme III). That the isomerization of 1-aroylaziridines into 2-aryl-2-oxazolines is catalyzed by a nitrone is not to be entirely unexpected. Dipolar species such as triphenylphosphonium phenacylides have been observed to catalyze this reaction[6] and it is well documented that nucleophiles such as iodide ion, thiocyanate ion, and tertiary amines are effective catalysts for this isomerization.

Scheme III

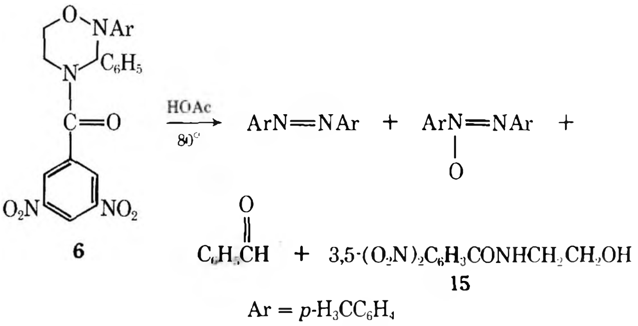


3

The factors determining whether intermediate **14** forms an 1,2,4-oxadiazine or displaces a nitrone to give an 2-oxazoline are subtle. 1,2,4-Oxadiazine formation involves bonding between the positive and negative centers of **14** while 2-oxazoline formation involves a nucleophilic displacement at a saturated carbon atom. The latter reaction would depend in part on the nucleophilicity of the ambident benzamido group of **14** and in part on the ability of the incipient nitrone moiety incorporated in **14** to act as a leaving group. More nitrone character would be imparted to **14** if R_1 were methyl rather than aryl since the methyl group can more effectively reduce the positive charge on the adjacent carbon atom than an aryl group. This would favor nitrone displacement from **14**. Such seems to be the case when α-phenyl-*N*-methylnitrone reacted with 1-(3,4-dichlorobenzoyl)- and 1-(*p*-nitrobenzoyl)aziridines. That this same nitrone reacted with 1-(3,5-dinitrobenzoyl)aziridine to give the 1,2,4-oxadiazine **7** in high yield rather than 2-oxazoline may be attributed to the low nucleophilicity of the negatively charged 3,5-dinitrobenzamido group of **14**.

Reactions of 4-Aroyltetrahydro-2*H*-1,2,4-oxadiazines. When 2-(*p*-tolyl)-3-phenyl-4-(3,5-dinitrobenzoyl)tetrahydro-2*H*-1,2,4-oxadiazine (6) was placed in glacial acetic acid and the solution was warmed to 80°, a mixture of *p*-azotoluene (50%), *p*-azoxytoluene (33%), *N*-(β-hydroxyethyl)-3,5-dinitrobenzamide (**15**, 60%), and benzaldehyde (57%) was produced (Scheme IV).

Scheme IV

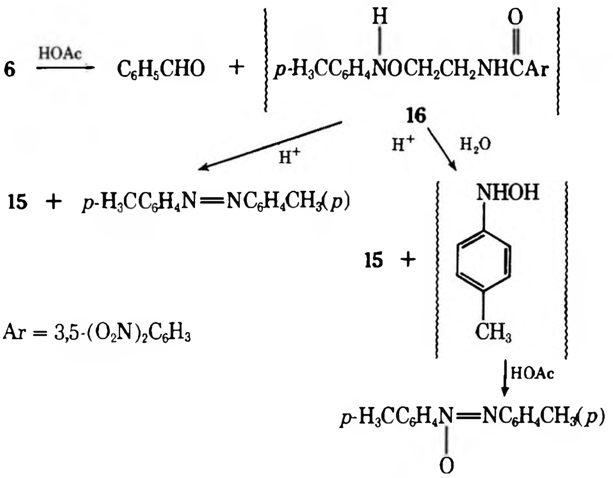


Ar = p-$H_3CC_6H_4$

Under similar conditions compound **10** formed *p*-azotoluene (37%), *p*-azoxytoluene (4%), *N*-(β-hydroxyethyl)-3,4-dichlorobenzamide (71%), and benzaldehyde (33%).

These products may arise from an acid-catalyzed hydrolysis of **6** to benzaldehyde and intermediate **16** (Scheme V). Hydrolysis of **16** would yield **15** and *N*-(*p*-tolyl)hydroxylamine, which under the reaction conditions employed would be converted into *p*-azoxytoluene (Scheme V). A control run of *N*-(*p*-tolyl)hydroxylamine in glacial acetic acid at 80° gave *p*-azoxytoluene in 95% yield. The autoxidation of phenylhydroxylamines to azoxy-

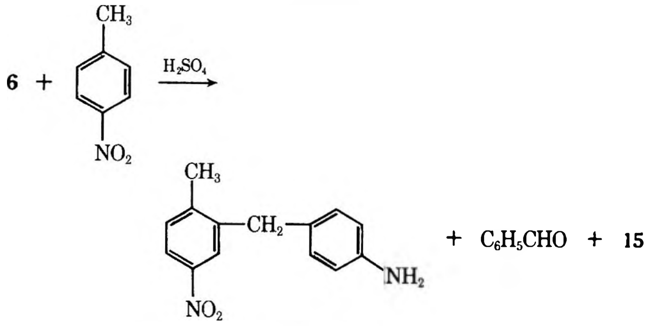
Scheme V



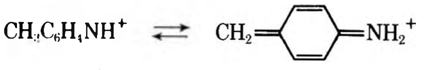
benzenes was observed over 70 years ago by Bamberger[8] and recently the kinetics of this transformation were studied.[9] The *p*-azotoluene (and some of **15**) may also arise from intermediate **16**. Thus, we have observed that when *O*-methyl-*N*-(2,4-dinitrophenyl)hydroxylamine was refluxed in glacial acetic acid, 2,2′,4,4′-tetranitroazobenzene was formed in 35% yield. Similarly, *O*,*N*-di(5-methyl-2,4-dinitrophenyl)hydroxylamine, when heated in acetic anhydride, gave 5,5′-dimethyl-2,2′,4,4′-tetranitroazobenzene.[10] Control runs in glacial acetic acid at 80° have established that *p*-azotoluene is not converted into *p*-azoxytoluene nor is *p*-azoxytoluene converted into *p*-azobenzene under these conditions.

Dissolution of oxadiazines **5**, **6**, and **10** (Table I) in concentrated sulfuric acid at room temperature gave benzaldehyde (isolated as its 2,4-dinitrophenylhydrazone) in high yield. Oxadiazine **11**, similarly treated, gave *p*-chlorobenzaldehyde. No other products were isolable under these reaction conditons. However, when *p*-nitrotoluene was dissolved with an oxadiazine such as **6** in concentrated sulfuric acid, the products 2-methyl-5-nitro-4′-aminodiphenylmethane, *N*-(*β*-hydroxylethyl)-3,5-dinitrobenzamide (**15**), and benzaldehyde were obtained in 83, 53, and 37% yields, respectively (Scheme VI). Similarly, a mixture of *p*-nitrotoluene and 2-(*p*-tolyl)-3-phenyl-4-(3,4-dichlorobenzoyl)tetrahydro-2*H*-1,2,4-oxadiazine (**10**) in concentrated sulfuric acid gave 2-methyl-5-nitro-4′-aminodiphenylmethane, *N*-(*β*-hydroxyethyl)-3,4-dichlorobenzamide, and benzaldehyde in 73, 20, and 80% yields, respectively. When a mixture of **6** and *p*-nitroanisole was added to concentrated sulfuric acid, 2-methoxy-5-nitro-4′-aminodiphenylmethane (82%) was obtained.

Scheme VI



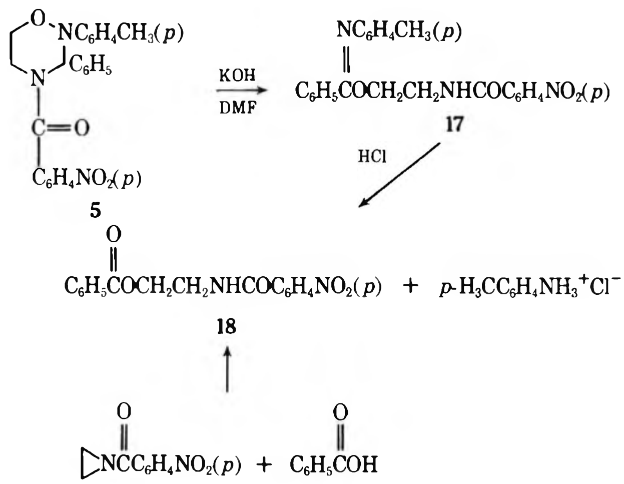
The reaction of **6** with *p*-nitrotoluene in sulfuric acid could also arise by acid hydrolysis of **6** to benzaldehyde, *N*-(*p*-tolyl)hydroxylamine, and **15**. The *N*-(*p*-tolyl)hydroxylamine, as previously shown by Bamberger,[11] then interacts with *p*-nitrotoluene in the presence of concentrated sulfuric acid to give 2-methyl-5-nitro-4′-aminodiphenylmethane. Presumably the *N*-(*p*-tolyl)hydroxylamine reacts with the concentrated sulfuric acid to give an electron-deficient nitrogen species such as the tautomeric nitrenium ion



which then condenses with the *p*-nitrotoluene. It is even likely that intermediate **16** (Scheme V) in concentrated sulfuric acid forms **15** and the nitrenium ion $H_3CC_6H_4NH^+$ directly. Bamberger had also reported that *p*-tolylazide with *p*-nitrotoluene in sulfuric acid gave 2-methyl-5-nitro-4′-aminodiphenylmethane,[12] probably through the intermediacy of the same nitrenium ion.

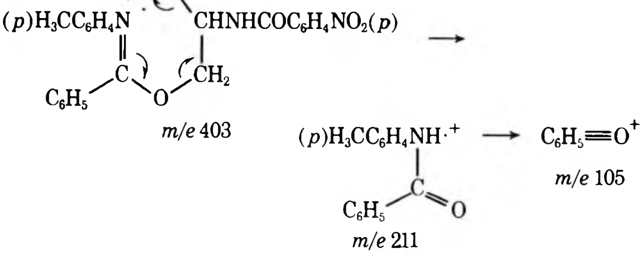
Treatment of **5** with potassium hydroxide in dimethylformamide gave the benzimidate **17** in 81% yield (Scheme VII). Evidence for the structure of **17** was obtained by hydrolyzing it in dilute hydrochloric acid. The products were *p*-toluidine hydrochloride and *β*-(*p*-nitrobenzamido)ethyl benzoate (**18**, 83%, Scheme VII). The latter compound was also prepared by refluxing benzoic acid and 1-(*p*-nitrobenzoyl)aziridine in chloroform. The reaction of carboxylic acids with 1-acylaziridines is a known synthetic method for the preparation of compounds akin to **18**.[13]

Scheme VII



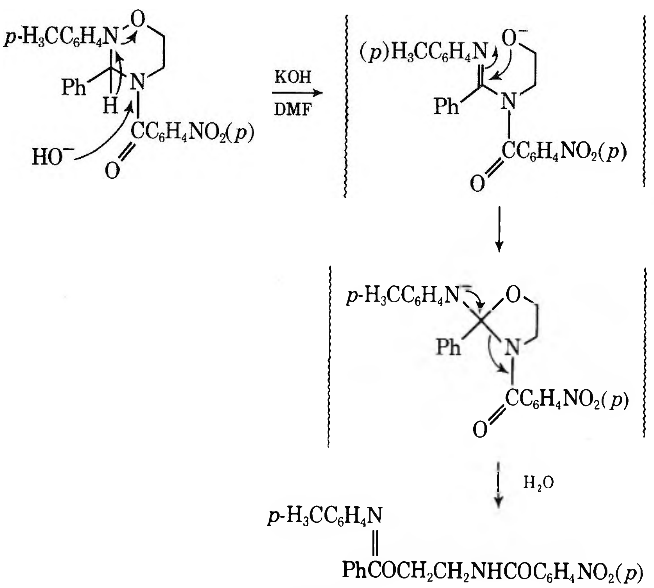
Corroborative evidence for the structure of **17** was obtained from its mass spectrum. The primary fragmentation pathway is a rearrangement of the molecular ion (*m/e* 403) with charge localization on nitrogen, giving *m/e* 211, which in turn cleaves to give a benzoyl ion at *m/e* 105 (Scheme VIII).

Scheme VIII



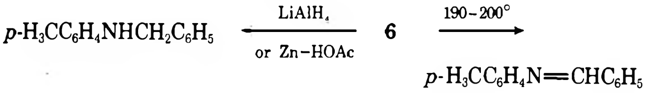
A plausible mechanism for the rearrangement of **5** to **17** is shown in Scheme IX.

Scheme IX



Reduction of the 1,2,4-oxadiazine derivative **6** with either lithium aluminum hydride or zinc–acetic acid produced *N*-benzyl-*p*-toluidine (Scheme X). **6** or **10** decomposed vigorously at 190–200° to give tar and *N*-benzal-*p*-toluidine.

Scheme X



$$p\text{-H}_3\text{CC}_6\text{H}_4\text{NHCH}_2\text{C}_6\text{H}_5 \xleftarrow[\text{or Zn-HOAc}]{\text{LiAlH}_4} \mathbf{6} \xrightarrow{190-200^\circ} p\text{-H}_3\text{CC}_6\text{H}_4\text{N}{=}\text{CHC}_6\text{H}_5$$

Experimental Section

Materials. 1-*p*-(Nitrobenzoyl)aziridine,[14] 1-(3,5-dinitrobenzoyl)-aziridine,[14] and 3,4-dichlorobenzoylaziridine[15] were prepared as described previously. The nitrones were prepared by reaction of N-substituted hydroxylamines with aldehydes according to literature procedures[16,17] and were known compounds.

4-Aroyltetrahydro-2*H*-1,2,4-oxadiazines (4-13). Equimolar quantities (1-10 mmol) of nitrone and 1-aroylaziridine were added to either dry toluene or *m*-xylene in the ratio of 10 ml of solvent for every millimole of 1-aroylazidine employed. Toluene was the solvent of choice for the preparation of compounds **4-7** and **10-12** and *m*-xylene for compounds **8**, **9**, and **13**. The reaction mixture was refluxed for the specified time (Table I) and then the solvent was evaporated. On occasion, unreacted starting material precipitated from the cool reaction mixture and it was filtered prior to the evaporation of the solvent. The residue was triturated with ether except in the cases of **8** and **13**, which were triturated with methanol and 95% ethanol, respectively. The crude 1,2,4-oxadiazine was filtered. Compounds **4**, **5**, **8**, **9**, and **13** were recrystallized from 95% ethanol; compounds **6** and **12** were recrystallized from acetonitrile; compounds **7** and **10** were recrystallized from butanone.

Reactions of 2-(*p*-Tolyl)-3-phenyl-4-(3,5-dinitrobenzoyl)tetrahydro-2*H*-1,2,4-oxadiazine (6) in Acetic Acid. A mixture of 1.006 g (2.24 mmol) of **6**, 15 ml of glacial acetic acid, and 4 drops of water was stirred at 80° for 2 hr. The dark red reaction mixture was poured onto 10 g of ice with vigorous stirring. A yellow solid precipitated (0.182 g) and was filtered. The filtrate was saved. An infrared spectrum of the solid revealed that it was a mixture of *p*-azotoluene and *p*-azoxytoluene. An analysis of the nmr spectrum showed that the mixture was 58% *p*-azotoluene and 42% *p*-azoxytoluene, which corresponds to an overall yield of 50% *p*-azotoluene and 33% *p*-azoxytoluene. A mixture composed of 58% authentic *p*-azotoluene and 42% *p*-azoxytoluene gave a nmr spectrum virtually identical with that of the crude product. Three recrystallizations of the crude product gave *p*-azotoluene, mp 139–144°.

The filtrate was extracted with three 25-ml portions of petroleum ether (bp 30–60°) to remove any benzaldehyde that formed. The aqueous layer was evaporated and the residue was extracted with 30 ml of hot water. Evaporation of the water gave 340 mg (60%) of crude *N*-(β-hydroxyethyl)-3,5-dinitrobenzamide (**15**) which was identified by comparison of its ir spectrum with that of an authentic sample.[18] Four recrystallizations from water gave **15**, mp 139-145° (lit. mp 146°).

In another run, 1.007 g of **6** in 15 ml of acetic acid was heated at 80° for 6 hr. The mixture was poured on ice and the precipitate (azotoluene and *p*-azoxytoluene) was filtered. To the filtrate was added an excess of a solution of 2,4-dinitrophenylhydrazine. The precipitate of benzaldehyde 2,4-dinitrophenylhydrazone was filtered and weighed 363 mg (57%). It was identified by melting point and infrared spectroscopy.

Reaction of 6 with *p*-Nitrotoluene in Concentrated Sulfuric Acid. In a 10-ml erlenmeyer flask equipped with a magnetic stirring bar were added 500 mg (3.8 mmol) of *p*-nitrotoluene and 510 mg (1.14 mmol) of **6**. The flask was immersed in an ice bath and 5 ml of concentrated H_2SO_4 was added with stirring. After 11 hr at room temperature, the mixture was poured onto 10 g of ice. The yellow precipitate that formed was filtered and the filtrate was saved. The solid was washed with three 15-ml portions of boiling petroleum ether (bp 30–60°) to remove unreacted *p*-nitrotoluene. The yellow residue was triturated with 20 ml of a 5% solution of sodium carbonate solution (foaming occurred) and then filtered. The crude 2-methyl-5-nitro-4′-aminodiphenylmethane weighed 230 mg (83%) and after several recrystallizations from aqueous ethanol melted at 120–122° (lit.[13,19] mp 117–118°). The ir spectrum of the product was identical with that of an authentic sample.[19]

The initial filtrate that was saved was extracted with four 20-ml portions of petroleum ether (bp 60–100°). To the petroleum ether extract was added an excess of a 1% ethanolic 2,4-dinitrophenylhydrazine solution. The benzaldehyde 2,4-dinitrophenylhydrazone that precipitated was filtered and weighed 106 mg (37%). The aqueous layer from the petroleum ether extraction was neutralized with 3 *M* NaOH and extracted with four 25-ml portions of $CHCl_3$. Evaporation of the chloroform gave 152 mg (53%) of crude *N*-(β-hydroxyethyl)-3,5-dinitrobenzamide (**15**) which melted after one recrystallization from water at 138–141° (lit.[18] mp 146°). The infrared spectrum of **15** was identical with that of an authentic sample.[18]

Table I[a]
4-Aroyltetrahydro-2*H*-1,2,4-oxadiazines Prepared by Reaction of 1-Aroylaziridines with Nitrones

	ArCONCH(R_2)N(R_1)OCH$_2$CH$_2$							
Compd	Ar	Aziridine registry no.	R_2	R_1	Nitrone registry no.	Crude yield, %	Mp, °C	Reaction time, hr
4	p-$O_2NC_6H_4$	19614–29–0	C_6H_5	C_6H_5	1137–96–8	51	147–150	65
5	p-$O_2NC_6H_4$		C_6H_5	p-$H_3CC_6H_4$	19064–77–8	88	157–160	16
6	3,5-$(O_2N)_2C_6H_3$	42790–32–9	C_6H_5	p-$H_3CC_6H_4$		99	190–191	3
7	3,5-$(O_2N)_2C_6H_3$		C_6H_5	CH_3	3376–23–6	73	133–134	0.33
8	3,5-$(O_2N)_2C_6H_3$		CH_3	C_6H_{11}	3376–30–5	27	123–125	0.05
9	p-$O_2NC_6H_4$		C_6H_5	$(H_3C)_3C$	3376–24–7	44	186–188	9
10	3,4-$(Cl)_2C_6H_3$	15257–82–6	C_6H_5	p-$H_3CC_6H_4$		78	135–138	22
11	3,5-$(O_2N)_2C_6H_3$		p-ClC_6H_4	p-$H_3CC_6H_4$	37056–74–9	84	218–221	0.75
12	3,5-$(O_2N)_2C_6H_3$		C_6H_5	p-$H_5C_2C_6H_4$	42790–35–2	66	182–183	1.5
13	p-$O_2NC_6H_4$		C_6H_5	CH_3		6.6	106–109	4.5

[a] Satisfactory analytical data for C, H, and N were reported for all new compounds listed in the table.

Reaction of 10 with *p*-Nitrotoluene in Concentrated Sulfuric Acid. Using the same procedure described above for 6, a mixture of 450 mg (1.02 mmol) of 10 and 500 mg (3.8 mmol) of *p*-nitrotoluene and 5 ml of concentrated H_2SO_4 gave 2-methyl-5-nitro-4′-aminodiphenylmethane (73%) and benzaldehyde (80%). The aqueous layer obtained after extracting the benzaldehyde with petroleum ether was extracted with ether instead of chloroform to give 46 mg (20%) of *N*-(β-hydroxyethyl)-3,4-dichlorobenzamide, mp 146–149°. The infrared spectrum was identical with that of an authentic sample of *N*-(β-hydroxyethyl)-3,4-dichlorobenzamide obtained by hydrolyzing 1-(3,4-dichlorobenzoyl)aziridine.

Reaction of 6 with *p*-Nitroanisole in Concentrated Sulfuric Acid. A mixture of 6 (300 mg, 0.67 mmol) and *p*-nitroanisole (300 mg, 0.78 mmol) was treated in sulfuric acid by the procedure described above for 6 and *p*-nitrotoluene. After stirring for 3 hr at room temperature, the reaction mixture was poured onto 5 g of ice and filtered. The filter cake was triturated with three 20-ml portions of a 1:1 solution of petroleum ether (bp 30–60°) and ether to remove the unreacted *p*-nitroanisole and the resulting suspension was filtered. The crude product was treated with 20 ml of 5% Na_2CO_3 and filtered to give 142 mg (82%) of 2-methoxy-5-nitro-4′-aminodiphenylmethane. The product was recrystallized from 95% ethanol, mp 146–148°.

Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.00; H, 5.58; N, 10,83.

No attempts were made to isolate any other products from this reaction.

2,2′,4,4′-Tetranitroazobenzene. A mixture of 600 mg (2.82 mmol) of *O*-methyl-*N*-(2,4-dinitrophenyl)hydroxylamine[20] and 15 ml of glacial acetic acid was refluxed for 20 hr. The reaction mixture was poured on ice and the crude 2,2′,4,4′-tetranitroazobenzene (177 mg, 35%) was filtered. Identification was made by comparison of its ir spectrum with that of an authentic sample.[21]

Conversion of 5 to 17. To a mixture of 100 mg (0.247 mmol) of 5 and 1.5 ml of dry DMF was added 15 mg of powdered KOH. After stirring for 2.5 hr, water was added to the reaction mixture until the final volume was 10 ml. Acetonitrile (3 ml) was added and the oily precipitate was triturated. The crude 17 (81 mg, 81%) was filtered and recrystallized from aqueous ethanol, mp 125–127°, molecular ion *m/e* 403.

Anal. Calcd for $C_{23}H_{21}N_3O_4$: C, 68.48; H, 5.25; N, 10.42. Found: C, 68.64; H, 5.27; N, 10.32.

Hydrolysis of 17 to 18 and *p*-Toluidine Hydrochloride. A mixture of 100 mg (0.427 mmol) of 17 and 5 ml of 6 *N* hydrochloric acid was heated to 90° for 5 min. The crude 18 was filtered from the hot reaction mixture and the filtrate was saved. The crude 18 (65 mg, 83%) melted after recrystallization from aqueous ethanol at 143–145° (lit.[22] mp 145–146°). An infrared spectrum of 18 was identical with that of an authentic sample. The filtrate was evaporated and the *p*-toluidine hydrochloride was identified by infrared spectroscopy.

Reduction of 6 by $LiAlH_4$. A mixture of 50 mg (1.32 mmol) of $LiAlH_4$ and 20 ml of dry tetrahydrofuran was refluxed for 15 min. To this mixture was added over a period of 20 min a solution of 1.00 g (2.28 mmol) of 6 in 30 ml of tetrahydrofuran. Refluxing was continued for 18 hr and then 15 ml of commercial anhydrous ether was added slowly followed by dropwise addition of 15 ml of ethyl acetate to destroy any unreacted $LiAlH_4$. The reaction mixture was filtered and the filtrate was evaporated to give 215 mg (47%) of crude *N*-benzyl-*p*-toluidine.

Reduction of 6 by Zinc and Glacial Acetic Acid. To a stirred solution of 452 mg (1.03 mmol) of 6 in 10 ml of dry tetrahydrofuran and 12.5 ml of glacial acetic acid was added in portions over a 5-min period 5.0 g of zinc dust. The mixture was stirred for 4.5 days and filtered. The filtrate was diluted with 25 ml of water and extracted with six 15-ml portions of C_6H_6. Evaporation of the benzene gave 64 mg (31%) of *N*-benzyl-*p*-toluidine.

Pyrolysis of 6. Formation of *N*-Benzal-*p*-toluidine. In a vacuum sublimator was placed 300 mg (0.685 mmol) of 6 and the pressure was lowered to not less than 10 mm. The sublimator chamber containing the sample was immersed in an oil bath held at 200°. Compound 6 melted and bubbled vigorously. After 5 min the oil bath was removed, the wall of the sublimator was rinsed with ether, and the washings were saved. The residual black tar in the reaction chamber was extracted with ether and the ether solutions were pooled and evaporated. The *N*-benzal-*p*-toluidine weighed 43 mg (32%) and was identified by comparison of its infrared spectrum with that of an authentic sample.

Isomerization of 1-(*p*-Nitrobenzoyl)aziridine to 2-(*p*-Nitrophenyl)-2-oxazoline. A mixture of 384 mg (2.04 mmol) of 1-(*p*-nitrobenzoyl)aziridine and 40 mg (0.29 mmol) of α-phenyl-*N*-methylnitrone and 20 ml of *m*-xylene was refluxed for 4.5 hr. The solvent was evaporated and the residual oil was triturated with a small quantity of ether. Filtration gave 306 mg (80%) of crude 2-(*p*-nitrophenyl)-2-oxazoline which melted after recrystallization from 95% ethanol at 176–182° (lit.[14] mp 180–181°).

In another run 384 mg (2.00 mmol) of 1-(*p*-nitrobenzoyl)aziridine and 270 mg (2.00 mmol) of α-phenyl-*N*-methylnitrone gave a lower yield of oxazoline (29%) probably because of the difficulty of separating the oxazoline from the excess nitrone. It was possible in this experiment to isolate 6.6% of the oxadiazine 13 from the filtrate that was obtained after isolating the 2-*p*-nitrophenyl-2-oxazoline.

Acknowledgment. We thank Professor Charles C. Sweeley for obtaining and interpreting several mass spectra. We also wish to thank Mr. Peter B. M. W. M. Timmermans and Mr. Arnold P. Uyttewaal for a preliminary investigation on the reactions of 1,2,4-oxadiazines in sulfuric acid and Mr. David Bellezza for his contributions to the experimental work. The investigation was supported by PHS Grant CA 10015 from the National Cancer Institute.

Registry No. 4, 50259-95-5; 5, 50259-96-6; 6, 50546-29-7; 7, 50259-97-7; 8, 50259-98-8; 9, 50259-99-9; 10, 50260-00-9; 11, 50260-01-0; 12, 50431-02-2; 13, 50260-02-1; 17, 42790-37-4; *N*-(β-hydroxyethyl)-3,4-dichlorobenzamide, 28298-26-2; 2-methoxy-5-nitro-4′-aminodiphenylmethane, 42790-36-3; *p*-nitrotoluene, 99-99-0; *p*-nitroanisole, 100-17-4; acetonitrile, 75-05-8.

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Quinazolines and 1,4-Benzodiazepines. LXIII.[1] Preparation and Nucleophilic Reactions of 7-Chloro-5-phenyl-3H-1,4-benzodiazepine

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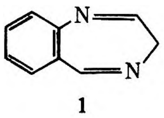
The title compound was obtained by manganese dioxide oxidation of the corresponding 1,2-dihydrobenzodiazepine. The 1,2-imine function exhibits greater reactivity toward nucleophiles than the 4,5-imino function and additions of methanol, piperidine, various mercaptans, and hydrogen cyanide proceeded selectively. Hydrogen sulfide adds to both imine functions to produce a 2,5-sulfur-bridged 1,4-benzodiazepine. Oxidation of the hydrogen cyanide adduct produced a 2-cyano-3H-1,4-benzodiazepine in which the α-iminonitrile function displayed a reactivity pattern qualitatively similar to that of acyl cyanides.

The many benzodiazepines synthesized for chemical and pharmacological investigation have generally been derivatives in the 2H-1,3-dihydro series.[2] Derivatives in the same oxidation state as the (yet unknown) parent heterocycle 1 which are unsubstituted in the 2 position are relatively rare and this prompted the study of some of the chemistry of compound 2 described in this paper.



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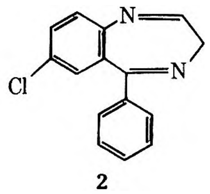

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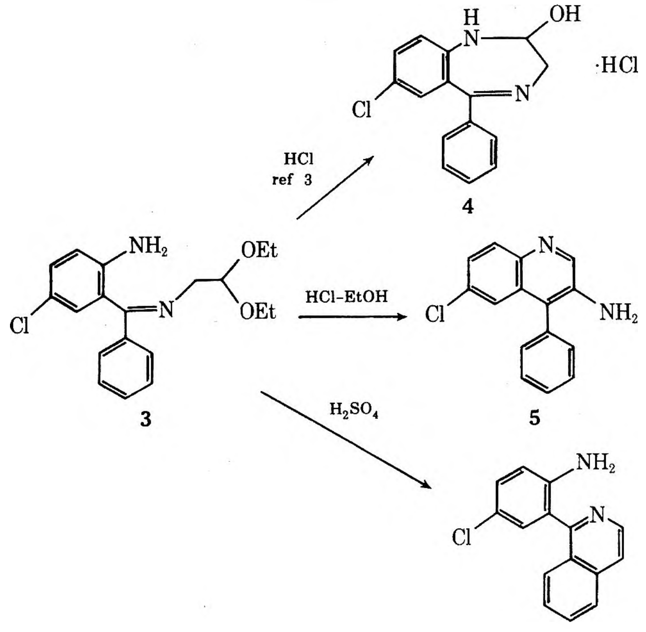
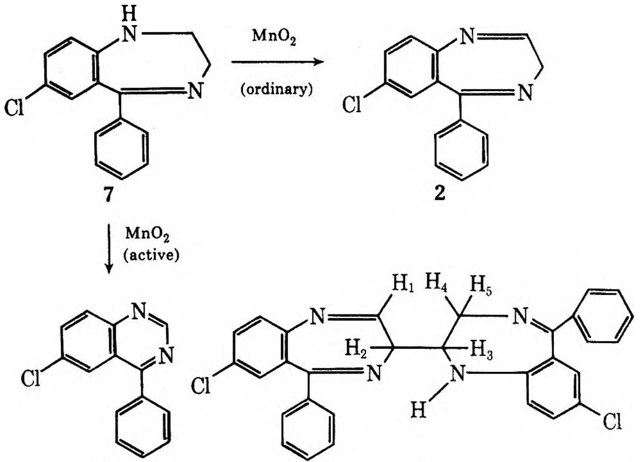
2-Amino-5-chlorobenzophenone can be condensed indirectly with aminoacetaldehyde diethyl acetal to give compound 3,[3] which was examined as a potential precursor to compound 2. The reactions of this substance with acid are remarkably dependent on the conditions employed (Scheme I). The reaction with HCl is reported[3] to give 4, a hydrate of 2, as its hydrochloride. This did not provide a convenient route to compound 2, as in our hands the precursor 4 was not accessible by this method. Moreover, we found that cyclization with HCl in boiling ethanol produces the known quinoline 5[4] and cyclization with concentrated sulfuric acid produces the isoquinoline 6[5] (Scheme I).

Scheme I



An alternative route to compound 2 was suggested by instances of imine formation in the oxidation of N-alkylanilines with manganese dioxide,[6] and a convenient preparation of 2 by oxidation of 7 was thus realized[7] (Scheme II).

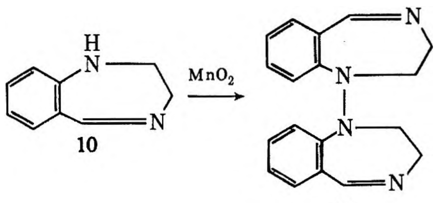
Scheme II



Initial attempts to oxidize the dihydrobenzodiazepine 7[8] with active manganese dioxide produced mixtures from which the quinazoline 8[9] was the only readily isolable substance. Ordinary manganese dioxide produced the desired product 2 but as a mixture with variable quantities of the dimer 9. High yields of 2 are contingent on preliminary removal of water from the manganese dioxide by azeotropic distillation with benzene; and if in addition a small quantity of acetic acid is added, the product is free of dimeric impurities. Crystallization of compound 2 is difficult but the crude product is sufficiently pure for subsequent transformations.

The structure (9) assigned to the dimer was based initially on analogy with that formed in the dimerization of Δ^1-piperideine.[10] This assignment was corroborated by the nmr spectrum, in which signals for the five numbered protons are clearly resolved. After washing with D_2O to remove the NH signal at 4.90 ppm, H_1 appears as a doublet at δ 7.69 ($J_{1,2}$ = 4 Hz), H_2 as a quartet at 3.09 ($J_{2,3}$ = 10 Hz), H_3 as a multiplet of seven lines at 4.83 ($J_{3,4}$ = 6, $J_{3,5}$ = 4 Hz), H_4 and H_5 as an AB quartet (J_{AB} = 11 Hz) with each line split again at 3.80 and 4.14 ppm.

An attempt to prepare 3H-1,4-benzodiazepine itself (1) by the same oxidation procedure gave strikingly different results. The hydrazobenzene derivative 11 was the sole product obtained from the oxidation of 10, indicating



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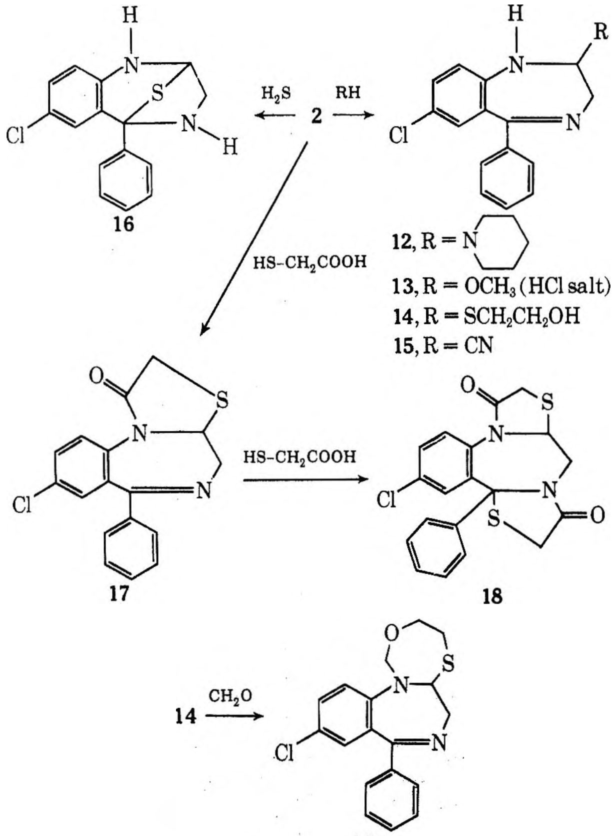
11

that, for reasons which are not at all clear, the reaction proceeds along the pathway that normally converts anilines to azobenzene derivatives[11] in the absence of the 5-phenyl and 7-chloro substituents.

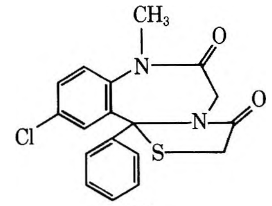
Treatment of compound 2 with excess piperidine in ether led to the formation of the piperidine adduct 12 (Scheme III). The crystalline product is stable with respect to reversal of this addition. Methanol adds to compound 2 in a similar fashion. The crystalline hydrochloride 13 was formed directly with methanolic HCl in ether. These and other nucleophilic additions[12] to compound 2 are presented in Scheme III.

Scheme III



16 12 17 18 19

Mercaptans were also found to add readily to compound 2.[13] Mercaptoethanol yields adduct 14, reflecting the superior nucleophilicity of the mercaptan function. Cyclization of this material with formaldehyde gave the oxathiazepinobenzodiazepine 19. Mercaptoacetic acid in boiling benzene produced a mixture of the thiazolones 17 and 18. The spontaneous lactam ring formations leading to these compounds are not surprising, as a recent article[14] describes amide formation from mercaptoacetic acid and ethylamine under even milder conditions. This type of addition across the 4,5 C=N bond was demonstrated with two other representative members of the benzodiazepine series, namely, 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one[15] and 8-chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (34),[16] which are converted to thiazolone derivatives 20 and 21 in this manner.



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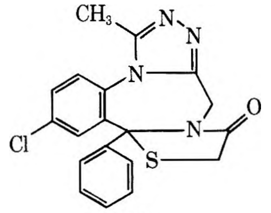

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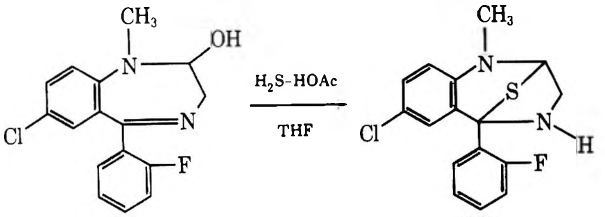
The addition of hydrogen sulfide to compound 2 proceeds rapidly and exothermically in THF solution. The simple adduct with a 2-mercapto function has not been detected, as the addition occurs across both C=N bonds to produce the 2,5-epithiobenzodiazepine 16.[17] 16 is thermally converted to 2, demonstrating the reversibility of the hydrogen sulfide addition. 16 can thus be used in place of 2 for some of these preparations. A similar sulfur-bridged benzodiazepine was prepared from the known 1-methyl-2-hydroxy precursor 22[18] by acid-catalyzed reaction with hydrogen sulfide.



22 23

As expected, 23 exhibits greater thermal stability than 16.

Another series of novel benzodiazepines was derived from 2 *via* its HCN adduct 15 (Scheme IV). This compound is readily formed by treatment of a solution of 2 in tetrahydrofuran with aqueous KCN and methanolic HOAc.

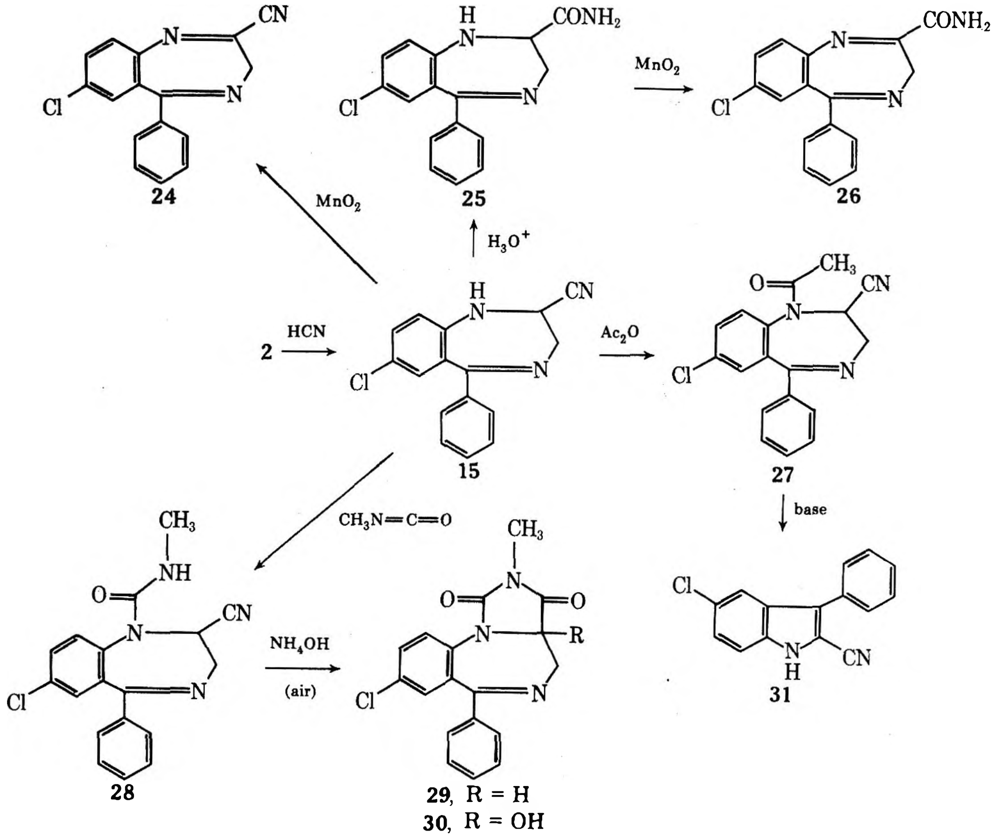
Reoxidation with manganese dioxide produces the 2-cyano-3*H*-1,4-benzodiazepine 24. The cyano group in this compound exhibits considerable reactivity toward nucleophilic substitution, presumably by the addition–elimination pathway, and is thus comparable to an acyl cyanide (Scheme V). If, however, the cyano group is first hydrolyzed to the amide 25 and this product oxidized, the resulting 3*H*-1,4-benzodiazepine 26 is one with greatly attenuated reactivity toward nucleophilic additions.

Acylation of 15 with acetic anhydride yields 27, and reaction with methyl isocyanate yields the urea derivative 28. Upon treatment with a methanol solution of ammonium hydroxide in air, a mixture of two benzodiazepine hydantoins, 29 and 30, is produced from the latter. Compound 29 is not converted to 30, the major product, under these conditions, indicating that the aerial oxidation occurs at an earlier stage. If 28 is partly hydrolyzed with acid before treatment with ammonia, hydantoin 29 is the only product obtained, suggesting that 28 itself is the air-oxidizable species.

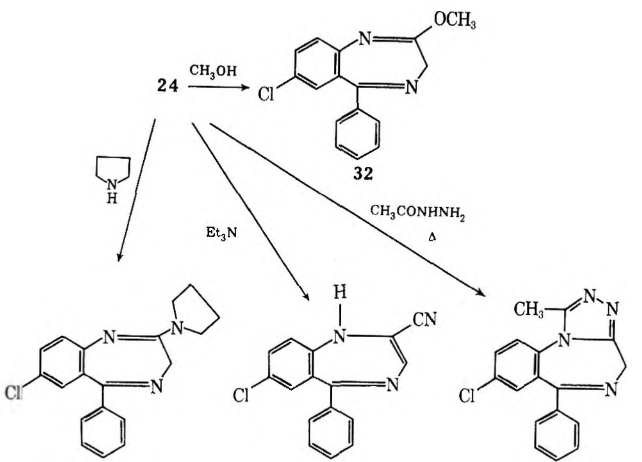
Attempts to effect analogous cyclization of 27 with base led to the known indole 31.[19] Ring contractions of this type have been encountered previously in the benzodiazepine series.[2a]

The substitution reactions in Scheme V illustrate how the acyl cyanide character of compound 24 makes it a convenient precursor to a variety of other 2-substituted 3*H*-1,4-benzodiazepines and also to the pharmacologically interesting[16] triazolobenzodiazepine 34. Treatment with triethylamine in THF at reflux effects isomerization to the dark red 1*H* isomer 35.

Scheme IV



Scheme V



Experimental Section[20]

3-Amino-6-chloro-4-phenylquinoline (5). A solution of the Schiff base 3[3] (2 g) in ethanol (40 ml) was saturated with dry hydrogen chloride, giving a red solution. Heating under reflux for 3.5 hr gave a yellow-orange solution, which was cooled, diluted with water, and gradually made basic by addition of aqueous sodium carbonate solution. The product was collected, washed, and dried to give 1.45 g (99%) of light yellow crystals, mp 155–160° (lit.[4] mp 161–162°), identified by ir and tlc comparison with an authentic sample.[4]

1-(2-Amino-5-chlorophenyl)isoquinoline (6). The Schiff base 3 (10 g) was added slowly to concentrated sulfuric acid (150 ml) and the resulting red solution was heated, first to 80° for 1 hr and then to 125° for 1 hr. This solution was cooled, poured over ice, made basic with aqueous sodium hydroxide and ammonia, and extracted with ether. The basic product was extracted from the ether with hydrochloric acid and then liberated by treatment with aqueous ammonia. Recrystallization of the crude product from ether-petroleum ether (bp 30–60°) gave 5.8 g (82%) of yellow crystals: mp 109–110°; ir (Nujol) 3400, 3300, 1625, 1585, and 1500 cm^{-1}; nmr ($CDCl_3$) δ 4.01 (s, broad, NH_2), 6.64–8.10 (m, 8 H, aromatic), and 8.58 (d, J = 5.5 Hz, N=CH); mass spectrum *m/e* 254 (100, M$^+$).

Anal. Calcd for $C_{15}H_{11}ClN_2$: C, 70.73; H, 4.35; N, 11.00; Cl, 13.92. Found: C, 70.31; H, 4.36; N, 11.40; Cl, 13.70.

Manganese Dioxide Oxidation of 7-Chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine (7). A. With Activated MnO_2. 7 (10 g) was added to a slurry of activated manganese dioxide (100 g) in benzene (1 l.) which had been dried by heating under reflux for 1 hr while collecting water in a Dean–Stark trap. The mixture was stirred and heated under reflux for 6 hr, then cooled and filtered through Celite. The solid was washed with benzene. Evaporation of the filtrate and washings left a red, syrupy mixture of several products which was taken up in ether. 6-Chloro-4-phenylquinazoline (0.9 g, 10%) crystallized out on chilling as tan crystals, mp 138–139° (lit.[9] mp 136–138°). Several subsequent crops were less pure but of the same material.

B. With Ordinary MnO_2. 7 (10 g) was added to a slurry of ordinary manganese dioxide[21] (100 g) in benzene (1 l.) which had been dried as in A. The reaction and work-up were also conducted as above. The oily residue crystallized (with difficulty) from ether–hexane to give 6.3 g (64%) of crude 2, mp 97–100°. An analytical sample was prepared by two recrystallizations from ethyl acetate, giving off-white prisms: mp 101–104°; ir (Nujol) 1610 and 1575 cm^{-1}; nmr ($CDCl_3$) δ 3.92 (s, broad, 2 H), 7.44 (m, 8 H), and 7.92 (t, J = 4 Hz, 1 H).

Anal. Calcd for $C_{15}H_{11}N_2Cl$: C, 70.73; H, 4.35. Found: C, 70.76; H, 4.48.

In some preparations, the product crystallizing from ether was a high-melting (223–224°), pale yellow solid (yield up to 14%) which was identified as the dimer 9, 7-chloro-3-(7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-5-phenyl-3*H*-1,4-benzodiazepine: ir (KBr) 3400, 1605, 1595, 1570, 1535 cm^{-1}; nmr ($CDCl_3$) δ 4.96 (s, broad, NH), 6.7–7.6 (m, 16 H, aromatic), and peaks listed in the text; mass spectrum *m/e* 255 (100) and 508 (M$^+$).

Anal. Calcd for $C_{30}H_{22}Cl_2N_4$: C, 70.73; H, 4.35. Found: C, 71.18; H, 4.30.

1,1-Bi(2,3-dihydro-1*H*-1',4-benzodiazepinyl) (11). Ordinary manganese dioxide (5 g) and acetic acid (5 drops) in benzene (50 ml) were heated and stirred under reflux for 1 hr while water was collected in a Dean-Stark trap. Compound 10[22] (500 mg) was added and stirring with reflux was continued for 16 hr. Tlc analysis of the reaction mixture showed only starting material and the dimer in approximately 1:1 ratio. After filtration and evaporation, the residue was separated by preparative layer silica gel chromatography, giving 60 mg of dimer 11 and 110 mg of starting material 10. Sublimation of the dimer [120° (0.03 mm)] afforded pale yellow crystals: mp 178–180°; ir (Nujol) 1630, 1590, and 1550 cm^{-1}; nmr (CDCl$_3$) δ 3.67 (t, J = 5 Hz, 4 H), 4.20 (t, 4 H), 6.8–7.6 (m, 8 H), and 8.30 (s, 2 H); mass spectrum m/e 117 (100), 145, 290 (M$^+$).

7-Chloro-2,3-dihydro-5-phenyl-2-piperidino-1*H*-1,4-benzodiazepine (12). A solution of 2 (1.2 g) in ether (20 ml) was treated with piperidine (1 ml) and kept overnight, during which 1.5 g (94%) of 12 separated out. Recrystallization from ethyl acetate gave pale yellow spars, mp 130–135° dec, ir (CHCl$_3$) 1610 cm^{-1}.

Anal. Calcd for $C_{20}H_{22}ClN_3$: C, 70.68; H, 6.53. Found: C, 70.72; H, 6.50.

7-Chloro-2,3-dihydro-2-methoxy-5-phenyl-1*H*-1,4-benzodiazepine Hydrochloride (13). A solution of compound 2 (4 g) in methanol (5 ml) was added to a solution of 6 *N* methanolic hydrogen chloride (8 ml) in ether (25 ml). Compound 13 (4.3 g, 85%) crystallized out. Recrystallization from methanol–ether gave yellow needles, mp 185–193° dec.

Anal. Calcd for $C_{16}H_{16}Cl_2N_2O$: C, 59.45; H, 4.99. Found: C, 59.52; H, 5.17.

7-Chloro-2,3-dihydro-2-(2-hydroxyethylthio)-5-phenyl-1*H*-1,4-benzodiazepine (14). Compound 7 (10 g) was oxidized to compound 2 as described above with the addition of 0.1 ml of acetic acid to inhibit dimerization. The crude oxidation product was taken up in THF (60 ml), treated with 2-mercaptoethanol (10 ml), and heated under reflux overnight. The resulting solution was concentrated under reduced pressure until the product began to crystallize and then diluted with 100 ml of ether. The product was collected and washed with ether to give 10.13 g (78%) of colorless crystals, mp 135–140° dec, ir (Nujol) 3260, 3200, 1610, and 1570 cm^{-1}.

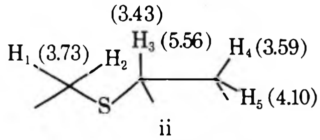
Anal. Calcd for $C_{17}H_{17}ClN_2OS$: C, 60.98; H, 5.72; Cl, 10.59; N, 8.37; S, 9.58. Found: C, 60.86; H, 5.49; Cl, 10.66; N, 8.40; S, 9.65.

10-Chloro-3,4,5a,6-tetrahydro-8-phenyl-1*H*-1,5,3-oxathiazepino[3,4-*a*][1,4]benzodiazepine (19). Compound 14 (500 mg) in THF (10 ml) was treated with 37% aqueous formaldehyde solution (2 ml) and kept for 5 hr. Dilution with water while scratching induced crystallization of 400 mg (78%) of yellow solid. Recrystallization from methylene chloride–ether gave pale yellow prisms: mp 160–164°; ir (CHCl$_3$) 1615 cm^{-1}; nmr (CDCl$_3$) δ 3.08 (t, J = 6 Hz, SCH$_2$), 3.26, 4.25, and 5.19 (ABX, J_{AB} = 11.5, J_{AX} = 12, J_{BX} = 4 Hz, NCH$_2$CHN), 4.12 (t, J = 6 Hz, OCH$_2$), 4.87 (q, J_{AB} = 12.5 Hz, NCH$_2$O), 7.05 (d, 1 H), 7.5 (m, 6 H), and 7.80 (d, 1 H); mass spectrum m/e 253 (100) and 344 (M$^+$).

Anal. Calcd for $C_{18}H_{17}ClN_2OS$: C, 62.69; H, 4.97; Cl, 10.28; N, 8.12; S, 9.30. Found: C, 62.59; H, 5.02; Cl, 10.55; N, 8.14; S, 9.49.

3a,4-Dihydro-8-chloro-6-phenylthiazolo[3,2-*a*][1,4]benzodiazepin-1(2*H*)-one (17) and 2-Chloro-8a,9-dihydro-13a-phenyl-13a*H*-bisthiazolo[3,2-*a*:3′,2′-*d*][1,4]benzodiazepin-6,11(7*H*,12*H*)-dione (18). Crude 2 from the oxidation of 7 (15 g) in benzene (1 l.) was treated slowly with excess mercaptoacetic acid (15 ml) and then stirred and heated under reflux for 23 hr. The cooled solution was washed with aqueous sodium carbonate, dried, and evaporated, and the oily residue was taken up in ether. A mixture of 17 and 18 (15 g) crystallized out on standing. Chromatography of 8.4 g of this mixture on 500 g of silica gel with hexane–ethyl acetate mixtures as eluent provided, after a recrystallization from methylene chloride–methanol, 1.9 g of 17, which is the more polar substance, and 3.3 g of 18.

17 was obtained as pale yellow crystals: mp 228–230°; ir (Nujol) 1680, 1605, and 1560 cm^{-1}; nmr (CDCl$_3$) δ 7.15–7.60 (m, 8 H, aromatic) and a multiplet for the aliphatic H with long-range couplings shown in partial structure ii, $J_{1,2}$ = 16; $J_{1,3}$ = 1.5; $J_{2,3}$ = 1.5; $J_{3,4}$ = 4; $J_{3,5}$ = 0; $J_{4,5}$ = 13 Hz; mass spectrum m/e 327 (100), 328 (M$^+$).



ii

Anal. Calcd for $C_{17}H_{13}N_2OSCl$: C, 62.10; H, 3.99; N, 8.52; S, 9.75; Cl, 10.78. Found: C, 62.24; H, 3.97; N, 8.41; S, 9.60; Cl, 10.90.

Compound 18 was obtained as colorless crystals: mp 256–257°; ir (Nujol) 1675 and 1585 cm^{-1}; nmr (CDCl$_3$) δ 2.8–3.5 (m, 3 H), 3.60 (s, 2 H), 4.30 (m, 1 H), 4.50 (m, 1 H), 6.9–7.6 (m, 7 H), and 8.52 (d, J = 2 Hz, 1 H); mass spectrum m/e 402 (100, M$^+$).

Anal. Calcd for $C_{19}H_{15}N_2O_2S_2Cl$: C, 56.64; H, 3.72; N, 6.95; S, 15.92. Found: C, 56.72; H, 3.72; N, 6.97; S, 15.51.

10-Chloro-7,11b-dihydro-7-methyl-11b-phenylthiazolo[3,2-*d*][1,4]benzodiazepin-3,6(2*H*,5*H*)-dione (20). A solution of 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one[15] (5 g) in benzene (200 ml) was treated with mercaptoacetic acid (2.9 ml) and heated under reflux for 5 days. The benzene was then evaporated from the solution, and the residue was taken up in methylene chloride, washed with aqueous sodium bicarbonate, dried, evaporated, and the oily residue allowed to crystallize from a small volume of methylene chloride. Two recrystallizations from methylene chloride–methanol gave colorless crystals (2.4 g, 38%): mp 212–214°; ir (Nujol) 1680, 1600, and 1570 cm^{-1}; nmr (CDCl$_3$) δ 2.43 (s, 3 H), 3.69 (q, J_{AB} = 16 Hz, 2 H), 3.43 and 4.73 (q, J_{AB} = 14 Hz, 2 H), 6.90–7.7 (m, 7 H), and 8.26 (d, J = 2 Hz, 1 H); mass spectrum m/e 285 (100) and 358 (M$^+$).

Anal. Calcd for $C_{18}H_{15}N_2O_2SCl$: C, 60.25; H, 4.21; N, 7.81; S, 8.93; Cl, 9.87. Found: C, 59.98; H, 4.19; N, 7.70; S, 8.73; Cl, 10.06.

10-Chloro-7,8a-dihydro-1-methyl-8a-phenyl-4*H*-*s*-triazolo[4,3-*a*]thiazolo[3,2-*d*][1,4]benzodiazepin-6-one (21). A solution of 34 (280 mg) in benzene (125 ml) was treated with mercaptoacetic acid (2 ml) and heated under reflux for 24 hr. Following the work-up procedure for compound 20, the crude product was recrystallized from ethanol to give 200 mg (58%) of colorless crystals: mp 278–280°; ir (Nujol) 1680 and 1530 cm^{-1}; nmr (CDCl$_3$) δ 1.97 (s, 3 H), 3.70 (s, 2 H), 3.98 and 5.53 (q, J_{AB} = 14 Hz, 2 H), 6.90–7.8 (m, 7 H), and 8.45 (d, J = 2 Hz, 1 H); mass spectrum m/e 382 (M$^+$).

Anal. Calcd for $C_{19}H_{15}N_4OSCl$: C, 59.60; H, 3.95; N, 14.63; S, 8.37; Cl, 9.26. Found: C, 59.38; H, 3.87; N, 14.51; S, 7.98; Cl, 9.17.

7-Chloro-2,3,4,5-tetrahydro-5-phenyl-2,5-epithio-1*H*-1,4-benzodiazepine (16). A stirred solution of crude compound 2 from the oxidation of compound 7 (120 g) in THF (1 l.) was saturated with hydrogen sulfide gas during 1.5 hr. The solvent was evaporated and the solid residue was triturated with ether, filtered, and washed with ether to give 77.3 g (57%) of pure 16 as a colorless powder. Crystals from methylene chloride–ether had mp 142–144° dec; ir (KBr) 3250 and 1600 cm^{-1}; nmr (DMSO-d_6) δ 3.27 (d, J_{AB} = 11.5 Hz, 1 H), 3.58 (q, J_{AB} = 11.5, J_{vic} = 4.5 Hz, 1 H), 3.88 (s, NH), 5.67 (t, $J_{vic} \cong J_{NH}$ = 5 Hz, 1 H), 6.10 (d, J = 2 Hz, 1 H), and 6.6–7.7 (m, 8 H incl NH); mass spectrum m/e 254 (100, M$^+$ − H$_2$S).

Anal. Calcd for $C_{15}H_{13}N_2SCl$: C, 62.38; H, 4.54; N, 9.70; S, 11.10; Cl, 12.28. Found: C, 62.66; H, 4.54; N, 9.80; S, 10.91; Cl, 12.04.

7-Chloro-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-1-methyl-2,5-epithio-1*H*-1,4-benzodiazepine (23). A solution of compound 22[18] (5.0 g) in glacial acetic acid (25 ml) was stirred overnight while bubbling in a slow stream of hydrogen sulfide gas. The solution was then poured slowly into excess aqueous sodium carbonate and the crude solid product (5 g) was filtered and washed. Two recrystallizations from methylene chloride–ether gave 3.3 g (63%) of pale yellow prisms: mp 177° dec; ir (Nujol) 3260 cm^{-1}; nmr (CDCl$_3$-DMSO-TFA) δ 3.18 (s, 3 H), 3.85 (m, 2 H), 5.76 (d, J_{vic} = 5 Hz, 1 H), 6.4–8.0 (m, 7 H); mass spectrum m/e 259 (100), 287, and 320 (M$^+$).

Anal. Calcd for $C_{16}H_{14}FN_2SCl$: C, 59.90; H, 4.40; N, 8.73; S, 9.99; Cl, 11.05. Found: C, 60.08; H, 4.25; N, 8.82; S, 9.84; Cl, 10.92.

7-Chloro-2-cyano-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (15). A stirred solution of crude 2 from the oxidation of 7 (128 g) in THF (500 ml) was cooled in a water bath with simultaneous addition of the following solutions: (a) potassium cyanide (88 g) in water (180 ml) and (b) glacial acetic acid (100 ml) in methanol (300 ml). The resulting mixture was stirred for 30 min after completion of the additions and then concentrated to *ca.* 400 ml under reduced pressure, during which the product began to separate. Crystallization of the crude product was completed by dilution with 2 l. of water and chilling. The solid was collected and dissolved in methylene chloride. This solution was dried and then boiled down with gradual addition of cyclohexane. Three crops of material were thus obtained of which the second and third crops were combined and recrystallized to give a total of 85.15 g (60%) of pale yellow crystals: mp 181–183° dec; ir[23] (Nujol) 3330, 1620, and 1580 cm^{-1}; nmr (CDCl$_3$) δ 3.73 (t, J_{AB} = 12, J_{vic} = 10.5 Hz, 1 H), 4.10 (s, NH), 4.18 (q, J_{AB} = 12, J_{vic} = 4 Hz, 1 H), 4.89 (m, 1 H), 6.92–7.65 (m, 8 H); mass spectrum m/e 253 (100) and 281 (M$^+$).

Anal. Calcd for $C_{16}H_{12}N_3Cl$: C, 68.21; H, 4.29; N, 14.91; Cl, 12.58. Found: C, 67.78; H, 4.19; N, 14.95; Cl, 12.57.

7-Chloro-2-cyano-5-phenyl-3*H*-1,4-benzodiazepine (24). Manganese dioxide[21] (25 g) slurried in benzene (150 ml) was stirred and heated under reflux for 1 hr while water was collected in a Dean-Stark trap. **15** (5 g) was added and stirring with reflux was continued for 16 hr. The solid was filtered and washed with methylene chloride. The filtrate and washings were evaporated to a yellow oil which was taken up in ether, giving 1.7 g of pure **24** as pale yellow crystals, mp 151–154°. A second crop of less pure material, 2.3 g (80% total yield), was obtained. Pure **24** has ir (Nujol) 1605, 1580, 1565, and 1540 cm^{-1}; Raman (neat powder, 4880 Å) band at 2225 cm^{-1}; nmr ($CDCl_3$) δ 4.20 (s, 2 H) and 7.5 (m, 8 H); mass spectrum *m/e* 279 (100, M^+).

Anal. Calcd for $C_{16}H_{10}N_3Cl$: C, 68.70; H, 3.60; N, 15.02; Cl, 12.67. Found: C, 69.06; H, 3.55; N, 15.20; Cl, 12.44.

2-Carboxamide-7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (25). **15** (10 g) was dissolved in concentrated hydrochloric acid (40 ml) and warmed in a 40° water bath for 45 min. The resulting solution was poured over ice, made basic with aqueous sodium carbonate, and extracted with methylene chloride. After drying and evaporation, the residue was recrystallized from methylene chloride–ether to give 6.3 g (60%) of the amide in four crops. Pure crystals of **25** are colorless: mp 210–213°; ir (KBr) 3460, 3260, 1695, 1620, and 1580 cm^{-1}; nmr ($CDCl_3$) δ 3.05 (s, NH_2), 3.96–4.28 (m, 3 H), 5.5 (s, broad, NH), 6.8–7.5 (m, 8 H); mass spectrum *m/e* 255 (100) and 299 (M^+).

Anal. Calcd for $C_{16}H_{14}N_3OCl$: C, 64.11; H, 4.71; N, 14.02. Found: C, 64.20; H, 4.74; N, 14.25.

2-Carboxamido-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (26). A slurry of manganese dioxide[21] (50 g) in benzene (250 ml) containing acetic acid (0.2 ml) was heated under reflux for 2 hr while water was collected in a Dean-Stark trap. The amide **25** (5 g) was added and stirring with reflux was continued for 17 hr. The mixture was cooled, filtered with washing of solid, and evaporated to give 4.45 g (85%) of tan solid. Recrystallization from chloroform–ether gave 3.35 g of colorless needles: mp 219–221° dec; ir (Nujol) 3200, 3100, 1680, 1600, and 1535 cm^{-1}; nmr ($CDCl_3$–DMSO) δ 3.40 (s, NH_2), 4.25 (s, broad, 2 H), and 7.5 (m, 8 H); mass spectrum *m/e* 297 (100, M^+).

Anal. Calcd for $C_{16}H_{12}N_3OCl$: C, 64.54; H, 4.06; N, 14.11; Cl, 11.91. Found: C, 63.84; H, 4.05; N, 14.09; Cl, 11.76.

1-Acetyl-7-chloro-2-cyano-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (27). A solution of aminonitrile **15** (1.41 g) in toluene (10 ml) was treated with acetic anhydride (3 ml) and potassium carbonate (2 g) and stirred with reflux for 16 hr. The mixture was cooled, washed with water and then with 0.1 *N* hydrochloric acid, dried, and evaporated. The residue crystallized from isopropyl alcohol and was recrystallized from ethyl acetate–ether to give 730 mg (45%) of pale yellow crystals: mp 208–210°; ir (KBr) 1670, 1600, 1590, 1565, and 1550 cm^{-1}; Raman (neat powder, 5145 Å) band at 2240 cm^{-1}; nmr ($CDCl_3$) δ 1.92 (s, 3 H), 3.37 (q, J_{AB} = 11.5, J_{vic} = 13 Hz, 1 H), 4.37 (q, J_{vic} = 5 Hz, 1 H), 5.90 (q, 1 H), and 7.6 (m, 8 H); mass spectrum *m/e* 323 (M^+).

Anal. Calcd for $C_{18}H_{14}N_3OCl$: C, 66.77; H, 4.36; N, 12.98; Cl, 10.95. Found: C, 66.69; H, 4.25; N, 12.98; Cl, 11.07.

7-Chloro-2-cyano-2,3-dihydro-1-methylaminocarbonyl-5-phenyl-1*H*-1,4-benzodiazepine (28). A mixture of the aminonitrile **15** (7.1 g) and methyl isocyanate (25 ml) in a sealed flask was heated in a 90–100° oil bath for 18 hr. The flask was cooled, excess methyl isocyanate was evaporated, and the residue was triturated with ether. After dilution with petroleum ether and chilling, the product was collected and washed to give 6.05 g (71%) of crude urea, mp 227–231°. An analytical sample from methylene chloride–ether crystallized as pale yellow prisms: mp 229–230°; ir (KBr) 3410, 1670, and 1595 cm^{-1}; Raman (neat powder, 5145 Å) band at 2240 cm^{-1}; nmr ($CDCl_3$) δ 2.71 (d, 3 H, $NHCH_3$), 3.33 (t, $J_{AB} \cong J_{vic} \cong$ 12 Hz, 1 H), 4.32 (q, 1 H), 4.42 (broad, NH), 5.76 (q, J'_{vic} = 5 Hz, 1 H), 7.2–7.8 (m, 8 H); mass spectrum *m/e* 253 (100) and 338 (M^+).

Anal. Calcd for $C_{18}H_{15}N_4OCl$: C, 63.81; H, 4.46; N, 16.58; Cl, 10.46. Found: C, 63.56; H, 4.40; N, 16.52; Cl, 10.37.

8-Chloro-3a,4-dihydro-2-methyl-6-phenyl-2*H*-imidazo[1,5-*a*]-[1,4]benzodiazepine-1,3-dione (29). The urea **28** (6.05 g) was added to ice-cold concentrated hydrochloric acid (26 ml) and the resulting solution was then warmed to 40° and stirred for 25 min. It was then cooled and diluted by adding ice and poured into a stirred slush of ice in aqueous ammonia. The resulting mixture was kept for 6 hr. The product was collected, dissolved in methylene chloride, dried, concentrated, and crystallized by adding ether to give 4.05 g (67%) of colorless crystals: mp 164–165°; ir (Nujol) 1770, 1700, 1600, and 1550 cm^{-1}; nmr ($CDCl_3$) δ 2.95 (s, 3 H), 3.50 (q, *J* = 5, 12 Hz, 1 H), 4.52 (d, 1 H), 4.67 (d, 1 H), and 7.2–7.6 (m, 8 H); mass spectrum *m/e* 339 (M^+).

Anal. Calcd for $C_{18}H_{14}ClN_3O_2$: C, 63.62; H, 4.15; Cl, 10.43; N, 12.36. Found: C, 63.59; H, 4.09; Cl, 10.21; N, 12.46.

8-Chloro-3a,4-dihydro-3a-hydroxy-2-methyl-6-phenyl-2*H*-imidazo[1,5-*a*][1,4]benzodiazepine-1,3-dione (30). Cyclization of the urea **28** (3.43 g) by heating under reflux with concentrated aqueous ammonia (17 ml) in methanol (60 ml) for 6 hr gave, after work-up with water and methylene chloride extraction, a mixture of **29** and **30**. Separation was accomplished by silica gel preparative layer chromatography (five plates) giving 400 mg (11.5%) of **29** and 1.2 g (33%) of **30**. The latter crystallized from ether as colorless crystals: mp 193–196°; ir (KBr) 3400, 1790, 1720, 1610, 1600, and 1565 cm^{-1}; nmr (DMSO-d_6) δ 2.86 (s, 3 H), 3.24 (d, J_{AB} = 11 Hz, 1 H), 3.42 (s, NCOH),[24] 4.37 (d, 1 H), and 7.2–7.9 (m, 8 H); mass spectrum *m/e* 355 (M^+).

Anal. Calcd for $C_{18}H_{14}ClN_3O_3$: C, 60.77; H, 3.97; Cl, 9.96; N, 11.81. Found: C, 60.21; H, 3.93; Cl, 10.01; N, 11.51.

7-Chloro-2-methoxy-5-phenyl-3*H*-1,4-benzodiazepine (32). **24** (200 mg) in methanol (5 ml) was heated under reflux for 3 hr and then evaporated down and the residue was crystallized from a small volume of ether. The crude product consisted of 193 mg (95%) of brownish-white crystals, mp 87–94° (lit.[25] mp 88–92°), identical by ir and tlc comparison with an authentic sample.[25]

7-Chloro-5-phenyl-2-pyrrolidino-3*H*-1,4-benzodiazepine (33). **24** (200 mg) was treated with excess pyrrolidine (0.5 ml), causing an exothermic reaction. Crystallization from ether–cyclohexane gave 150 mg (65%) of crude product. Recrystallization from ethanol gave pale yellow prisms, mp 140–143° (lit.[24] mp 139–141°). This material was identical by ir and tlc comparison with an authentic sample.[26]

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (34). Compound **15** (25 g) was oxidized to compound **24** with 250 g of manganese dioxide as described above. The benzene solution containing crude **24** was treated with acetylhydrazide (10 g) and concentrated by boiling to *ca.* 300 ml during 2 hr. The remaining solvent was removed under reduced pressure and replaced by 1-butanol (250 ml). This solution was heated under reflux for 16 hr and then concentrated under reduced pressure, causing the product to crystallize in a brown paste. Trituration with ether, filtering, and washing with water and then more ether gave 16.4 g (60%) of light tan, crystalline solid, mp 227–230° (lit.[16] mp 228°). This material was identical by ir and tlc with an authentic sample.[16]

7-Chloro-2-cyano-5-phenyl-1*H*-1,4-benzodiazepine (35). A solution of compound **24** (1.5 g) in THF (50 ml) was treated with triethylamine (1 ml) and heated under reflux for 1 hr. Evaporation under reduced pressure left a dark red oil which was taken up in hot cyclohexane. Gradual cooling with scratching induced crystallization and 1.0 g (66%) of brownish-red needles was thus obtained. A further recrystallization from cyclohexane afforded an analytical sample: mp 148–150°; ir (Nujol) 3300, 2220, 1625, 1590, and 1575 cm^{-1}; nmr ($CDCl_3$) δ 4.6 (s, broad, 1 H, NH), 6.70 (d, *J* = 8 Hz, 1 H, aromatic), 6.97 (d, *J* = 2 Hz, 1 H, aromatic), 7.10 (d, *J* = 1.5 Hz, 1 H, vinyl H), and 7.5 (m, 6 H, aromatic) (upon washing with D_2O the signal at δ 4.6 vanishes and the doublet at δ 7.10 becomes a singlet); mass spectrum *m/e* 252 (100) and 279 (M^+).

Anal. Calcd for $C_{16}H_{10}ClN_3$: C, 68.70; H, 3.60; N, 15.02; Cl, 12.67. Found: C, 68.67; H, 3.55; N, 14.95; Cl, 12.73.

Registry No. 2, 16398-00-8; **3**, 26418-94-2; **6**, 42915-30-0; **7**, 1694-78-6; **9**, 42915-32-2; **10**, 5945-91-5; **11**, 42915-34-4; **12**, 16398-01-9; **13**, 42915-36-6; **14**, 43000-57-3; **15**, 42915-37-7; **16**, 42915-38-8; **17**, 43000-58-4; **18**, 42915-39-9; **19**, 42915-40-2; **20**, 42915-41-3; **21**, 42915-42-4; **22**, 41218-65-9; **23**, 42915-44-6; **24**, 42915-45-7; **25**, 42915-46-8; **26**, 42915-47-9; **27**, 42915-48-0; **28**, 42915-49-1; **29**, 42915-50-4; **30**, 42915-51-5; **34**, 28981-97-7; **35**, 42915-53-7; 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, 439-14-5.

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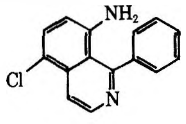

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1,3-Bridged Aromatic Systems. IX. Reactions of Syn and Anti Derivatives of 1-Substituted 12,13-Benzo-16-chloro[10](2,4)pyridinophanes[1]

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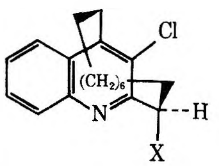
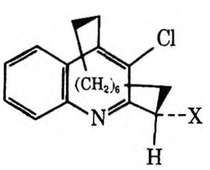
The reactions of 2,4-bridged meta cyclophanes of type 1 and 2, containing *syn-* and *anti-p*-toluenesulfonyloxy groups (**1a** and **2a**) and *syn-* and *anti*-bromine atoms (**1b** and **2b**) at a benzylic carbon atom in the highly constrained methylene bridge, with a variety of reagents normally employed to effect substitution or elimination reactions are described. The behavior of these compounds is atypical of aliphatic benzyl substituents, which is a consequence of the steric constraint of the fused methylene bridge. The derivatives are highly resistant to bimolecular substitution and elimination reactions and also to ionization reactions. Under forcing conditions ionization reactions can be effected which are highly stereospecific in the syn series with retention of configuration. With silver acetate solvolyses of both **1b** and **2b** are stereospecific (S_Ni).

The availability of the meta cyclophanes (pyridinophanes) **1a,b** and **2a,b**, of known stereochemistry,[3] has prompted us to investigate in more detail the reactivity of side-chain substituents in these rigid systems. Models show that the back sides of the bridge methine carbon atoms in 1 and 2 are severely shielded to S_N2 reactions; furthermore, change in hybridization of these carbon atoms from sp^3 to sp^2, which might be expected for S_N1 type reactions, would not be favorable since such change in geometry would introduce additional strain into the tightly compacted and rather rigid methylene bridge. Lack of reactivity of such substituents was previously noted by the recovery of **1d** and **2d** unchanged from hot hydrobromic acid.[4]



1a, X = p-$CH_3C_6H_4SO_2O$
b, X = Br
c, X = H
d, X = OH
e, X = OC_2H_5
1f, X = $OCOCH_3$
g, X = $\mathrm{O}\underset{\substack{\| \\ \mathrm{O}}}{\mathrm{C}}\mathrm{H}$
h, X = OCH_3



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Reactions of *syn-* and *anti*-1-*p*-Toluenesulfonyloxy-12,13-benzo-16-chloro[10](2,4)pyridinophane (1a and 2a). A. With Formic Acid–Water. Reaction of the anti tosylate **2a** in the highly ionizing solvent 90% formic acid–water was slow, but was complete after 48 hr at the reflux temperature. The crude product, which contained only anti alcohol **2d** contaminated with anti formate **2g** (tlc and nmr), was hydrolyzed with potassium hydroxide in methanol to remove formate, and the product thus obtained was analyzed by tlc and by isolation of products. The only product formed (~100% by tlc, 79% by isolation) was anti alcohol **2d**; no syn alcohol **1d** and no more than possible trace quantities of reduced cyclophane **1c** were produced (tlc).

Similar results were obtained by reaction of the syn tosylate **1a** with 90% formic acid under the conditions described for **2a**. Conversion to **1d** (100% tlc, 87% isolated) occurred with complete reaction of configuration; tlc confirmed that no detectable quantities of the anti alcohol **2d** were produced.

Complete retention of configuration in these solvolysis reactions is consistent with two explanations: (A) ionization occurs to give carbonium ions or ion pairs which, owing to structural constraint, retain their stereochemistry during solvolysis, or (B) conversion of **1a** and **2a** to the corresponding alcohols occurs by acid-catalyzed solvolysis of the sulfur–oxygen bond.[5] While no unequivocal decision can be made at this time between these two alternatives, support for B was obtained by studies of the behavior of carbonium ions or ion pairs derived from the related syn and anti bromides **1b** and **2b**, which is discussed subsequently in this report.

B. With KOH–Methanol. The anti tosylate **2a** was quite stable to potassium hydroxide in methanol; after 20 hr at the reflux temperature only low conversion to product was observed. The only product present in the reaction mixture other than recovered **2a** was the anti alcohol **2d** (20%); no syn alcohol **1d** or ethers **1h** or **2h** were detected (tlc).

Similar results were obtained with the syn tosylate **1a**. Analysis of the mixture obtained after **1a** was treated for 24 hr at the reflux temperature with methanolic potassium hydroxide showed the presence of unchanged **1a** (61% recovery, pure) and syn alcohol **1d** (28% yield, pure); no anti alcohol **2d** or ethers were detected (tlc). It was significant to note that the recovered tosylate (63% recovery) from this reaction was pure **2a**, with no evidence for epimerization to **1a** which could occur through a possible carbanion intermediate at the methinyl carbon atom.[6]

Complete retention of configuration of the alcohols obtained from **1a** and **1b** confirmed that no S$_N$2 substitution occurred; the alcohols **1d** and **2d** were most likely formed by sulfur–oxygen bond cleavage.[7]

C. With Other Nucleophiles. It was apparent from B, above, that both S$_N$2 and/or E2 reactions of tosylates **1a** and **2a** must have high energies of activation, the former because of hindrance at C-1, and the latter because elimination would introduce two sp^2 carbon atoms into the strained system. This conclusion was further corroborated by the complete lack of reactivity (96% recovery after 30 hr) of both tosylates **1a** and **2a** with the strong nucleophile thiourea in hot 95% ethanol containing enough dioxane to ensure homogeneity. Reactions of undetermined nature could be effected with tosylates **1a** and **2a** with nucleophiles in aprotic solvents under severe conditions; however, even under drastic conditions the tosylates are remarkably unreactive. Thus, anti tosylate **2a** (0.53 mmol) was recovered largely unchanged (91%) after treatment with a solution of sodium cyanide (1.3 mmol) in dimethyl sulfoxide (10 ml) at 100° for 24 hr. Similarly, anti **2a** was recovered unchanged (>50%) after similar treatment at 100° for 48 hr.[8]

Reactions of *syn*- and *anti*-1-Bromo-12,13-benzo-16-chloro[10](2,4)pyridinophane (1b and 2b). A. With Nucleophiles. Reaction of syn bromide **1b**[9] under conditions normally employed to effect S$_N$2 or E2 reactions with ordinary alkyl halides corroborated the lack of reactivity observed for the tosylates **1a** and **1b**. Thus, **1b** was recovered largely unchanged (84% pure) after treatment with glacial acetic acid containing potassium acetate at the reflux temperature (20 hr). Furthermore, there was little or no reaction of **1b** with lithium chloride in hot (100°) dimethylformamide (16 hr, 86% recovery), or with thiourea in boiling 95% ethanol–dioxane (48 hr, 99% recovery). The reaction with sodium ethoxide in ethanol, which showed formation of a trace of product after 4 hr (tlc), was allowed to continue for 115 hr to give a mixture containing one major and two minor components. The major product, obtained pure in 71% yield, was not a substitution product, but rather the reduced cycophane **1c**.[10] The two minor products (~5 and 6%, respectively) had the same $R_f{}^3$ values as syn and anti ethers **1e** and **2e**, respectively; however, they were not further characterized.[11]

It is clear from these results, together with those described for the tosylates **1a** and **2a**, that bimolecular substitution and/or elimination reactions on carbon do not occur readily if at all in these cyclophane systems.

B. With Silver Acetate in Acetic Acid. The syn bromide **1b** reacted slowly with silver acetate in hot glacial acetic acid. The reaction was complete after 48 hr and the syn acetate **1f**, isolated as the alcohol (~100%), was the only product observed; careful analysis (tlc) showed that no anti alcohol was present. Similar results were obtained with the anti bromide **2b**; the only product formed was the anti acetate (isolated 74% yield).

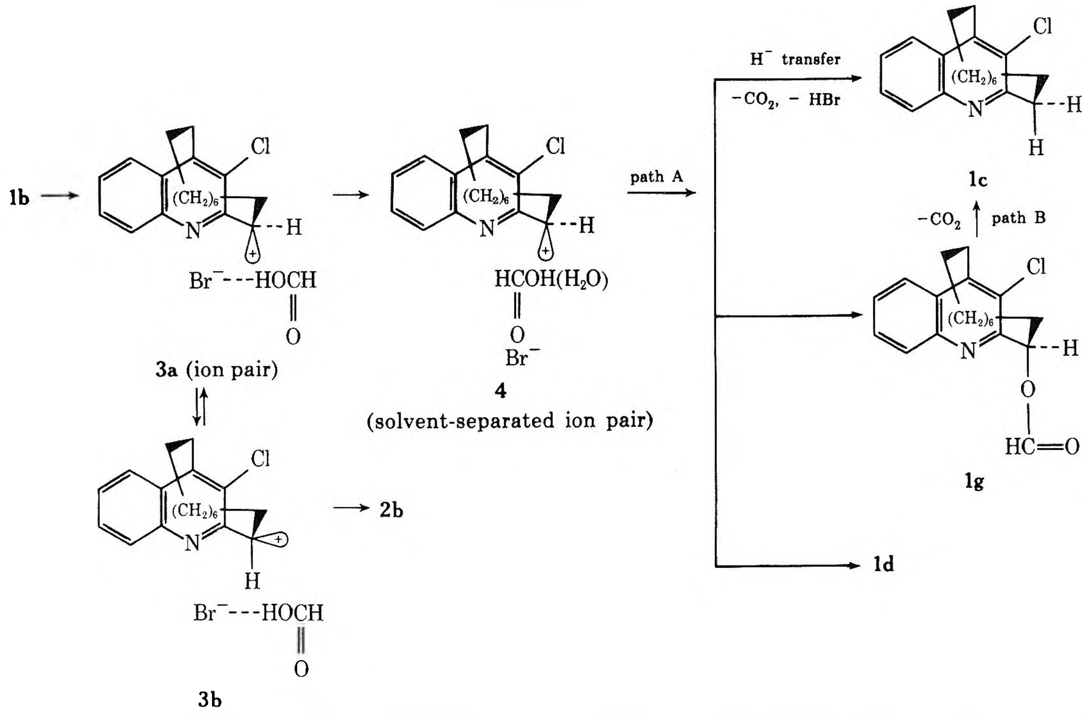
The complete stereospecificity of these reactions is consistent with the conclusion that the reactions are effectively concerted (S$_N$i) or that the ion pairs formed in these rigid systems have a high energy barrier to rehybridization.

C. With Formic Acid. The syn bromopyridinophane **1b** was observed to react slowly with hot formic acid (90%). The reaction, which was monitored by tlc, was quenched after 10 days. The resulting mixture contained two minor components (~2 wt % each) and three major components, which were identified as unchanged bromide (23%), reduced cyclophane **1c** (27% based on recovered **1b**), syn alcohol **1d** (60% based on recovered **1b**), and no more than a trace, if any, of anti alcohol. The recovered halide was mostly unchanged **1b**; however, both nmr and tlc indicated that some (~10% of bromide) epimeric bromide **2b** was present. We believe, at this time, that the reaction occurs by a process formally represented as shown in Scheme I. We tentatively suggest that the initial produce formed in this reaction is the tight ion pair **3a**, which can slowly rearrange to the epimeric ion **3b**; either **3a** or **3b** can collapse to regenerate halide (**1b** and **2b**, respectively). The solvolysis studies to be described subsequently with the anti bromide **2b** offer little support for a common planar carbonium ion derived from **1b** and **2b.**

The solvent-separated ion pair 4 (Scheme I) provides a logic for the formation of both **1c** and **1g** (or the alcohol **1d**). Formic acid is a good reducing agent[12] and either hydride transfer to **1c** or solvolysis to **1g** are reasonable paths.

An alternative route for the formation of reduced product **1c** would involve intramolecular hydride transfer from the formate as shown in **1g** (path B) of Scheme I; such reduction would be formally analogous to the Clarke–Eschweiler reaction.[13] If this alternative was the correct one, prolonged treatment of the syn and anti alcohols with hot formic acid, either with or without added hydrogen bromide, should lead to reduction in yield comparable to that observed during the formolysis of the syn bromide **1b**. This was not observed experimentally. Thus, reaction (240 hr) of syn alcohol **1d** with hot (130°) formic acid (90%) containing 1 equiv of hydrogen bromide gave a mixture of unchanged **1d** and syn formate **1g**; no reduction to **1c** or epimerization to **2d** occurred. Similar results were obtained with the anti alcohol **2d**; under the same conditions formate formation (**2g**) was observed but no more

Scheme I



than a possible trace of reduction to **1c** or epimerization to **1d** occurred. Reactions of syn and anti alcohols (240 hr) with hot (130°) formic acid (90%) in the absence of added mineral acid lead to mixtures of alcohols and formates, but to only low yields (~2% and 6% from **1d** and **2d**, respectively) of reduced product **1c**. The low yields of reduction to **1c** in these experiments are in sharp contrast to the relatively high yield of reduction noted during the formolysis of **1b**, an observation more consistent with path A than path B.

The reaction of the anti bromide **2b** with hot (130°) formic acid (90%) was much slower than with the syn bromide **1b** and gave significantly different results; after twice the reaction time used for **1b**, the product obtained from **2b** contained 28% unchanged **2b**, no more than a possible trace of syn bromide **1b**, 11% of anti alcohol **2d**, 36% of the epimeric syn alcohol **1d**, and 19% of reduced material **1c**.

The contrasting results obtained for the formolysis of syn and anti bromides **1b** and **2b** provides rather convincing evidence that a free planar carbonium ion is not involved as a common intermediate for formolysis of **1b** and **2b**. Clearly the ion pair **3b**, derived from **2b**, does not maintain its stereochemical identity, nor does the ion pair **3a**. The anti bromide **2b** is clearly more stable to solvolysis than the syn bromide **1a**. The product distribution, which favors formation of syn products, is consistent with the conclusion that either: (a) the rearrangement of halides **1b** and **2b**, presumably through **3a** ⇄ **3b**, favors formation **1b** (possibly for steric reasons), or (b) the equilibrium **3a** ⇄ **3b** favors **3a** (possibly due to the lone pair on nitrogen).

Attention should also be called to the product distribution obtained when the syn and anti alcohols **1d** and **2d** were treated for prolonged periods with hot (130°) formic acid (90%). Reaction of syn **1d** for 162 hr gave a mixture containing unchanged **1d** (91%), syn formate **1g** (5.5%), and a small amount of reduced pyridinophane **1c** (~2%). By contrast, reaction of anti alcohol **2d** for 240 hr gave a mixture containing unchanged **2d** (52%), anti formate **2g** (30%), **1g** (~6%), and epimeric alcohol **1d** (~10%). Thus, as in the solvolysis of the bromide **1b** and **2b**, the reaction of the anti alcohol with formic acid is slower than that with the syn isomer, and that syn products are favored.

An alternative explanation for the result described above for the solvolysis of bromides **1b** and **2b** in hot formic acid is that substitution is stereospecific and that isomerization **1b** ⇄ **2b** occurred by a thermal reaction involving rotation of the bridge to the other face of the aromatic ring rather than epimerization caused by carbon-bromine bond cleavage. However, available evidence does not support this possibility. If thermal isomerization was effecting product distribution then similar product distributions should be observed during solvolysis of both **1b** and **2b**. More compelling, however, is the observation that the hydrochloride salts of the alcohols **1d** and **2d** were stable and underwent no interconversion when heated in formic acid for extensive periods (10 days). In these cases carbon-oxygen bond cleavage (carbonium ion formation) is inhibited by the positively charged nitrogen atom; no chemically or thermally induced epimerization was observed.

That thermal isomerization of **1b** ⇄ **2b** was not occurring was also suggested by studies of the thermal behavior of **1b** and **2b** in boiling xylene (9 days, N_2 atmosphere). Both samples darkened appreciably which suggested thermal instability; however, the syn bromide was recovered in 82.3% yield; no epimerization to **2b** was observed (by nmr). The anti bromide **2b** was, however, completely destroyed by such treatment and the principal product formed (>50% yield) was reduced cyclophane **1c** (possibly formed by a radical process involving homolytic cleavage of the C–Br bond with subsequent abstraction of hydrogen from solvent). The crude product contained none of the stable epimeric bromide **1b**; consequently, there is no evidence for thermal equilibration of **1b** and **2b**.

Experimental Section

Analysis. By proper choice of conditions it is possible to analyze mixtures of most of the pyridinophanes by tlc on silica gel. Using petroleum ether (bp 60–90°) and ether (1:1) the following R_f values were observed: **1a** (0.34), **1b** (0.65), **1c** (0.57), **1d** (0.48), **1f** (0.40), **1g** (0.37), **2a** (0.37), **2b** (0.63), **2d** (0.16), **2f** (0.40), and **2g** (0.50). Using petroleum ether–ether (3:1) they were as follows: **1a** (0.14), **1b** (0.51), **1c** (0.38), **1d** (0.31), **1f** (0.21), **1g** (0.21), **2a** (0.15), **2b** (0.47), **2d** (0.05), **2f** (0.21), and **2g** (0.28). For those cases where tlc was not conclusive because of close R_f values (for example, syn and anti acetates **1f** and **2f**, anti formate **2g** and syn alcohol **1d**, and syn and anti tosylates **1a** and **2a**), differentiations were made on the basis of the characteristic[3] nmr spectrum of the methine proton on the bridge; syn acetate **1f** and anti acetate **2f** also showed sharp $CH_3C{=}O$ at δ 2.10 and 2.08, respectively.

Preparative separations were performed using Brinkman Silica Gel PF 254 (2 mm thick plates) with multiple evelopments using petroleum ether (bp 30–60°)–ether mixtures.

Reaction of syn tosylate 1a[3] (206 mg, 0.44 mmol) with formic acid (6 ml, 90%) was carried out for 48 hr at a pot temperature of 130°, after which the mixture was treated with methanol (40 ml) containing potassium hydroxide (6.2 g, 0.11 mol) for 4 hr at the reflux temperature. The mixture was diluted with water (40 ml) and extracted with chloroform. The nmr spectrum of the crude product (143.6 mg) obtained from the dried ($MgSO_4$) chloroform extract was identical with that of syn alcohol. The product was purified by preparative tlc. Pure syn alcohol **1d** (105.7 mg, 84% yield, mp and mmp 159–160°) was obtained; no detectable quantities of other products were noted.

Reaction of anti tosylate 2a (193.2 mg) with formic acid under identical conditions gave 130 mg (100% yield) of **2d** (mp and mmp 204–206°).

Reaction of syn tosylate 1a[3] (180 mg, 0.38 mmol) with potassium hydroxide (174 mg, 3.1 mmol) in boiling methanol (10 ml) was monitored by tlc. Reaction was quite slow and after 4 hr little reaction was noted. After 24 hr the mixture showed two components which were separated by tlc, subsequent to removal of solvent and extraction with chloroform, into recovered **1a** (61% pure) and syn alcohol **1d** (28%, pure); no detectable quantities of **2d** were formed.

Reaction of anti tosylate 2a[3] (193 mg) with potassium hydroxide in methanol was carried out as described for **1a** with similar results. After 20 hr there was obtained recovered **2a** (61% yield pure, subsequent to preparative tlc and recrystallizatiion) and anti **2d** (20% yield); no detectable quantity of syn **1a** was formed.

Reaction of tosylates 1a and 2a (0.43 mmol) with thiourea (0.80 mmol) was carried out in 95% ethanol (3 ml) and dioxane (3 ml) for 30 hr at the reflux temperature. Only unchanged reactants were detected (tlc) and recovered.

Reaction of syn bromide 4b (890 mg, 2.3 mmol) with potassium acetate (1.00 g, 10 mmol) in acetic acid (20 ml) was carried out for 10 hr at 117°. The mixture was diluted with water and extracted with ether, and the ether extract was washed with aqueous sodium bicarbonate (10%) and water. The dried ($MgSO_4$) ether extract was concentrated to give recovered **1b** (84% pure, mp and mmp 147–148°).

Reaction of syn bromide 4b (0.51 g, 1.3 mmol) with sodium ethoxide in ethanol [prepared from sodium (0.413 g, 18 mg-atoms) and ethanol (10 ml)] was maintained at the reflux temperature for 115 hr and then excess alcohol was removed (rotary evaporator). The residue was diluted with ether and the ether was washed with water and dried ($MgSO_4$). The residue (444 mg) obtained from the ether was analyzed by preparative tlc. Five fractions were noted. The principal product (71% yield, mp and mmp 78–81° [3]) was reduced cyclophane **1c.** Two other fractions obtained in low yield (~6% and 4.5% yields, respectively) had the same R_f value as authentic **1e** and **2e**; however, no further attempt to characerize these products was made.

Reaction of syn bromide 1b (276 mg, 1.64 mmol) with silver acetate (1.64 mmol) was carried out under nitrogen in boiling glacial acetic acid (11 ml) for 20 hr. The mixture was filtered and the filtrate was diluted with water, neutralized, and extracted with chloroform. The yellow oil obtained from the filtrate was heated with potassium hydroxide (2.5 g) in methanol (100 ml) for 8 hr at reflux to hydrolyze the ester. The slightly impure syn **1d** (~100% yield) was recrystallized from chloroform–petroleum ether (bp 60–80°) to give pure **1d** (134 mg, 49% yield, mp and mmp 160–163°). Analysis of the mother liquor by tlc showed only one spot corresponding to **1d**; no **2d** could be detected.

Reaction of anti bromide 2b with silver acetate was carried out for 22 hr as described for **1b.** The reaction mixture was then treated with saturated NaCl solution, cooled, and filtered, and the salts were washed with ether. The filtrate was extracted with 5% KOH to remove acetic acid, and the ether solution was then extracted with saturated ammonium chloride and dried ($MgSO_4$). The ether was evaporated (*in vacuo*) to give 73.7 mg of a white solid, which showed only anti acetate **2f** by nmr (a single methyl resonance at δ 2.08; the syn acetate **1f** shows resonance at δ 2.10). Recrystallization of this product from ligroin gave 46.1 mg (74% yield) of syn acetate, mp 143–144°, mmp 145–146°. Examination of the mother liquor by nmr showed a single methyl resonance at δ 2.08.

Reaction of syn bromide 1b (0.525 mmol) with formic acid (5 ml, 90%) was carried out for 10 days at a pot temperature of 130°. The cooled mixture was diluted with water (10 ml) and extracted with chloroform. The organic extract was washed successively with saturated sodium bicarbonate and with water (10 ml). Preparative tlc [silica gel developed three times with petroleum ether (bp 30–60°)–ether (6:1)] showed three major components and two minor components (~2% by weight each). The major components were syn alcohol **1d** (22% based on recovered bromide, mp 152–153°, mmp[3] 153–156°), reduced cyclophane **1c** (20% based on recovered bromide, mp and mmp 80–81°), and recovered bromide (34.6%, mp 140–141°). Examination of the nmr spectrum of recovered bromide confirmed the presence of about 10% epimeric bromide **2b.**

The anti bromide 2b was prepared by the reaction of 12,13-benzo-14-oxo-16-chloro[10](2,4)pyridinophane (1.59 g, 5.00 mmol) with 25 ml of refluxing acetyl bromide (protected by $CaSO_4$ drying tube) for 6 hr. Excess acetyl bromide was then removed by distillation. The residue was dissolved in chloroform (25 ml) and washed with saturated $NaHCO_3$ (15 ml) and water (15 ml). The dried (Na_2SO_4) chloroform solution was concentrated (*in vacuo*), yielding 2.1 g of a viscous yellow oil. Column chromatography on neutral alumina step gradient eluted with petroleum ether–ether gave two major fracions listed in order of increasing R_f: (1) 1.00 g, (55.6%), a mixture of syn and anti acetates **1f** and **2f**; (2) 0.68 g (35.8%), a mixture of bromides. Preparative tlc of these bromides showed four principal bands. The band with highest R_f was syn bromide **1b**, 42.5 mg, mp and mmp 145–146°. The next highest fraction was the anti 1-bromide: 181.5 mg (9.5%); mp 152–153° (from $CHCl_3$–petroleum ether); nmr ($CDCl_3$) δ 8.14–7.50 (m, 4, aromatic H), 5.42 (q, X portion of ABX, $J_{AX} + J_{BX} = 17$ Hz, 1, CHBr), 3.80–3.04 (m, 3, benzylic CH_2 plus H from bridge), and 2.54 to −0.30 (m, 15, bridge H).

Anal. Calcd for $C_{19}H_{23}NClBr$: C, 59.93; H, 6.08; N, 3.67. Found: 60.11; H, 5.96; N, 3.50.

Evidence for assignment of anti stereochemistry was obtained as previously reported.[3]

The two other fractions (70 and 193 mg, respectively) were not characterized.

Reaction of anti bromide 2b with formic acid (90%) was carried out as described for **1b.** The reaction was monitored by tlc and was much slower than that observed for **1b.** The reaction was continued for 20 days and resolved by preparative tlc [silica gel developed twice with petroleum ether–ether (4:1)]. There was obtained in order of increasing R_f (1) anti alcohol **2d** (11% based on recovered halide, mp and mmp 201–203°); (2) trace (not processed); (3) syn alcohol **1d** (~36% based on recovered halide, mp and mmp 154–165°); (4) a mixture which was resolved by subsequent chromatography [silica gel PF 254 using petroleum ether (bp 30–60°)–ether (9:1)] into reduced **1c** (19% based on recovered halide, mp 79.5–80°, mmp 81–82.5°) and pure anti bromide **2b** (14%, mp 147–149°); and (5) nearly pure anti bromide **2b** (mp 141–145°, combined recovery 27%). The nmr spectrum of this fraction showed[3] no more than a trace of syn bromide **1b.**

Reaction of Syn Alcohol 1d with Formic Acid. The syn alcohol **1d** (300 mg, 0.946 mmol) was heated (pot at 130°) in formic acid (15 ml, 90%) for 162 hr and the mixture was then cooled, poured into water (50 ml), and extracted with chloroform (40 ml total). The chloroform extract was washed with saturated sodium bicarbonate and then with water and was dried (Na_2SO_4) and concentrated to a yellow solid (306 mg, mp 149–153°). This solid was recrystallized [chloroform–petroleum ether (bp 60–90°)] to give 230 mg (76.5% recovery) of pure (tlc, nmr, mp 156–157°) recovered syn alcohol **1d.** The mother liquor was purified by preparative tlc [silica gel developed four times with petroleum ether (bp 30–60°)–ether (4:1)] to give three fractions.

The band of lowest R_f (19.4 mg, 5.5%) was recrystallized with little loss from petroleum ether to give *syn*-1-formyloxy-12,13-benzo-16-chloro[10](2,4)pyridinophane (**1g**): mp 122–122.5°; nmr ($CDCl_3$) δ 8.15 (s, 1, O_2CH), 8.10–7.40 (m, 4, aromatic H), 6.60 (q, X portion of ABX, $J_{AX} + J_{BX} = 14$ Hz, 1, CHOCHO), 3.60–3.15 (m, 2, benzylic CH_2), 2.6–0.2 (m, ~16 H, bridge CH_2); ir (KBr) $\nu_{C=O}$ 1740 cm^{-1}, ν_{C-H} 2880 cm^{-1}, ν_{C-O} 1170 cm^{-1}.

Anal. Calcd for $C_{20}H_{24}NO_2Cl$: C, 69.45; H, 6.99; N, 4.05. Found: C, 69.65; H, 6.75; N, 4.03.

The second fraction (42.1 mg) was recovered **1d** (total recovery 91%). The third fraction (5 mg, 2% yield), obtained as an oil, crystallized (mp 74–76°) and was shown to be pyridinophane **1c** by conversion to the picrate (mp and mmp[4b] 172–173°).

Reaction of anti alcohol 2d with formic acid was carried out as described for **1d.** The mother liquor obtained subsequent to removal of some pure recovered **2d** (32%, mp 204–204.5°) by recrystallization from chloroform–petroleum ether (bp 60–90°) was chromatographed on a preparative plate [silica gel PF254 developed with petroleum ether (bp 30-60°)-ether (2:1)] to give two fractions in addition to additional pure **2d** (total recovery 52%).

The first of these was a mixture (nmr)[3] of syn alcohol **1d** (~10% yield by nmr) and anti formate **2g** (30% yield) which have nearly identical R_f values. The anti formate, which was unknown, was purified by recrystallization of this mixture from chloroform-petroleum ether (bp 60-90°): nmr ($CDCl_3$) δ 8.19 (1, s, O_2CH), 8.19-7.58 (4, m, aromatic H), 6.23 (1, X portion of ABX, $J_{AX} + J_{BX}$ = 16 Hz, q, CHO_2CH), 3.75-0 (broad m, 18, bridge CH_2).

Anal. Calcd for $C_{20}H_{24}NO_2Cl$: C, 69.45; H, 6.99; N, 4.05. Found: C, 69.68; H, 7.01; N, 4.04.

The mother liquor from this recrystallization contained (tlc and nmr) syn alcohol **1d**, anti formate **1d**, and trace amounts of another material assumed to be syn formate **1g**.

The other fraction (5.5 mg, 6% yield) was reduced pyridinophane **1c** (mp and mmp[4b] of picrate 173-174°).

Thermal Stability of Syn and Anti Bromides (1b and 2b). **A.** A solution of syn **1b** (50.5 mg, 0.133 mmol) in xylene (ACS grade, 0.5 ml) was heated at the reflux temperature under nitrogen for 220 hr. Xylene was removed (*in vacuo*) from the brown, tarry mixture; the residue showed (nmr) unchanged **2a** (δ 6.06) and no epimer **2b** (δ 5.42). The sample was dissolved in chloroform and washed with dilute sodium bicarbonate and the product was recrystallized from petroleum ether to give 41.6 mg (82.3% recovery) of **2a**, mp 141-142°, mmp 143-144° with material melting at 144-145°.

B. A sample of anti **2b** (65.8 mg, 0.173 mmol) was treated in xylene as described above. The nmr spectrum of the crude product showed no **2b** (δ 5.42) or **2a** (δ 6.06) and was quite similar to that of **1c**. The product was decolorized as above and purified by preparative tlc [silica gel, petroleum ether-ether (3:1)] to give 26 mg (50% yield) of **1c** (mp and mmp 78-79°).

Registry No. 1a, 37781-25-2; **1b**, 25859-37-4; **1d**, 25866-36-8; **1g**, 42880-43-3; **2a**, 37781-31-0; **2b**, 42880-45-5; **2d**, 25907-82-8; **2g**, 42962-81-2.

References and Notes

(1) Support by the National Science Foundation, Grant GP 35429.

(2) Address correspondence to Paul Gross Chemical Laboratory, Duke University, Durham, N. C. 27706.

(3) W. E. Parham, K. B. Sloan, K. R. Reddy, and P. Olson, *J. Org. Chem.*, **38**, 927 (1973).

(4) (a) W. E. Parham, K. B. Sloan, and J. B. Biasotti, *Tetrahedron*, **27**, 5767 (1971); (b) W. E. Parham, R. W. Davenport, and J. B. Biasotti, *J. Org. Chem.*, **35**, 3775 (1970).

(5) Alkylsulfonates normally undergo carbon-oxygen scission under these conditions; the authors are unaware of related acid-catalyzed S-O bond cleavage.

(6) 2- and 4-methylpyridines undergo hydrogen-deuterium interchange on the methyl group, presumably through a carbanion intermediate, under rather mild conditions; *cf.* K. Schofield, "Hetero-Aromatic Nitrogen Compounds," Butterworths, London, 1967, pp 324-327, and references cited therein.

(7) Sulfur-oxygen bond cleavage of alkylsulfonates by base is uncommon, since substitution or elimination at carbon generally occurs. However, arylsulfonates readily undergo S-O bond cleavage by nucleophiles: *cf.* W. D. Closson and P. Wriede, *J. Amer. Chem. Soc.*, **88**, 1581 (1966).

(8) Reactions of **1a** and **1b** with KBr in hot dimethylformamide and in dimethyl sulfoxide were also studied with similar results. The principal products were unchanged starting materials along with complex mixtures which were not examined.

(9) In view of the parallel in reactivity of tosylates **1a** and **2a**, coupled with the fact that the anti bromide **2b** is difficult to obtain in quantity, only selected reactions of both epimers **1b** and **2b** were carried out.

(10) Reduction of alkyl halide by *strong* base is *uncommon* but not unknown. Iodoform, for example, is reduced to methylene iodide by base, and the reaction is thought to involve nucleophilic attack at halogen; *cf.* S. Bagnara, *Eng. Mining J.-Press*, **116**, 51 (1923).

(11) Reduction of aryl halides by alkoxide is well known; *cf.* J. F. Bunnet and R. R. Victor, *J. Amer. Chem. Soc.*, **90**, 810 (1968). Formation of low yields of syn and anti ethers under these drastic conditions is not interpreted as evidence for SN2 reactions, since a variety of routes can be postulated for their formation.

(12) Triphenylcarbinol, for example, is efficiently reduced to triphenylmethane; *cf.* H. Kauffmann and P. Pannwitz, *Chem. Ber.*, **45**, 766 (1912).

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Nitration and Bromination of Isocytosine-6-acetic Acid. Some Corrections[1]

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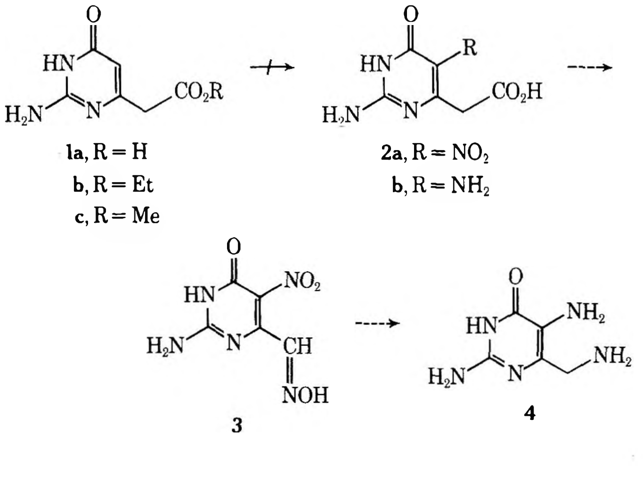
The reported nitration and bromination of isocytosine-6-acetic acid (**1a**) was reinvestigated. Under nitration conditions, oxidation of **1a** occurred to give isocytosine-6-carboxylic acid (**12a**), instead of the reported 5-nitroisocytosine-6-acetic acid (**2a**). Consequently, the reported reduction of **2a** to 5-aminoisocytosine-6-acetic acid (**2b**) may not have occurred. The nitrosation of **1a** produced 6-hydroxyiminomethylisocytosine (**11**), which could also be oxidized to **12a** by nitric acid. By a modification of the reported preparation of **1a**, the direct preparation of ethyl isocytosine-6-acetate (**1b**) was accomplished. Bromination of **1a** at room temperature gave 5-bromoisocytosine-6-acetic acid (**13**) hydrobromide. However, the reported **13** could not be obtained without decarboxylation of **13** to 5-bromo-6-methylisocytosine (**14**). Bromination of **1a** could also be controlled to give di- and tribromo derivatives of **14**.

The preparation of 5-nitroisocytosine-6-acetic acid[2] (**2a**) and the subsequent reduction to 5-aminoisocytosine-6-acetic acid[3] (**2b**) had been reported by Worrall. We desired **2a** as a precursor for 5-amino-6-aminomethylisocytosine (**4**, Scheme I) which we had intended to use as the key intermediate in an improved synthesis of an isomer of ethyl pteroate.[4] Consequently, our isolation of the product from our attempted nitration of **1a** other than the reported **2a** was quite disappointing. We report here our reinvestigation of the nitration of isocytosine-6-acetic acid (**1a**), as well as its bromination as reported by Worrall.[2,3]

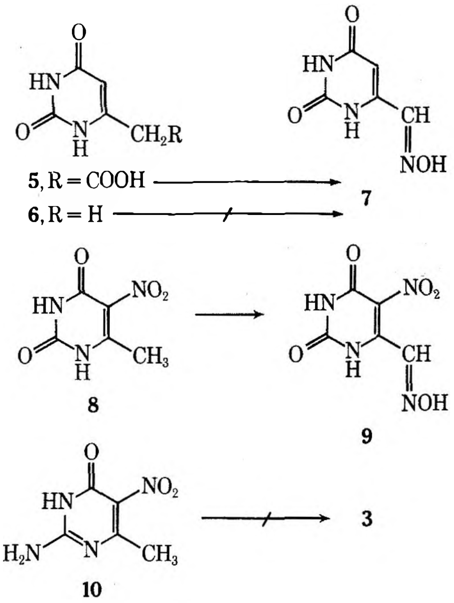
The selection of this mode of preparation of **4** was based on similar reactions on pyrimidine substrates of slightly different structures (see Scheme II). Uracil-6-acetic acid (**5**) had been shown to nitrosate and spontaneously decarboxylate to give **7**.[5] Similarly, the 6-methyl group activated by the 5-nitro group of 5-nitrouracil (**8**) could also be

Scheme I



nitrosated to give **9**, while nitrosation of 6-methyuracil (**6**) had failed.[6] The known deactivating effect of a 2-amino group was sufficient to prevent our attempted nitrosation of 5-nitro-6-methylisocytosine (**10**) under the same conditions ($\mathbf{10} \nrightarrow \mathbf{3}$). However, we hoped that the combined activating effects of the 5-nitro and the carboxyl groups would overcome the deactivating effect of the 2-amino group and permit the nitrosation and decarboxylation of **2a** to obtain **3**. Subsequent reduction of **3** would afford **4**.

Scheme II



We prepared **1a** from diethyl acetonedicarboxylate with 2 equiv of guanidine by Worrall's procedure.[2,3] We also found that, by using only 1 equiv of guanidine, the ethyl ester **1b** was easily obtained.

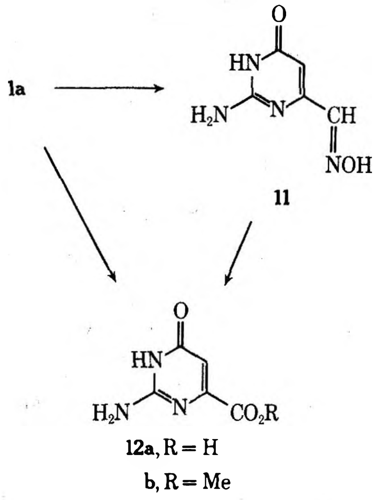
The nitration of **1a** was carefully performed according to the procedure of Worrall (70% nitric acid at 70°).[2] Although the nmr of the isolated material showed several new peaks, the bulk of this material was the starting acid **1a**.[7]

The nitration procedure of Wempen, *et al.*[8] (concentrated sulfuric acid and potassium nitrate), which we had successfully used to prepare **10**, was applied to **1a** and we obtained a new product A, free of starting material. The highest mass of significance in the mass spectrum was *m/e* 155, with the parent peak at *m/e* 44 (CO_2). Repeated attempts to obtain a reasonable analysis were unsuccessful. Attempts to calculate an empirical formula from the obtained analysis gave carbon to nitrogen ratios between 6:4 and 5:3. The ir of A indicated that a carboxylic acid was still present, as had the mass spectrum.

Some nitrations are known to proceed by nitrosation, followed by oxidation of the nitroso group to the nitro group.[9] The procedure of Wempen employed in the "nitration" of **1a** was repeated in a modified manner; the addition of 1 equiv of potassium nitrate to the sulfuric acid solution of **1a** was preceded by the addition of 1 equiv of potassium nitrite. The yield of A increased from 24 to 56%.

Concurrently we had nitrosated **1a** in dilute acid and had obtained 6-hydroxyiminomethylisocytosine (**11**) hydrochloride (Scheme III). This identity was also confirmed by the synthesis of **11**·HCl from 6-diethoxymethylisocytosine.[10] Since nitrosation had strongly been implicated in the preparation of A, we subjected **11** to the "nitration" conditions and indeed obtained A. This reaction established the number of carbons in A at five, and the crude analysis obtained had suggested a possible 5:3 carbon to nitrogen ratio. This and the ir and mass spectral data mentioned earlier suggested the product to be isocytosine-6-carboxylic acid (**12a**). Comparison of the physical properties of A and its methyl ester (**12b**) with authentic samples confirmed this identity. That our product A was **12a**, rather than 5-nitroisocytosine-6-carboxylic acid, was consistent with Shepard's unsuccessful attempts to nitrate **12a**.[11]

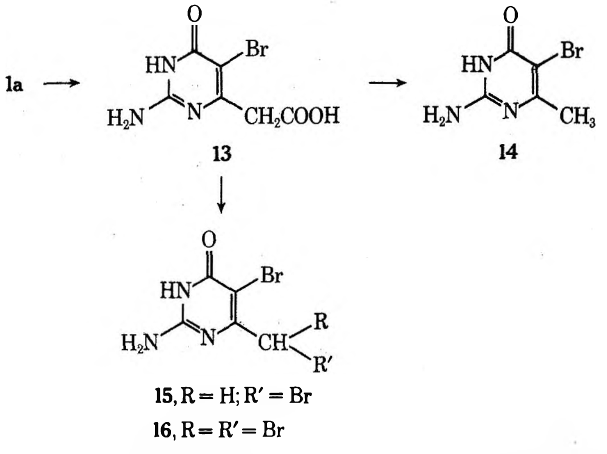
Scheme III



Worrall also had reported[3] the reduction of the alleged nitro acid **2a** to 5-aminoisocytosine-6-acetic acid (**2b**) (*Anal.* Calcd for $C_6H_8N_4O_3$: C, 39.1; H, 4.3. Found: C, 38.7; H, 4.5.). However, since it is unlikely that he prepared **2a**, perhaps he subjected an impure sample of **12a** to the reduction conditions and recovered a purified **12a** (*Anal.* Calcd for $C_5H_5N_3O_3$: C, 38.72; H, 3.25.). Thus it would seem that Worrall's reported **2b** was actually **12a**, and that **2b** has not yet been prepared.

The bromination of **1a** had also been reported by Worrall[3] to produce 5-bromoisocytosine-6-acetic acid (**13**) hydrobromide (Scheme IV) as well as the hydrobromide-free **13** after treatment with base and repeated recrystallization to avoid a high bromine analysis. We found that, even in the presence of 3 equiv of bromine, monobromination occurred quickly at room temperature in acetic acid. Dilution of the reaction mixture with acetone removed the excess bromine and an analytically pure **13** · HBr precipitated. We were unable to obtain pure **13** by neutralizing the hydrobromide. Nmr indicated that the decarboxylation easily occurred at room temperature and we apparently obtained a mixture of **13** and 5-bromo-6-methylisocytosine (**14**). We also obtained the decarboxylated dibromo and tribromo derivatives, **15** and **16**, in refluxing ace-

Scheme IV



tic acid in low yields; however, no attempt was made to maximize the yields. Keana and Mason have recently prepared several mono-, di-, and trihalo derivatives of the 2-acetyl derivative of **1c**.[12]

Experimental Section

The elemental analyses were carried out by Micro-Tech Laboratories, Skokie, Ill. Samples were dried *in vacuo* at 100° over phosphorus pentoxide. Melting points were taken on a Fisher-Johns melting point apparatus or in sealed capillaries on an aluminum block, and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 257 grating infrared spectrophotometer and calibrated with reference to polystyrene peaks at 3027 and 1601 cm^{-1}. Nmr spectra were determined on a Varian Model A-60 spectrometer or on a Jeol Model JNM-C60HL spectrometer, employing TMS as internal reference.[13,15] Low-resolution mass spectra were obtained on a Hitachi RMU-62 mass spectrometer. The high-resolution mass spectrum was determined on a AEI MS 902 mass spectrometer at The Research Triangle Center for Mass Spectrometry, Research Triangle Park, N. C., supported under Grant RP-330 from the Biotechnology Resources Branch of the Division of Research Resources of the National Institutes of Health.

Isocytosine-6-acetic acid (1a).[2,3] Diethyl acetonedicarboxylate and 2 equiv of guanidine carbonate were condensed according to Worrall[2,3] to obtain **1a** in 44% yield. For analysis, a sample was recrystallized once from water: mp (sealed capillary) frothing at 185–190°, remelts at 295–300° (same as 6-methylisocytosine); ir (KBr) 3475, 3400–2500 (broad), 1710, 1660 cm^{-1} (sh); nmr (TFA) τ 6.50 (s, 2, CH_2), 3.67 (s, 1, H-5), 1.88 (s, 2, NH_2); mass spectrum (70 eV), *m/e* (rel intensity) 125 (73), 97 (13), 96 (7), 84 (15), 68 (7), 44 (100), 43 (14), 42 (10). With the exception of *m/e* 44, the spectrum is identical with that of 6-methylisocytosine.

Anal. Calcd for $C_6H_7N_3O_3 \cdot H_2O$: C, 38.51; H, 4.85; N, 22.45. Found: C, 38.15: H, 4.95; N, 22.63.

Ethyl Isocytosine-6-acetate (1b). This was prepared in the same manner as **1a**, except that only 1 equiv of guanidine carbonate was employed. For analysis, a 10-g sample was stirred at room temperature for 1 hr with 200 ml of water, recovering, after drying, 5.1 g of pure **1b**: mp 178° dec (frothing); ir (KBr) 1727, 1687–1605 cm^{-1}; nmr (DMSO-d_6) τ 8.80 (t, 3, J = 7 Hz, $\mathbf{CH_3}CH_2O$), 6.60 (s, 2, CH_2CO_2), 5.85 (q, 2, J = 7 Hz, $CH_3\mathbf{CH_2}O$), 4.45 (s, 1, H-5), 2.7 and 3.1 (two broad overlapping singlets, 3, NH_2, possibly some guanidine impurity, analysis shows high nitrogen). On addition of D_2O, the peaks at 2.7 and 3.1 disappear immediately, while the methylene protons at τ 6.6 exchange more slowly.

Anal. Calcd for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.80; H, 5.56; N, 21.83.

5-Nitro-6-methylisocytosine (10). Wempen's procedure[8] for the nitration of monooxopyrimidines was adapted for the preparation of **10**. Addition of 4.3 g (0.043 mol) of potassium nitrate to a suspension of 5.36 g (0.043 mol) of 6-methylisocytosine in 40 ml of concentrated sulfuric acid produced a rapid temperature rise to 80–100°. After cooling to room temperature, the acid solution was carefully poured into 1500 ml of rapidly stirred ether. The ether was decanted and fresh ether was added; this sequence was repeated twice. The precipitated pyrimidine salt was dissolved in 200 ml of water and made basic with 50% sodium hydroxide, and the solution was cooled in an ice bath. Any precipitate was collected and discarded. Acidification with acetic acid precipitated the product, which after drying at room temperature yielded 5.4 g (67%) of **10** · H_2O, mp >300°.

Anal. Calcd for $C_5H_6N_4O_3 \cdot H_2O$: C, 31.92; H, 4.29: N, 29.78. Found: C, 31.61; H, 4.22; N, 30.61.

If **10** · H_2O is dried at 100°, or stirred in glacial acetic acid overnight, water of hydration is lost. The analytical sample below was stirred with glacial acetic acid, filtered, and dried at 100°, nmr (DMSO-d_6) τ 7.70 (s, 3, CH_3), 2.5 (broad s, 2, NH_2).

Anal. Calcd for $C_5H_6N_4O_3$: C, 35.30; H, 3.55; N, 32.93. Found: C, 34.31; H, 3.47; N, 33.33.

Attempted Preparation of 5-Nitro-6-hydroxyiminomethylisocytosine (3). Attempted nitrosation in acetic or formic acid by the procedure of Davis, *et al.*,[6] resulted in only the recovery of starting material. However, a suspension of 0.85 g (5.0 mmol) of **10** in 10 ml of 8 *N* perchloric acid, followed by addition of 0.345 g (5.0 mmol) of sodium nitrite in 2 ml of water, produces a vigorous exothermic reaction. The reaction mixture was immediately cooled. A small amount of a light yellow precipitate was collected. This was dissolved in a few ml of water, made basic with concentrated ammonium hydroxide, and acidified with acetic acid. There was no immediate precipitate, but crystals did form after several days. Yellow crystals (30 mg) were thus collected. From the above filtrate, 0.35 g of starting material was recovered. After drying, the yellow crystals (sealed capillary) decomposed at *ca.* 181°: ir (KBr) very sharp spectrum, 3402 (s), 3380 (s), 3265 (m), 3242 (m), 1701 (m), 1682 (m), 1660 (m), 1575 (m), 1528 (m), 1482 (m), 1455 (m), 1410 (m), 1370 (m) 1260 (s), 1225 (m), 1142 (m), 1085 (m), 892 (w), 810 (w), 778 (w), 760 (w), 725 cm^{-1} (w); mass spectrum, sample decomposes.

Anal. Found: C, 19.14, 19.06; H, 2.55, 2.68; N, 36.74, 36.17.

The extremely high proportion of nitrogen and oxygen indicated that this was other than the desired product **3**. This material could probably be prepared in good yield by increasing the nitrite ratio; however, *the explosive nature of the reaction mixture and/or product should be considered.*

Attempted Nitration of Isocytosine-6-acetic Acid (1a). A. By the Procedure of Worrall.[2] **1a** ("guanidine salt") (0.7 g) prepared by Worrall's procedure was added in small amounts to 4 ml of 70% nitric acid and warmed to 70° for 0.5 hr. No precipitation of six-sided plates (or any precipitate) was observed. The mixture was poured into five volumes of water; no precipitate was observed. Ammonium hydroxide was employed to adjust the pH to 7, followed by addition of acetic acid. Crystals formed slowly over a weekend. After drying, 0.120 g of white needles were obtained. Nmr (TFA) showed that this was predominately starting material.

B. With Potassium Nitrate in Concentrated Sulfuric Acid. The procedure of Wempen, *et al.*[8] was used. **1a** (4 g, 0.022 mol) was dissolved in 20 ml of concentrated sulfuric acid. Upon addition of 2.15 g (0.0215 mol) of potassium nitrate, a vigorous exothermic reaction occurred. After cooling, the sulfuric acid solution was poured into 800 ml of ether. The ether was decanted and the residue was washed with fresh ether several times. The yellow solid was dissolved in 200 ml of water, 50% sodium hydroxide was added until the solution was alkaline, and acetic acid was added to precipitate the product. After drying, 0.820 g (24%) of product A subsequently identified as isocytosine-6-carboxylic acid (**12a**) was obtained.

C. With Potassium Nitrite and Potassium Nitrate in Concentrated Sulfuric Acid. Procedure B was followed carefully, with the exception that 1.85 g (0.0215 mol) of potassium nitrite was added, immediately followed by the addition of the potassium nitrate. The product A weighed 1.87 g (56%).

The products A from procedures B and C above were identical and also identical with the product obtained by the attempted nitration of 6-hydroxyiminomethylisocytosine (**11**). The physical data and proof of structure for A as isocytosine-6-carboxylic acid (**12a**) are given below with that procedure.

Nitrosation of Isocytosine-6-acetic Acid (1a) to Prepare 6-Hydroxyiminomethylisocytosine (11). Cautiously, 4.00 g (0.058 mol) of sodium nitrite was added to 8.95 g (0.050 mol) of **1a** in 50 ml of 3 *M* hydrochloric acid. The solution was heated on a steam bath for 30 min. After standing overnight, the product was collected and dried to give 5.20 g (55%) of **11** · HCl: ir (KBr) 3400, 1680, 1670, 986 cm^{-1} (characteristic of hydroxyiminomethylpyrimidines); nmr (DMSO-d_6) τ 3.60 (s, 1, 5-H), 1.92 (s, 1, CH=N), 1.34 (broad s, 2, NH_2), −2.75 (very broad singlet, probably a combination of some or all of the labile NOH, N-3 H, and N-1 H^+ hydrogens).

Anal. Calcd for $C_5H_6N_4O_2 \cdot HCl$: C, 31.51; H, 3.70; N, 29.40. Found: C, 31.41; H, 3.63; N, 28.54.

The free base **11** was obtained by dissolving **11** · HCl in water, adjusting the pH to 8 with potassium carbonate, and collecting the precipitate: ir (KBr) 3420, 1700–1655, 995 cm^{-1}; nmr (DMSO-d_6) τ 4.20 (s, 1, 5-H), 3.20 (broad s, 2, NH_2), 2.30 (s, 1, CH=N), −1.7 (broad s, 1, NOH).

The products obtained by the above procedure were also prepared from 6-diethoxymethylisocytosine[16] by the procedure of Bedenbaugh,[10] *via* the reaction of isocytosine-6-carboxaldehyde hydrochloride with hydroxylamine hydrochloride.

Attempted Nitration of 6-Hydroxyiminomethylisocytosine (11). Preparation of Isocytosine-6-carboxylic Acid (12a). The oxime **11** (1.65 g, 0.0107 mol) was dissolved in 10 ml of sulfuric acid. After addition of 1.07 g (0.0107 mol) of potassium nitrate, the mixture was heated at 100° for 30 min. After cooling, the solution was poured into ether, the ether was decanted, and the residue was triturated with fresh ether. The residue was made basic with 50% sodium hydroxide, and the product was precipitated with acetic acid. After drying at 100°, 0.35 g of isocytosine-6-carboxylic acid (**12a**) was obtained: mp >300°; ir (KBr) 1685 cm^{-1};

mass spectrum (70 eV) *m/e* (rel intensity) 155 (7), 111 (20), 44 (100), 43 (86).

Anal. Calcd for $C_5H_5N_3O_3$: C, 38.72; H, 3.25; N, 27.09. Found: C, 37.44; H, 3.40; N, 27.35.

A sample of authentic methyl isocytosine-6-carboxylate (**12b**) prepared in this laboratory by Shepard[11] was hydrolyzed at room temperature with 0.1 *M* potassium hydroxide. The ir and mass spectra of this acid were identical with those reported above, obtained from the oxime **11**. The sample is insoluble in most standard solvents for nmr.

However, since the analysis of the product from the acid **1a**, and the oxime **11**, was not acceptable, 10 g of the product prepared by the above method from the oxime was esterified with 400 ml of absolute methanol containing 35 ml of sulfuric acid according to Shepard's procedure.[11] The solution volume was reduced to about 100 ml by rotary evaporation and the solution was diluted with an equal volume of water. Careful adjustment to pH 6 with ammonium hydroxide resulted in precipitation of the product. Recrystallization from DMF-water afforded 3.34 g (28%) of a light brown powder. A second recrystallization, preceded by treatment with activated charcoal, produced 2.47 g of cream needles of methyl isocytosine-6-carboxylate (**12b**), mp >270° dec, principally 290–300° (lit.[11] mp 293–294° dec). The ir and nmr spectra were identical with those of the authentic sample of **12b** prepared by Shepard:[11] ir (KBr) 2910, 2755, 1750, 1665, 1590, 1560, 1495, 1445, 1395, cm^{-1}; nmr (TFA) τ 5.86 (s, 3, CH_3), 3.07 (s, 1, 5-H), 1.84 (br s, 2, NH_2); mass spectrum (70 eV) *m/e* (rel intensity) 169 (49), 154 (4), 139 (11), 138 (8), 137 (4), 112 (9), 111 (100), 110 (25).

Anal. Calcd for $C_6H_7N_3O_3$: C, 42.61; H, 4.17; N, 24.84. Found: C, 42.64; H, 4.20; N, 25.14.

5-Bromoisocytosine-6-acetic Acid (13) Hydrobromide. Approximately 3 equiv (1.35 mol) of bromine was added to 1 g of isocytosine-6-acetic acid (**1a**) suspended in 4 ml of acetic acid. The pyrimidine appeared to dissolve and promptly reprecipitated. The mixture was stirred for 9 hr, becoming a very pasty suspension. The mixture was diluted with 10 ml of acetone to remove the excess bromine (*caution: the bromoacetone formed is a strong lachrymator*) and stirred for 2 hr. The precipitate was collected and dried, yielding 1.5 g (87%) of **13** · HBr: mp 230–232° dec; ir (KBr) 3220, 2880, 1701, 1685, 1668, 1603, 1202 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 205 (11), 203 (11), 164 (2), 162 (2), 82 (23), 81 (80), 80 (23), 79 (86), 44 (100). With the exception of the peaks at *m/e* 44 and the increase in 82–79 the mass spectrum of **13** · HBr was essentially the same as that of 5-bromo-6-methylisocytosine (**14**).

Anal. Calcd. for $C_6H_7N_3O_3Br_2$: C, 21.91; H, 2.15; N, 12.77; Br, 48.59. Found: C, 22.05; H, 2.14; N, 13.01; Br, 48.71.

An attempt was made to recover the free 5-bromoisoisocytosine-6-acetic acid (**13**) by adjusting the pH of 1 g of **13** · HBr in 25 ml of water to pH 8 with sodium carbonate and back to pH 4 with hydrochloric acid. The nmr of the 0.669 g of white powder, after drying, showed singlets at τ 6.55 (CH_2), and 7.75 (CH_3) (identical with an independently prepared sample of **14**) that indicated that this was a mixture of **13** and about 35% 5-bromo-6-methylisocytosine (**14**). The increased sensitivity of **13** to decarboxylation is an expected effect of the electron withdrawal by the 5-bromo group.

5-Bromo-6-bromomethylisocytosine (15). Bromine (1.1 ml, 0.02 mol) was added dropwise to 3.4 g (0.02 mol) of **1a** suspended in 20 ml of glacial acetic acid. The suspended pyrimidine dissolved as it reacted. A faint orange color persisted after addition of the bromine. An undissolved residue was removed by filtration, and the clear solution was heated overnight at 115°. A white precipitate separated. This was filtered after cooling to room temperature and washed with acetic acid. After drying, 1.5 g of product was obtained. This was heated in 250 ml of water for several hours and the insoluble residue was removed by filtration. The clear solution was allowed to cool slowly overnight. After drying at 100°, 0.39 g of 5-bromo-6-bromomethylisocytosine (**15**) were obtained: mp 200–210° dec; ir (KBr) 3435, 3320, 3090, 2870, 2730, 1660, 1604, 1560, 1475, 1405, 1215, 1150, 1095, 1028, 1005, 776, 668 cm^{-1}; nmr (DMSO-d_6) τ 5.70 (s, 2, CH_2Br), 3.15 (s, 2 NH_2).

Anal. Calcd for $C_5H_5N_3Br_2O$: C, 21.22; H, 1.78; N, 14.85; Br, 56.49; *m/e* 282.8778 for ^{81}Br ^{79}Br. Found: C, 22.19; H, 2.40; N, 15.29; Br, 55.63; *m/e* 282.8783.

Over a period of several days, the DMSO-d_6 nmr sample turned red. DMSO has been used to oxidize halomethyl compounds to aldehydes.

5-Bromo-6-dibromomethylisocytosine (16). Bromine (0.9 ml, 0.0175 mol) was added to 1.0 g (0.0056 mol) of **1a** suspended in 4 ml of acetic acid. The solution was heated overnight at 120°. Upon cooling, a product precipitated. The precipitate was collected and triturated with hot water and sufficient sodium bisulfite was added to remove the faint orange trace of bromine. The hot suspension was filtered and washed with water to give, after drying, 1.3 g of fine white crystals. This was redissolved in dilute sodium hydroxide and reprecipitated with dilute hydrobromic acid. After recrystallization from hot water, the 5-bromo-6-dibromomethylisocytosine (**16**) was dried: mp 240–247° dec; ir (KBr) 3550, 3390, 3310, 3200, 3080, 3015, 2915, 1655, 1628, 1585, 1468, 1369, 1218, 1152, 1102, 1021, 786, 735, 695, 642 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 365 (34), 363 (98), 361 (100), 359 (34).

Anal. Calcd for $C_5H_5N_3Br_3O$: C, 16.59; H, 1.40; N, 11.6; Br, 66.25. Found: C, 16.08; H, 1.77; N, 10.93; Br, 72.54.

Registry No. 1a, 42822-67-3; **1b,** 42822-68-4; **10,** 42822-69-5; **11,** 42822-70-8; **11** · HCl, 42822-71-9, **12a,** 34415-11-7; **12b,** 21615-64-5; **13** · HBr, 42822-74-2; **15,** 42822-75-3; **16,** 42822-76-4; diethyl acetone-dicarboxylate, 105-50-0; guanidine carbonate, 3425-08-9; potassium nitrate, 7757-79-1; 6-methylisocytosine, 5414-09-5; sodium nitrite, 7632-00-0; bromine, 7726-95-6.

References and Notes

(1) Abstracted in part from the dissertation submitted by Gordon N. Mitchell in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry of The University of North Carolina, Chapel Hill, N. C., 1972.

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Syntheses of Eisenin and Its Amide by the *N*-Carboxy α-Amino Acid Anhydride Method

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Eisenin (L-pyroglutamyl-L-glutaminyl-L-alanine) and its amide derivative were synthesized in high yields by a new method using the controlled reaction of *N*-carboxy α-amino acid anhydride (NCA) in the heterogeneous reaction system acetonitrile–water. A tripeptide precursor, γ-methyl-L-glutamyl-γ-methyl-L-glutamyl-L-alanine, and the amide were successfully prepared by two successive reactions of γ-methyl L-glutamate NCA with L-alanine and the amide. The tripeptides were converted into eisenin and the amide through cyclization of the N-terminal γ-methyl ester and simultaneous amidation of the internal L-glutamic acid residue by the action of ammonia.

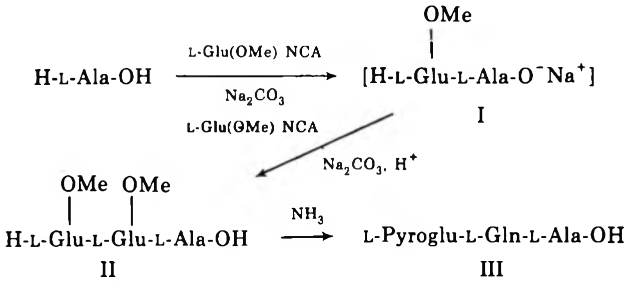
Eisenin is a naturally occurring tripeptide isolated from *Eisenia bicyclis* (Kjellm.) Stetchell by Oohira.[1] The primary structure of the peptide was determined as L-pyroglutamyl-L-glutaminyl-L-alanine.[2] Recently, a peptide with biological activity having an N-terminal pyroglutamyl residue was found. The peptide was named thyroid-stimulating hormone releasing factor (TRF) and has the sequence L-pyroglutamyl-L-histidyl-L-prolinamide.[3] It is of interest that the N-terminal amino acid and the chain length of the newly obtained TRF resemble those of eisenin. The synthesis of TRF has been carried out by conventional[4] and solid-state[5] methods for peptide synthesis and recently by a modified solid-state method involving the simplest strategy.[6]

This paper describes the synthesis of eisenin[7] and its amide derivative by a simple procedure using the controlled reaction of *N*-carboxy α-amino acid anhydride (NCA) in the heterogeneous system acetonitrile (ACN)–water.[8-10]

Synthesis of Eisenin. The NCA method of peptide synthesis is the simplest procedure for the preparation of free peptides because it involves direct acylation of an amino acid or a peptide by the NCA.[8,11-13] As the reaction of the NCA proceeds almost quantitatively at optimal conditions,[8,11,14] small peptides can be prepared by successive addition of NCA's to the reaction system without isolation and purification of intermediate peptides.[8,15]

In the synthesis of eisenin, a synthetic scheme using two reaction steps, first, the preparation of a tripeptide precursor of eisenin, γ-methyl-L-glutamyl-γ-methyl-L-glutamyl-L-alanine, by the NCA method, and second, the treatment of the precursor with ammonia, was considered as the simplest route to eisenin. The latter treatment could convert the tripeptide precursor into eisenin through the cyclization[16] of the N-terminal and the simultaneous amidation[17] of the internal γ-methyl L-glutamyl residue.

The eisenin precursor (II) was prepared by two successive reactions of γ-methyl L-glutamate NCA with L-alanine. The intermediate dipeptide, γ-methyl L-glutamyl-L-alanine (I), as a sodium salt resulting from the initial reaction of the NCA was not isolated, but thin layer chromatography revealed no appreciable by-products. After the second reaction of the NCA with the crude dipeptide, the tripeptide II was isolated from the reaction system, purified by recrystallization from aqueous methanol (86% yield), and dissolved in methanol saturated by ammonia. Subsequently, the product III was isolated and purified by the method reported by Oohira[1] (89% yield).



$$\text{H-L-Ala-OH} \xrightarrow[\text{Na}_2\text{CO}_3]{\text{L-Glu(OMe) NCA}} [\text{H-L-}\overset{\text{OMe}}{\text{Glu}}\text{-L-Ala-O}^-\text{Na}^+] \quad \text{I}$$

$$\text{I} \xrightarrow[\text{Na}_2\text{CO}_3,\ \text{H}^+]{\text{L-Glu(OMe) NCA}} \underset{\text{II}}{\text{H-L-}\overset{\text{OMe}}{\text{Glu}}\text{-L-}\overset{\text{OMe}}{\text{Glu}}\text{-L-Ala-OH}} \xrightarrow{\text{NH}_3} \underset{\text{III}}{\text{L-Pyroglu-L-Gln-L-Ala-OH}}$$

The synthetic product (III) was demonstrated to be identical with naturally occurring eisenin, kindly supplied by Dr. Oohira, by measurement of physical properties including ir and nmr spectra. This shows that cyclization and amidation of the γ-methyl ester of the glutamyl residues was achieved at the same time expected.

Eisenin may be synthesized by the NCA method through an alternative simplified scheme that involves two successive reactions of L-glutamine NCA[18] with L-alanine followed by heating the aqueous solution of the product. However, L-glutamine NCA is not easily obtained in high yield compared with those NCA's having nonpolar and protected polar side chains, as is shown by a reported synthesis[18] involving treatment of the benzyloxycarbonyl derivative of L-glutamine with PBr_3 followed by column chromatography. Thus the synthetic scheme adopted in this study has a practical merit in obtaining L-glutaminyl peptide in high yield because of very easy preparation of γ-methyl L-glutamate NCA from the amino acid by phosgenation.[19]

Synthesis of Eiseninamide. Eiseninamide was synthesized by the same procedure as that for eisenin except for the use of L-alaninamide. Prior to the synthesis, it was demonstrated that there is no hydrolysis of the amide group during reaction with NCA in the heterogeneous system.[20] For this purpose, NCA's were treated with L-glutamine and L-asparagine, which have the amide group in the side chains, at optimal conditions for the NCA method in this system. Subsequently the aqueous solution of the heterogeneous system was analyzed by paper chromatography. The chromatogram contained a single spot of the dipeptide with C-terminal glutamine and asparagine different from spots of dipeptides containing C-terminal glutamic acid and aspartic acid and the amino acids com-

Table I
Results of Syntheses of Dipeptides with C-Terminal Glutamine and Asparagine

Registry No.	Dipeptide[a]	Yield, %	$[\alpha]_D$, deg	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
42854-54-6	H-Val-Gln-OH	80	15.7 (*c* 3.2, 1 *N* HCl)[b]	48.96	7.81	17.13	49.20	7.90	17.05
38062-70-3	H-Leu-Gln-OH	82	13.6 (*c* 2.9, 1 *N* HCl)[c]	50.95	8.16	16.21	50.63	8.26	16.37
39537-24-1	H-Phe-Gln-OH	88	18.7 (*c* 2.4, 1 *N* HCl)[d]	57.32	6.53	14.33	57.95	6.60	14.45
14608-81-2	H-Leu-Asn-OH	82	14.4 (*c* 2.1, 80% MeOH)[e]	48.96	7.81	17.13	48.67	8.01	17.20
39537-20-7	H-Phe-Asn-OH	78	4.9 (*c* 3.1, 1 *N* HCl)	55.90	6.14	15.05	55.87	6.20	15.21

[a] All amino acid residues have the L configuration. [b] 15.8° (*c* 3.08, 1 *N* HCl): Y. Shimonishi, *Bull. Chem. Soc. Jap.*, **37**, 200 (1964). [c] 14.2° (*c* 3.57, 1 *N* HCl); see footnote *b*. [d] 17.3° (*c* 3.42, 1 *N* HCl); see footnote *b*. [e] 15.7° (*c* 5.0, H_2O): A. Miller, A. Neidle, and H. Waelsch, *Arch. Biochem. Biophys.*, **56**, 11 (1955).

ing from the starting material and hydrolysis of the NCA. For example, the system containing the product resulting from the reaction of L-leucine NCA with L-glutamine gave a spot with R_f[21] 0.55 while L-leucyl-L-glutamic acid showed a spot with R_f 0.63. This suggests that no side reactions such as hydrolysis of the amide group occur during the reaction carried out in the heterogeneous system and is in accord with results by methods using aqueous systems.[13,20] Results of the syntheses are shown in Table I.

On the basis of these results, eiseninamide was synthesized by the NCA method in the heterogeneous system. L-Alaninamide, which was prepared by treatment of the free benzyl ester of L-alanine with ammonia, was dissolved in the heterogeneous system of ACN–water which had been cooled to −10° in order to avoid hydrolysis of the amide. A solution of γ-methyl L-glutamate NCA in cooled ACN was added to the system and allowed to react. The resulting dipeptide amide was not isolated but was again treated with NCA as before.

When an amino acid amide is allowed to react in a heterogeneous system, attention must be paid to the solubility of the amide in the ACN layer. Since an appreciable quantity of L-alaninamide appears to be present in the ACN layer as well as in the aqueous one, higher temperatures may result in undesirable polymerization of the NCA initiated by the amide in the ACN layer. Indeed, the controlled reaction of γ-methyl L-glutamate NCA with L-alaninamide carried out at −7° gave not only the dipeptide amide but a small portion of by-products, which were identified as the tripeptide amide, γ-methyl-L-glutamyl-γ-methyl-L-glutamyl-L-alaninamide and the higher tetrapeptide amide by tlc. However, this is not true at −10°. Therefore the temperature of the reaction with amide should be carefully kept below −10°.

After the second reaction of the NCA and nautralization of the aqueous solution of the heterogeneous system with dilute sulfuric acid, the tripeptide amide was carefully isolated and purified by recrystallization from methanol (87% yield from L-alaninamide). The product was treated with anhydrous ammonia to yield eiseninamide (91% yield).

Experimental Section

γ-Methyl L-Glutamate NCA.[19] Into a suspension of 20 g of γ-methyl L-glutamate in 400 ml of tetrahydrofuran was bubbled dry phosgene at 40° with stirring. After the amino acid derivative had dissolved to give a clear solution, the solvent was removed at reduced pressure to yield an oil. The oily product was crystallized by addition of 200 ml of *n*-hexane followed by cooling. The crystals of NCA were twice recrystallized from ethyl acetate to give 20.5 g (88%) of pure NCA, mp 100°, $[\alpha]_D$ −20.2° (c 1.8, ACN). *Anal.* Calcd for $C_7H_9NO_5$: C, 44.92; H, 4.85; N, 7.48. Found: C, 44.76; H, 4.83; N, 7.50.

γ-Methyl-L-glutamyl-γ-methyl-L-glutamyl-L-alanine. To a solution of 0.89 g (0.01 mol) of L-alanine and 1.06 g (0.01 mol) of anhydrous sodium carbonate in 50 ml of 0.2 *N* sodium hydroxide was added 40 ml of ACN to yield a heterogeneous system, which was cooled to −10°. A solution of 2.07 g (0.011 mol) of γ-methyl L-glutamate NCA in 20 ml of ACN was added to the heterogeneous system and allowed to react for 2 hr at −10° with magnetic stirring. After 2 hr, the system was taken into a separating funnel. The upper layer of the heterogeneous system was removed and the aqueous layer was washed with 50 ml of ethyl acetate to remove unreacted NCA. The resulting aqueous solution was analyzed by tlc. Chromatography on silica gel plate developing 1-butanol–acetic acid–water (4:1:2) showed a single spot with R_f 0.11. Then the aqueous solution was diluted to 60 ml of water and 40 ml of ACN was added. The heterogeneous system was cooled again to −10°. After addition of 2.07 g of γ-methyl L-glutamate NCA in 20 ml of ACN, the system was stirred for 2 hr at −10°. Removal of the ACN layer and washing the aqueous solution by ethyl acetate was followed by neutralization of the aqueous solution with 6 *N* sulfuric acid. The sodium sulfate resulting from the neutralization was precipitated by addition of 200 ml of ethanol and removed by filtration. The filtrate was concentrated at reduced pressure to yield a syrup, which was crystallized by addition of 100 ml of ethanol and 100 ml of diethyl ether. The product was recrystallized from 80% methanol to give 3.2 g (86%) of crystalline γ-methyl-L-glutamyl-γ-methyl-L-glutamyl-L-alanine, mp 97°, $(\alpha)_D$ −21.1° (*c* 2.0 water). *Anal.* Calcd for $C_{15}N_{25}N_3O_8 \cdot 4H_2O$: C, 40.26; H, 7.43; N, 9.39. Found: C, 40.41; H, 7.38; N, 9.26.

The tripeptide (5 g) was dissolved in 150 ml of dry methanol saturated with ammonia and the solution was allowed to stand for 3 days at room temperature. Then the solvent was removed at reduced pressure at 25° to give a residue, which was dissolved in 100 ml of methanol, and the solution was concentrated again. The resulting product was recrystallized from aqueous methanol, 3.27 g (89%), mp 223–227° dec, $[\alpha]_D$ −52.8° (*c* 6.5, water). *Anal.* Calcd for $C_{13}H_{20}N_4O_6$: C, 47.55; H, 6.14; N, 17.07. Found: C, 47.68; H, 6.23; N, 17.01.

The sample of eisenin which had been isolated by Dr. Oohira gave mp 224–226° dec and $[\alpha]_D$ −53.5° (c 6.5, water).

General Procedure for the Synthesis of Dipeptides with C-Terminal Glutamine and Asparagine. An aqueous solution of 1.06 g (0.01 (0.01 mol) of sodium carbonate in 50 ml of 0.2 *N* sodium hydroxide was cooled to −5°. To the solution was added 0.01 mol of the amino acid and then 40 ml of ACN was added to form the heterogeneous system. After the addition of a solution of 0.011 mol of NCA in 20 ml of ACN, the reaction was allowed to proceed in a usual manner. Isolation of the dipeptide from the aqueous solution gave a white, crystalline product, which was recrystallized from aqueous ethanol.

Synthesis of Eiseninamide. L-Alaninamide. L-Alanine benzyl ester *p*-toluenesulfonate (17.5 g, 0.05 mol) was dissolved in 50 ml of water and the solution was neutralized carefully to pH 7.5 by addition of 0.1 *N* sodium hydroxide. Then the solution was immediately extracted by one 150-ml portion of diethyl ether and two 75-ml portions of ether. The combined extract was dried overnight with anhydrous sodium sulfate at −20°. The ether solution was concentrated at reduced pressure at 10° to give an oily residue of the free benzyl ester of L-alanine, 7.3 g (82%). The ester was dissolved in 220 ml of methanol saturated with ammonia and the solution was allowed to stand for 3 days at room temperature. Solvent was removed *in vacuo* at 15° to yield an oil, which was crystallized by addition of 50 ml of diisopropyl ether and 100 ml of *n*-hexane. Recrystallization from methanol gave plate crystals of L-alaninamide, 2.4 g (78%), mp 72°, $[\alpha]_D$ 6.5° (c 2.0, water). *Anal.* Calcd for $C_3H_8N_2O \cdot H_2O$: C, 33.95; H, 9.50; N, 26.40. Found: C, 34.14; H, 9.65; N, 26.68.

γ-Methyl-L-glutamyl-γ-methyl-L-glutamyl-L-alaninamide. To the heterogeneous system of 50 ml of ACN and 50 ml of an aqueous solution of 1.06 g (0.01 mol) of anhydrous sodium carbonate, which had been cooled to −10°, was dissolved 0.88 g (0.01 mol) of L-alaninamide. A solution of 2.07 g of γ-methyl L-glutamate NCA in 20 ml of ACN was added to the system and allowed to react for 2 hr under −10° with stirring. After the reaction, the aqueous layer was washed with 50 ml of ethyl acetate. The resulting aqueous solution was demonstrated to contain only one component which showed a single spot having an R_f of 0.26 on silica gel tlc. Then the solution was diluted to 60 ml by addition of fresh ice and 50 ml of ACN was added. The system was cooled to −10°. After the addition of 2.07 g of γ-methyl L-glutamate NCA and reaction by the same procedure as that for eisenin, the tripeptide amide was isolated from the alcoholic solution free from sodium sulfate resulting from the neutralization, by concentrating *in vacuo* at 20° followed by addition of 50 ml of ethanol and 150 ml of diethyl ether. Recrystallization from 150 ml of methanol gave a crystalline tripeptide amide, 3.3 g (87% yield from L-alaninamide), mp 126–127°, $[\alpha]_D$ −25.8° (c 2.0, water). *Anal.* Calcd for $C_{15}H_{26}N_4O_7 \cdot 4H_2O$: C, 40.35; H, 7.68; N, 12.55. Found: C, 40.42; H, 7.62; N, 12.78.

The tripeptide amide (3.74 g, 0.01 mol) was dissolved in 100 ml of dry methanol saturated with ammonia and the solution was allowed to stand for 3 days. The solution was concentrated at 20° to give a residue, which was redissolved in 50 ml of methanol. The solution was concentrated again to give a white residue. The product was recrystallized from water, 3.0 g (91%), mp 251–254° dec, $[\alpha]_D$ −46.0° (*c* 2.0, water). *Anal.* Calcd for $C_{13}H_{21}N_5O_5$: C, 47.70; H, 6.47; N, 21.40. Found: C, 47.86; H, 6.56; N, 21.26.

Acknowledgment. The authors wish to express their gratitude to Dr. T. Oohira, Professor Emeritus of Shinshyu University, for a generous gift of eisenin and his suggestive discussion. This work was supported partly by the Scientific Grant of the Japanese Ministry of Education.

Registry No. γ-Methyl L-glutamate NCA, 1663-47-4; γ-methyl L-glutamate, 1499-55-4; γ-methyl-L-glutamyl-γ-methyl-L-glutamyl-L-alanine, 42854-60-4; L-alanine, 56-41-7; eisenin, 21477-57-6; L-alaninamide, 7324-05-2; L-alanine benzyl ester *p*-toluenesulfonate, 42854-62-6; γ-methyl-L-glutamyl-γ-methyl-L-glutamyl-L-alanine amide, 42854-63-7; eiseninamide, 38357-81-2.

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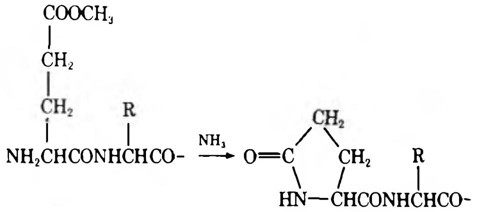

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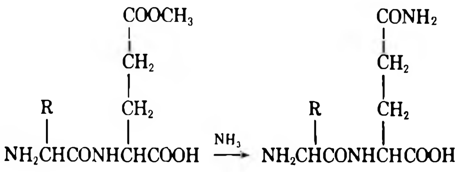

$$NH_2\overset{\displaystyle R}{\overset{|}{C}}HCONH\overset{\displaystyle COOCH_3}{\overset{|}{\overset{CH_2}{\overset{|}{\overset{CH_2}{\overset{|}{C}}}}}}HCOOH \xrightarrow{NH_3} NH_2\overset{\displaystyle R}{\overset{|}{C}}HCONH\overset{\displaystyle CONH_2}{\overset{|}{\overset{CH_2}{\overset{|}{\overset{CH_2}{\overset{|}{C}}}}}}HCOOH$$

(18) R. Hirschmann, H. Schwam, R. G. Strachan, E. F. Schoenewaldt, H. Barkemeyer, S. M. Miller, J. B. Conn, V. Garsky, D. F. Veber, and R. G. Denkewalter, *J. Amer. Chem. Soc.*, **93**, 2746 (1971).

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(20) Though a dipeptide amide has been synthesized by the NCA method in an aqueous system involving the reaction of NCA with an amino acid amide [R. Hirschmann, R. G. Strachan, H. Schwam, E. F. Schoenewaldt, H. Joshua, B. Barkemeyer, D. F. Veber, W. J. Paleveda, Jr., T. A. Jacob, T. E. Beesley, and R. G. Denkewalter, *J. Org. Chem.*, **32**, 3415 (1967)], the possibility that the amide group of the amino acid amide is partially hydrolyzed during the reaction with NCA in the heterogeneous system is present, because the heterogeneous system requires a higher pH (>11) and longer reaction time (2 hr) for optimal condition than the homogeneous one (pH 10.2 and a few minutes).

(21) A solvent system of 1-butanol–acetic acid–water (4:1:2) was used as a developer.

Octahydrophenanthrene Derivatives. Stereoselective Synthesis of the Isomeric 9,10-Dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrenes[1]

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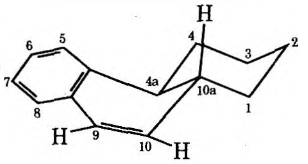
The four isomeric 9,10-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrenes were prepared. Permanganate oxidation of 1,2,3,4,4a,10a(*trans*-4a,10a)-hexahydrophenanthrene (**1**) afforded the 9(e),10(a) isomer, **2**. Wet Prévost conditions, followed by hydrolysis, gave the 9(a),10(e) diol, **3**. Opening of the syn 9,10-epoxide, **6**, using trichloracetic acid in benzene, followed by hydrolysis, afforded the 9(e),10(e) diol, **4**. Aqueous acid opening of anti 9,10-epoxide (**7**) afforded **5**, the 9(a),10(a) diol.

In previous work related to preparation of derivatives of 9,10-disubstituted octahydrophenanthrenes, addition of a number of electrophiles to 1,2,3,4,4a,10a(*trans*-4a,10a)-hexahydrophenanthrene (**1**)[3] has been reported.[2] Addition of peracid, hypobromous acid, and iodine isocyanate all occur primarily from the α face of the molecules (steroid nomenclature); *i.e.*, on the side opposite the 10a hydrogen atom. With reference to other studies it was necessary to find routes to the isomeric 9,10-diols, **2**–**5**.[3] This led to an investigation of the use of other electrophiles to this olefin, as well as the openings of the isomeric epoxides, as potential routes to the isomeric diols.



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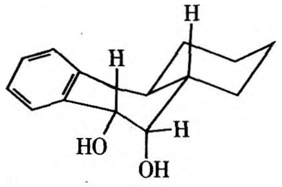

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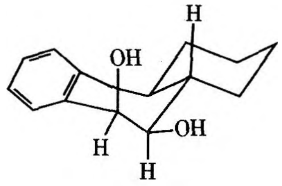

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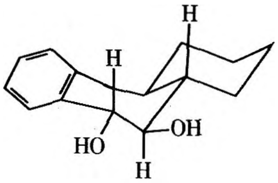

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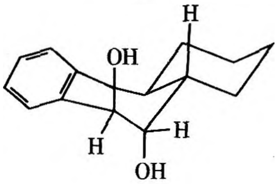


5

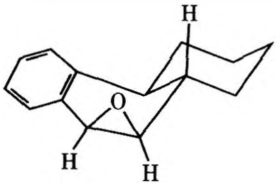
Our first approach to the desired diols involved the judicious choice of reagents for electrophilic addition to olefin **1**. Permanganate oxidation afforded a single diol, which must be a cis diol,[4] which was assigned structure **2**, based on its nmr spectrum and the known net course of addition.

Structure assignments based on the nmr spectra (Table I) are extremely facile for **3** and **4**, since $J_{10,10a}$ is large, and $J_{9,10}$ varies only with the position of the 9-hydroxyl group.[5] In the 10(a)-hydroxy compounds, **2** and **5**, where $J_{10,10a} \cong 0$ and $J_{9,10}$ is relatively constant, additional evidence is required, *e.g.*, known course of addition being cis or trans.

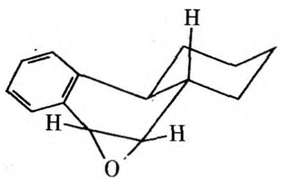
The selectivity of addition of permanganate ion and other electrophiles such as iodine isocyanate to the α face suggested use of another electrophilic iodonium ion generating reagent to prepare **3**. By using conditions of the wet Prévost reaction,[6,7] where the iodonium ion attacks the α face, it is possible to add both hydroxyl groups on the opposite side, the β face, thus affording a route to **3**.

Refluxing the intermediate iodoacetate with wet acetic acid afforded a miture of monoacetates of **3**, readily demonstrated by acetylation to a single diester, which is hydrolyzed to a single diol. The structure is readily assigned from nmr evidence (Table I), since $J_{10,10a}$ is large.

The isomeric syn and anti epoxides,[8] **6** and **7**, proved to be key intermediates in preparation of **4** and **5**, respectively. The epoxides **6** and **7** were prepared from olefin **1**. Peracid oxidation of **1** afforded **7**,[2a] and addition of hypobromous acid to **1**, followed by treatment with sodium hydroxide in methanol, gave **6**.[2a] Attack of these electrophiles also occurs from the α face of this tricyclic olefin.



6



7

Trichloroacetolysis (benzene) of the syn epoxide **6** afforded a route to diol **4**, somewhat unexpectedly. Previous openings under these conditions on substrates of *trans*-stilbene oxide,[9] and the isomeric-1-phenyl-4-*tert*-butylcyclohexane oxides,[10] had afforded products of cis opening.

Our previous experiences in opening of epoxide **6** with nucleophiles such as azide or ammonia[2a] had demonstrated regiospecific opening at the benzylic position, possibly indicative of the preferred route of opening regardless of conditions, consistent with some positive character of the benzylic carbon, C-9. The stereochemistry of the product of ring opening was readily assigned from the nmr spectrum, $J_{9,10} = 8.0$, $J_{10,10a} = 10$ Hz.

The differences in this result compared with those of Berti[10,11] may be a consequence of additional steric restraints of this system in the transition state, and/or differences in degrees of polarization compared to noncyclic systems.

Acid-catalyzed hydrolysis of the anti epoxide **7** in aqueous DMSO afforded diol **5** in excellent yield. The specific trans opening of similar epoxides under these hydrolytic conditions has been previously reported.[10,11] Only structure **5** was consistent with a small coupling constant for $J_{9,10}$.

The successful synthesis of the isomeric 9,10-epoxy-*trans*-octahydrophenanthrenes, **6** and **7**, and the cis diols, **2** and **3**, is dependent on the fact that all of the chosen electrophilic reagents *m*-chloroperbenzoic acid, potassium permanganate, silver acetate–iodine, and hypobromous acid, add stereoselectively to the α face of 1,2,3,4,4a,10a(*trans*-4a,10a)-hexahydrophenanthrene, *i.e.*,

Table I
60-MHz Nmr Spectral Data for the Isomeric 9,10-Diols[a]

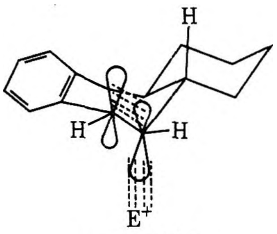
	H_9			H_{10}		
Compd	Orientation of H_9	Multiplicity and chemical shift, δ	$J_{9,10}$, Hz	Orientation of H_{10}	Multiplicity and chemical shift, δ	$J_{10,10a}$, Hz
2	Axial	d, 4.57	4	Equatorial	d, 3.75	~0
3	Equatorial	d, 4.55	4	Axial	dd, 3.50	9
4	Axial	d, 4.43	8	Axial	dd, 3.33	10
5	Equatorial	d, 4.30	2.5	Equatorial	d, 3.61	~0

[a] Spectra were recorded in DMSO-d_6.

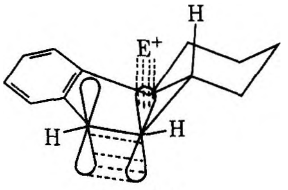
antiparallel to the axial hydrogen at C-10a. From models no great steric differences in the ease of parallel or antiparallel approach can be seen. In fact, the parallel approach (not observed) would seem to be the least sterically hindered owing to less 1,3 interaction with the hydrogens on the alicyclic rings.

The stereoselectivity observed may be explained in terms of stereotorsional control described by Garbisch.[12] Antiparallel approach would decrease torsional strain energy between proton H_{10} and the equatorial group at carbon 10a, whereas parallel approach would increase this torsional strain energy.

Stereoelectronic control of the reaction[14-16] may also be a factor contributing to the stereoselectivity of these reactions. In this case, if one assumes some degree of polarization at the benzylic position, C-9, as seems likely, an antiparallel (axial) attack at C-10 would allow maximum orbital overlap between the forming σ bond and the partial carbonium ion at C-9 with the central ring in its energetically most favorable, half-chair conformation. In contrast, parallel attack at C-10 would require a twisted boat conformation of the central ring to maintain orbital overlap in the transition state.



antiparallel



parallel

The preparation of these diols will allow for further study of epoxide openings in this system, and other related work, some of which is presently under investigation.

Experimental Section[17]

9(e),10(a)-Dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (2). A solution of potassium permanganate, 8.69 g (0.055 mol), and sodium hydroxide, 3.0 g (0.075 mol), in 340 ml of water was cooled to 0° and added over a 30-min period to a stirred solution of 1,2,3,4,4a,10a(*trans*-4a,10a)-hexahydrophenanthrene (1),[2a] 9.21 g (0.05 mol), in 300 ml of *tert*-butyl alcohol and 210 ml of water, maintaining the temperature below 5° with an ice bath. The solution was stirred for an additional 15 min at 0°, 10% aqueous sodium bisulfite (500 ml) was added to destroy the manganese dioxide, and the solution was continuously extracted with 300 ml of ether for 67 hr. The ether solution was dried and evaporated and the white solid remaining was recrystallized from ether to give 9(e),10(a)-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (2): 7.2 g (66%); mp 97–100°; λ_{max} (H_2O) 263 nm (ϵ 325); ir (KBr) 3360 (OH), 2900 and 2840 (aliphatic CH), 1440 (CO), and 720 and 750 cm^{-1} (aromatic CH); nmr ($CDCl_3$, DMSO-d_6) δ 7.50–7.67 (m, 1, H_8), 7.17–727 (m, 3, $H_{5,6,7}$), 4.57 (d, 1, $J_{9,10}$ = 4.0 Hz, H_9), 4.12 (s, broad, 1, OH), 3.75 (d, 1, $J_{10.9}$ = 4.0, $J_{10,10a} \cong 0$ Hz, H_{10}), 1.33–2.13 (m, 10, CH_2CH envelope), D_2O was added and the nmr absorption at δ 4.12 disappeared and an absorption at δ 3.57 (s, 2, HDO) appeared; mass spectrum (70 eV) *m/e* (rel intensity, fragment) 218 (4, M^+), 201 (19, M − OH), 200 (100, M − H_2O), 182 (82, M − $2H_2O$), 171 (23, $C_{12}H_{11}O$), 157 (33, $C_{11}H_9O$), 141 (43, $C_{11}H_9$), 129 (43, $C_{10}H_9$), 115 (25, C_9H_7), 107 (18, C_7H_7O), 91 (34, C_7H_7), 77 (26, C_6H_5).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03: H, 8.31; *m/e* 218.1306. Found: C, 76.91; H, 8.08; *m/e* 218.1258.

9(a),10(e)-Dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (3). Powdered iodine, 1.27 g (0.005 mol), was added in small portions over a 30-min period to a stirred solution of 1,2,3,4,4a,10a(*trans*-4a,10a)-hexahydrophenanthrene (1),[2a] 921 mg (5.0 mmol), and silver acetate (J. T. Baker Chemical Co.), 1.84 g (0.011 mol), in 20 ml of glacial acetic acid (99.5%) and the stirring was continued an additional 40 min. Wet acetic acid (4% water), 20 ml, was added and the mixture was heated at 100° for 3 hr with stirring. Ether and sodium chloride were added, the mixture was filtered, and the precipitate was washed with ether. The combined ether filtrates were washed with water followed by 10% aqueous sodium bicarbonate and water, dried, and evaporated to give 1.41 g of colorless oil. The nmr spectrum of this oil contained two signals for the acetate methyl group and two sets of multiplets for H_9 and H_{10}, indicating a mixture of *cis*-9-hydroxy-10-acetoxyl and 9-acetoxy-10-hydroxyl compounds.

The oil was treated with acetic anhydride, 4.0 g (0.04 mol), and 4 drops of pyridine for 20 hr and then diluted with water and extracted with ether. The ether solution was washed with water followed by 10% aqueous sodium bicarbonate, 10% aqueous hydrochloric acid, and water, dried, and evaporated. The solid remaining was recrystallized from hexane to yield 9(a),10(e)-diacetoxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (8): 1.39 g (96%); mp 135–136°; ir (KBr) 2940 and 2870 (aliphatic CH), 1740 (C=O), 1235 (CO), and 670, 685, 735, 755, and 785 cm^{-1} (aromatic CH); nmr ($CDCl_3$) δ 7.34–7.16 (m, 4, ArH), 6.18 (d, l, $J_{9,10}$ = 4.0 Hz, H_9), 5.00 (dd, l, $J_{10,10a}$ = 11.0 Hz, H_{10}), and 1.00–2.68 (m, 16, CH_2CH envelope).

A solution of 9(a),10(e)-diacetoxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (8), 145 mg (0.5 mmol), and potassium hydroxide, 561 mg (0.01 mol), in 10 ml of ethanol (95%) was stirred at room temperature for 6 hr, diluted with water, and extracted with ether. The ether solution was washed with 10% aqueous hydrochloric acid followed by water, dried, and evaporated. The solid remaining was recrystallized from hexane to yield 9(a),10(e)-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (3): 90 mg (83%); mp 151–153°; λ_{max} (H_2O) 263 nm (ϵ 335); ir (KBr) 3360 (OH), 2920 and 2850 (aliphatic CH), and 745 and 765 cm^{-1} (aromatic CH); nmr (DMSO-d_6) δ 7.07–7.33 (m, 4, ArH), 4.85 (d, l, $J_{HO.9}$ = 4.5 Hz, OH), 4.47 (t, l, $J_{9.10}$ = 4.0 Hz, H_9), 4.27 (d, l, $J_{HO,10}$ = 7.5 Hz, HO), 3.41 (ddd, l, $J_{10.10a}$ = 9.0 Hz, H_{10}), 1.0–2.58 (m, 10, CH_2CH envelope); nmr (DMSO-d_6, D_2O) δ 4.55 (d, l, $J_{9.10}$ = 4.0 Hz, H_9), 3.85 (s, 2, HDO), 3.50 (dd, l, $J_{10,10a}$ = 9.0 Hz, H_{10}); mass spectrum (70 eV) *m/e* (rel intensity, fragment) 218 (27, M^+), 201 (17, M − OH), 200 (100, M − H_2O), 182 (42, M − $2H_2O$), 171 (18, $C_{12}H_{11}O$), 157 (33, $C_{11}H_9O$), 141 (35, $C_{11}H_9$)R 129 (64, $C_{10}H_9$), 115 (35, C_9H_7), 107 (37, C_7H_7O), 91 (50, C_7H_7), 77 (27, C_6H_5).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; *m/e* 218.1306. Found: C, 77.34; H, 8.35; *m/e* 218.1292.

9(e),10(e)-Dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (4). To a solution of *syn*-9,10-epoxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (6),[2a] 500 mg (2.5 mmol), in 17 ml of benzene was added a solution of trichloroacetic acid, 490 mg (3.0 mmol), in 3.7 ml of benzene and the mixture was stored overnight at room temperature. The benzene solution was washed with 10% aqueous sodium bicarbonate, followed by water, and dried, and the organic solvent was evaporated under reduced pressure. The solid remaining was recrystallized from hexane to give 9(e)-trichloroacetoxy-10(e)-hydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (9): 385 mg (43%); mp 119–120°; ir (KBr) 3580 (OH), 2920 and 2845 (aliphatic CH), 1755 (C=O), 1250 (CO), and 680 and 760 cm^{-1} (aromatic CH); nmr ($CDCl_3$) δ 7.18–7.37 (m, 4, ArH), 6.13 (d, 1, $J_{9,10}$ = 8.0 Hz, H_9), 3.87 (dd, 1, $J_{10,10a}$ = 11.5 Hz, (H_{10}), and 0.67–2.70 (m, 10, CH_2CH envelope).

A solution of 9(e)-trichloroacetoxy-10(e)-hydroxy-1,2,3,4,4a,-9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (**9**), 363 mg (1.0 mmol), and potassium hydroxide, 1.34 g (0.024 mol), in 12 ml of 95% ethanol was stirred at room temperature for 3 hr. The mixture was diluted with water and extracted with several portions of ether. The combined ether solutions were dried and evaporated. The remaining solid was recrystallized from benzene to give 9(e),10(e)-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (**4**): 188 mg (82%); mp 174–176°; λ_{max} (H_2O) 263 nm (ϵ 330); ir (KBr) 3340 (OH), 2910 and 2840 (aliphatic CH), 1445 and 1480 (CO), and 750 cm^{-1} (aromatic CH); nmr (DMSO-d_6) δ 7.47–7.60 (m, 1, H_8), 7.23 (m, 3, $H_{5,6,7}$), 5.20 (s, broad, 1, OH), 4.70 (s, broad, 1, OH), 4.43 (d, 1, $J_{9,10}$ = 8.0 Hz, H_9), 3.33 (t, broad, 1, $J_{10,10a} \cong 9$ Hz, H_{10}), 1.0–2.57 (m, 10, CH_2CH envelope); nmr (DMSO-d_6, D_2O) δ 3.97 (s, 2, HDO), 3.27 (dd, 1, $J_{10,10a}$ = 10.0 Hz, H_{10}); mass spectrum (70 eV) *m/e* (rel intensity, fragment) 218 (11, M^+), 201 (15, M − OH), 200 (100, M − H_2O), 182 (25, M − $2H_2O$), 171 (23, $C_{12}H_{11}O$), 157 (16, $C_{11}H_9O$), 141 (14, $C_{11}H_9$), 129 (28, $C_{10}H_9$), 115 (19, C_9H_7), 107 (21, C_7H_7O), 91 (14, C_7H_7), 77 (11, R_6H_5).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; *m/e* 218.1306. Found: C, 77.16; H, 8.06; *m/e* 218,1324.

9(a),10(a)-Dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (5). *anti*-9,10-Epoxy-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**7**)[2a] 400 mg (2.0 mmol), in 90 ml of dimethyl sulfoxide (DMSO) was treated with a solution of sulfuric acid, 120 mg (1.33 mmol), in 30 ml of water (0.02 *N* H_2SO_4 in 75% aqueous DMSO) and stirred for 3 hr. The solution was diluted with water and extracted with benzene, and the benzene solution was washed with water, dried, and evaporated. The residual oil was crystallized and recrystallized from hexane–ether (2:1) to yield 9(a),10(a)-dihydroxy-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (**4**): 309 mg (71%); mp 124.5–125°; λ_{max} (H_2O) 264 nm (ϵ 340); ir (KBr) 3350 (OH), 2910 and 2850 (aliphatic CH), 980 and 1010 (CO), and 705, 720, 750, and 780 cm^{-1} (aromatic CH); nmr (DMSO-d_6) δ 7.21 (s, 4, ArH), 4.47 (m, 2, OH), 4.30 (d, 1, $J_{9,10}$ = 2.5 Hz, H_9), 3.61 (d, 1, $J_{10,9}$ = 2.5, $J_{10,10a} \cong 0$ Hz, H_{10}), 2.37–2.63 (m, 2, ArH), 1.07–2.00 (m, 8, CH_2CH envelope); nmr (DMSO-d_6, D_2O) the broad multiplet at δ 4.47 disappears and a signal appears at δ 3.47 (s, broad, 2, HDO); mass spectrum (70 eV) *m/e* (rel intensity, fragment) 218 (5, M^+), 201 (14, M − OH), 200 (100, M − H_2O), 171 (14, $C_{12}H_{11}O$), 157 (30, $C_{11}H_9O$), 129 (32, $C_{10}H_9$), 115 (24, C_9H_7), 107 (30, C_7H_7O), 91 (28, C_7H_7), 77 (19, C_6H_5).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; *m/e* 218.1306. Found: C, 77.14; H, 8.57; *m/e* 218.1292.

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Registry No. 1, 42879-32-3; **2,** 42879-33-4; **3,** 42879-34-5; **4,** 42879-35-6; **5,** 42879-36-7; **6,** 42879-37-8; **7,** 42879-38-9; 8, 42879-39-0; **9,** 42879-40-3.

References and Notes

(1) (a) A preliminary account of this work was presented at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972, Abstract MEDI 09. (b) Taken in part from the Ph.D. Thesis of B. E. Sherwood, submitted to the Graduate School, University of Washington, Feb 1973.

(2) (a) W. L. Nelson and D. D. Miller, *J. Med. Chem.*, **13,** 807 (1970); (b) W. L. Nelson, D. D. Miller and E. Shefter, *J. Org. Chem.*, **35,** 3433 (1970).

(3) All materials are racemic, although only a single isomer is shown.

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(5) The central ring is arbitrarily assigned the half-chair conformation where the equatorial (e) and axial (a) substituents at C-9 are in fact pseudo-equatorial and pseudo-axial respectively.

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(8) Syn and anti refer to the hetero three-membered ring as being on the same side, or opposite side, of the tricyclic skeleton as the C-10a hydrogen atom.

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(17) Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were recorded on Beckman IR-5 and IR-20 spectrometers. Ultraviolet spectra were obtained on a Cary 14 spectrophotometer. Nuclear magnetic resonance spectra were recorded on 60-MHz Varian A-60 and T-60 spectrometers in the solvent stated with tetramethylsilane (TMS) as an internal standard. In nmr descriptions, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Gas chromatographic data were determined on a Hewlett-Packard 5752 research gas chromatograph. The column and temperature utilized are stated for each determination. Mass spectral data were recorded on an Associated Electronics Industries MS-9 mass spectrometer. A Digital Equipment Corp. PDP-12 computer equipped with programs available from the Mass Spectrometry Laboratory, Department of Chemistry, University of Washington, Seattle, Wash. 98195, was used for data collection and mass spectral fragment determinations. Peaks given in the mass spectral fragmentations are within 5.0 millimass units from calculated values. Elemental microanalyses were performed by Dr. F. B. Strauss, Microanalytical Laboratories, Oxford, England, and Huffman Laboratories, Wheatridge, Colo. Unless otherwise stated, anhydrous sodium sulfate was used to dry solutions of organic solvents.

Conversions of α-Methyl to α-Methylene γ-Lactones. Synthesis of Two Allergenic Sesquiterpene Lactones, (−)-Frullanolide and (+)-Arbusculin B[1]

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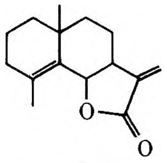
Two new routes to α-methylene-γ-butyrolactones starting from the corresponding α-methyl lactones are outlined. In the case of cis lactones, the conversion of α-methyl → α-methylene lactone has been realized by stereospecific introduction of bromine, α to the lactone carbonyl, followed by antidehydrobromination. In the case of trans lactones the conversion has been realized by stereospecific introduction of the benzoyloxy group, α to the lactone carbonyl, followed by pyrolytic syn elimination of benzoic acid. These conversions have been studied on appropriate lactone models and their generality has been illustrated by the syntheses of (−)-frullanolide (1) and (+)-arbusculin B (2).

The α-methylene-γ-butyrolactone moiety characterizes a rapidly expanding group of sesquiterpenes, comprising to date more than 400 lactones fused on various skeletons.[2] These unsaturated lactones are very often biologically active, showing strong allergenic activity,[3] exhibiting growth-inhibitory activity *in vivo* against animal tumor systems and *in vitro* against cells derived from human carcinoma of the nasopharynx (KB),[4] and/or effecting regulation of plant growth and antimitotic activity.[5] Very recently some α-methylene-γ-lactone sesquiterpenes have been shown to have antischistosomal activity.[6] α-Methylene-γ-butyrolactone itself, isolated from tulips, is not only an allergenic agent but also a fungicide in the white tulip bulb.[7] In all these cases, the presence of an α-methylene-γ-butyrolactone is essential for significant activity.

Efficient construction of the α-methylene-γ-butyrolactone moiety is a synthetic challenge which has received much attention during the past few years.[8] Many ingenious synthetic schemes have resulted but none permits access to this grouping *via* the corresponding α-methyl lactone. This transformation is of definite interest since appropriate α-methyl lactones are often readily available from synthetic procedures[9] and/or natural sources.[2]

We now report the synthesis of (−)-frullanolide (1), isolated from *Frullania tamarisci* (L.) Dum.,[3a,b] and (+)-arbusculin B (2), isolated from *Artemisia arbuscula*[10a] and from *Artemisia tridentata*,[10b] and thereby demonstrate the utility of two potentially general techniques for achieving the α-methyl → α-methylene conversion for cis- and trans-fused lactones.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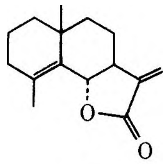
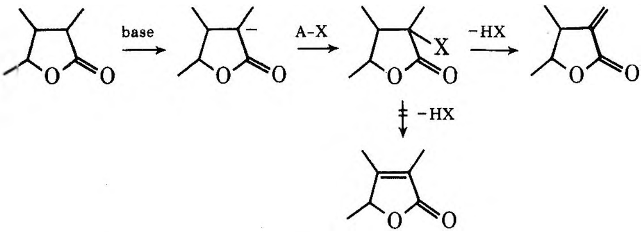

2

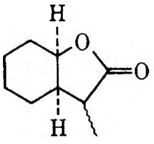
We envisioned an approach which consisted of introducing a group X α to the carbonyl of the methyl lactone, and then eliminating HX to afford the α-methylene lactone (Scheme I). We had shown earlier that α-methyl lactones can be readily converted to the corresponding enolates using triphenylmethyllithium and subsequently methylated (X = CH_3).[11]

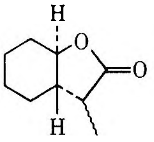
The method of introduction of X had to be compatible with the presence of at least a double bond in the molecule and the elimination of HX had to lead to the exocyclic olefin in preference to the isomeric endocyclic olefin. Therefore X had to be introduced stereospecifically since it was anticipated that the direction of elimination for a given X group would be governed by the stereochemical outcome.

Scheme I



The viability of Scheme I was demonstrated by the conversion of the α-methyl lactones[12] 3 and 4 to the corresponding unsaturated lactones 5 and 6, which constitute structural prototypes of naturally occurring cis- and trans-fused sesquiterpene lactones.


3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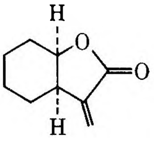
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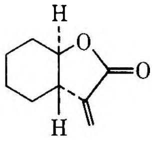

6

Bromine was first selected for the X group and could be introduced by treatment of the α-methyl lactone enolates with 1,2-dibromoethane. This reagent, which had been used for the formation of cyclopropanes,[13,14] in coupling reactions,[15] as an alkylating agent,[16] as a protonating agent,[17] and as a brominating agent of 1-propenyllithium,[18] had never been previously used for the formation of isolable α-bromocarbonyl compounds.

The carbanion A (Chart I), obtained by treatment of lactone 3 in 1,2-dimethoxyethane (DME) with a slight ex-

Chart I

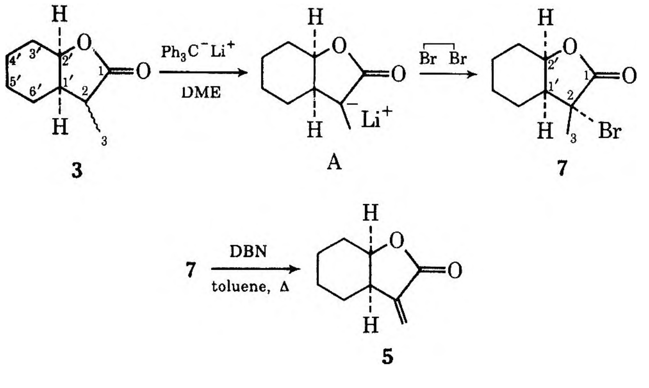
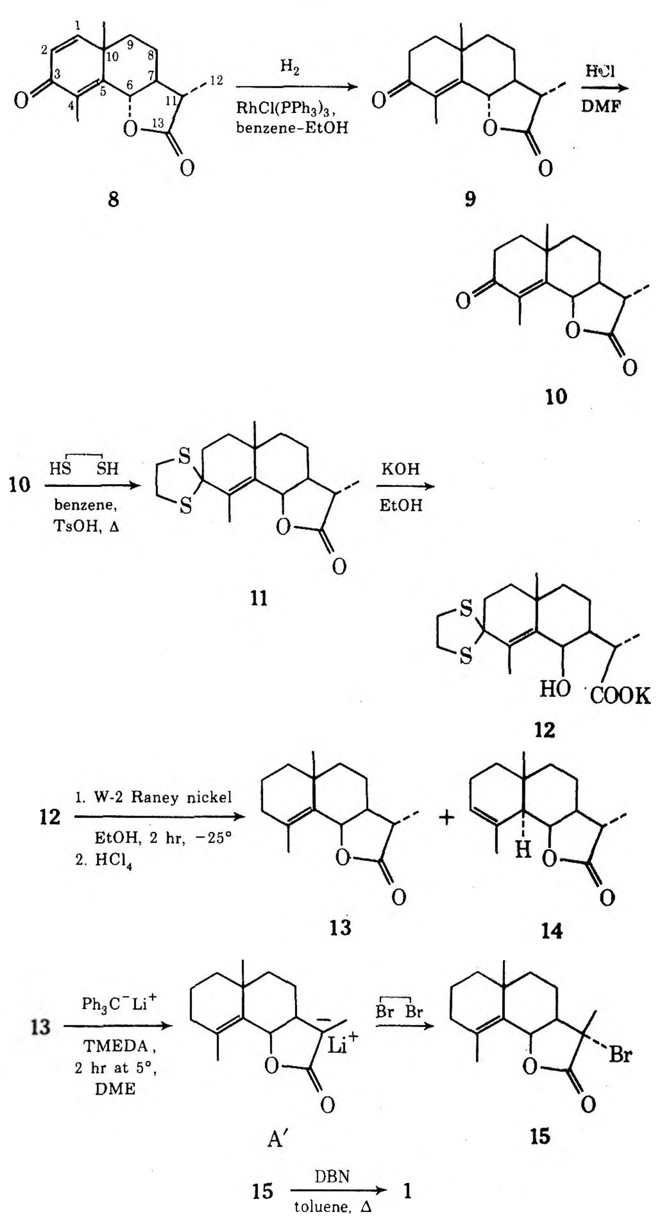


Chart II



cess of triphenylmethyllithium, attacked bromine[19] rather than carbon to afford a single isolable α-bromo lactone, **7**, in 85% yield.

The (*r*-2′,*c*-2)[20] configuration assigned to the C–Br bond in lactone **7** is based on the following evidence: (a) this configuration corresponds to the introduction of bromine from the less hindered side; (b) the H-2′ proton is deshielded by 0.6 ppm with respect to starting material **3**; this deshielding is explained by a spatial proximity[21] between the H-2′ proton and bromine.

The α-bromo lactone **7** on treatment for a few minutes with 1,5-diazabicyclononene (DBN) in refluxing toluene afforded as the sole isolable product the known[8c] α-methylene lactone **5** in 80% yield (overall yield of conversion of α-methyl lactone → α-methylene lactone = 65%).

No endocyclic olefin could be detected from treatment of the α-bromo cis lactone **7** under these anti (or trans) dehydrobromination conditions, thus giving further evidence for the assignment of the (*r*-2′,*c*-2) configuration to the C–Br bond. [The relatively low reaction temperature should preclude a syn (or cis) elimination.][22]

For the synthesis of (−)-frullanolide (**1**), (−)-α-santonin (**8**)[23] was choosen as starting material because of its availability. 1,2-Dihydro-6-episantonin (**10**) was secured from α-santonin in 90% overall yield *via* 1,2-dihydro-α-santonin (**9**), by hydrogenation over tris(triphenylphosphine)chlororhodium(I)[24] followed by epimerization in DMF saturated with HCl gas[25] (Chart II).

Removal of the C-3 oxygen was effected using modifications of the general thioketalization–reduction procedure.[26] The known thioketal **11** was obtained in a much improved yield[27] (>90%) by heating **10** in benzene with excess ethanedithiol in the presence of a catalytic amount of *p*-toluenesulfonic acid. Initial attempts to reduce **11** with Raney nickel in absolute ethanol at room temperature led solely to acidic material by hydrogenolysis[28] of the axial C-6–O bond, in dramatic contrast to the trans system **16** (*vide infra*).

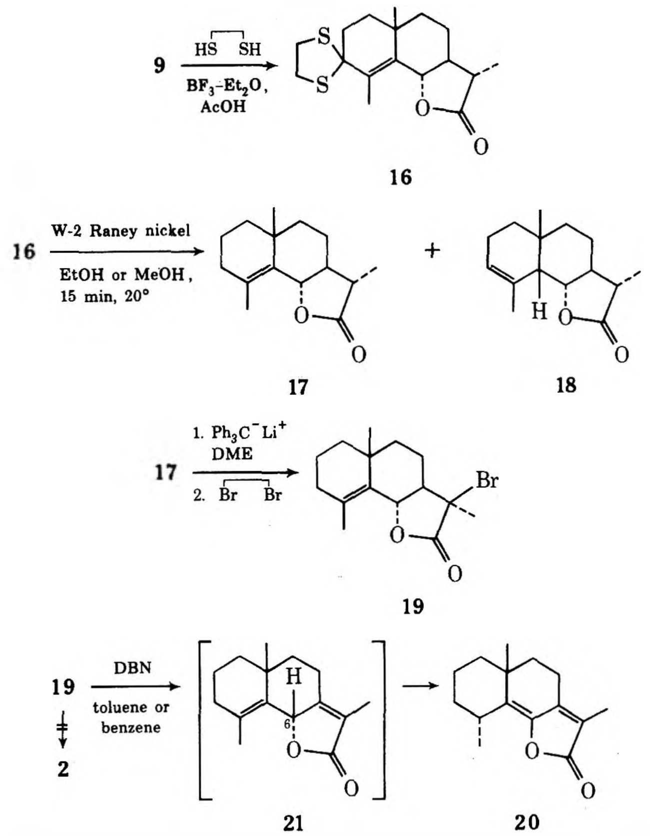
However, the hydroxy salt **12**, obtained by treatment of **11** with KOH in 95% EtOH, was much less prone to hydrogenolysis.[29] The salt **12** was stirred with W-2 Raney nickel (10 ml/g of **11**) in 95% EtOH (or MeOH) containing KOH at −25° and the mixture was then acidified and chromatographed to give 11β(H),11,12-dihydrofrullanolide (**13**)[30] in better than 40% overall yield. A second nonacidic product, tentatively identified as lactone **14**, was formed in about 10% yield. In the desulfurization reactions examined, higher yields were obtained by treatment of the thioketals with *active* W-2 Raney nickel at *low* temperatures than under the more often used desulfurization conditions[31] for sensitive systems (reflux for several hours with deactivated Raney nickel in acetone or ethanol). In the case of thioketal **11**, the desulfurization is complete in 2 hr at −25°.

The carbanion A′ (Chart II), unlike that of the model system **3**, is very unstable, and could only be obtained satisfactorily by treatment of **13** with excess triphenylmethyllithium in 1,2-dimethoxyethane in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). Carbanion A′, when quenched with 1,2-dibromoethane, afforded a single α-bromo lactone **15** in *ca.* 50% yield. The stereochemical assignment of an α configuration for the C–Br bond was made on the same basis as in the model experiment (steric considerations, deshielding by 0.6 ppm of the H-6 proton, and course of the subsequent elimination of HBr). The α-bromo lactone **18** on treatment with 1,5-diazabicyclononene in refluxing toluene afforded (−)-frullanolide (**1**) (mp 75–76°, $[\alpha]_D$ −112°) in 80% yield, identical in all respects with natural (−)-frullanolide[3a,b] (including skin tests).

Having found an efficient route for α-methyl → α-methylene conversion for cis-fused lactones, we attempted to utilize the same method in a synthesis of (+)-arbusculin B (**2**), an isomer of (−)-frullanolide with a trans-fused lactone junction (Chart III).

The known[27] 11,12-dihydro-γ-cyclocostunolide (**17**) was secured in 70% overall yield from 1,2-dihydro-α-santonin (**9**) by thioketalization to give **16** followed by treatment with Raney nickel. Removal of the thioketal group in **16** with active W-2 Raney nickel was complete after 15 min at room temperature and led to more than 80% of the desired 11,12-dihydro-γ-cyclocostunolide (**17**).[32] The same thioketal **16**, when treated with W-2 Raney nickel in refluxing ethanol for 4 hr, led to only 33% of the deoxy compound **17**.[27] Dihydro-γ-cyclocostunolide (**17**), by successive treatment with triphenylmethyllithium followed by 1,2-dibromoethane, afforded a single α-bromo lactone **19** in 80% yield. The β configuration assigned to the C–Br bond in **19** is based on the following evidence: (a) this configuration corresponds to the introduction of bromine from the less hindered side; (b) the H-6 proton is deshielded by 0.3 ppm with respect to starting material **17**; this deshielding is explained by a 1,3-diaxial interaction[21]

Chart III



between the axial H-6 proton and bromine, which is only compatible with a β configuration of the C–Br bond.

The α-bromo lactone **19** upon treatment with DBN does not afford (+)-arbusculin B (**2**) but the endocyclic unsaturated lactone **20** in 78% yield (λ_{max} 289 nm). Endocyclic lactone **20** probably arises from **21** (formed *via* trans elimination of HBr) through a facile enolization of the axial and doubly activated H-6 proton in the presence of excess DBN.

Since in the trans lactone series a trans elimination of HBr leading to the corresponding endocyclic unsaturated lactones[33] seemed to be the preferred pathway, a different approach was investigated for the synthesis of α-methylene-γ-butyrolactones from trans-fused α-methyl butyrolactone precursors. It appeared that an X group that possessed the same stereochemistry but could undergo an elimination in a syn manner (Scheme I) might give rise to the desired products, *e.g.*, *via* ester pyrolysis.[34]

A modification of the procedure of Larsen and Lawesson[35] was used to effect benzoyloxylation (X = PhCO$_2$). By treatment of the enolate of lactone **4**, formed as usual, with dibenzoyl peroxide[35,36] at 5°, the expected α-benzoyloxylactone **22**[37] could be isolated in 50% yield.[38] Pyrolysis at 600° of α-benzoyloxy lactone **22** gave after silica gel chromatography a readily separated 3:1 mixture of the known α-methylene-γ-butyrolactone[8c] **6** and the known[39] endocyclic unsaturated lactone **23** in 60% yield (Chart IV).

For the synthesis of (+)-arbusculin B (**2**) the enolate of 11,12-dihydro-γ-cyclocostunolide (**17**) was added to a cooled solution of dibenzoyl peroxide, the excess peroxide was destroyed, and the product was chromatographed on silica gel, affording the benzoyloxy lactone **24** (Chart V) in 50% yield (70% based on consumed **17**). The β configuration assigned to the C–OC(=O)Ph bond in lactone **24** was based on the following evidence: (a) this configuration corresponds to the introduction of the benzoyloxy group from the less hindered side; (b) the axial H-6 proton is deshielded by 0.65 ppm with respect to starting material **17**. This deshielding is explained by a spatial 1,3-diaxial proximity between H-6 and the benzoyloxy group which involved a field effect[40] due to either the carbonyl or the phenyl group, and is only compatible with a β configuration for the C–OC(=O)Ph bond.

Chart IV

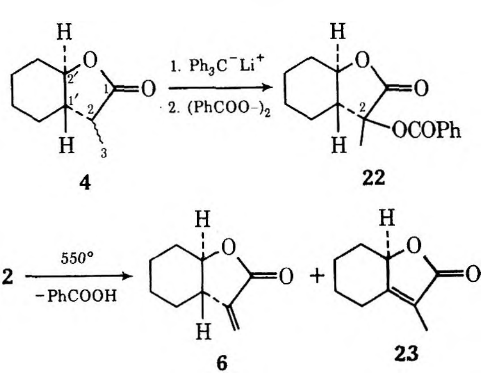
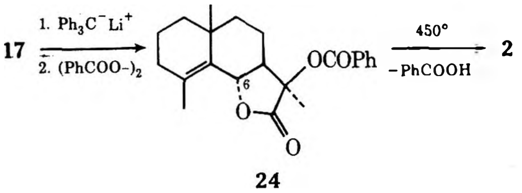


Chart V



Pyrolysis at 450° of α-benzoyloxylactone **24** gave, after silica gel chromatography, (+)-arbusculin B (**2**), mp 86–88°, $[\alpha]_D$ +46° (CHCl$_3$), in 35% yield.[41] Spectroscopic[10] and chromatographic[42] properties of the synthetic compound were in full agreement with those of authentic material.

Since the pyrolysis of carboxylic esters is a unimolecular syn elimination[34] (which may proceed in two steps[22b,43]) the stereospecificity in which (+)-arbusculin B was obtained (no trace of the endocyclic isomer could be detected) from pyrolysis of benzoyloxylactone **24** gives further evidence for the assignment of a α configuration to the C–OC(=O)Ph bond.

In summary, both cis- and trans-fused α-methylene-γ-butyrolactones have been synthesized from the corresponding α-methyl lactones by procedures which should be capable of application to cis and trans α-methyl-γ-butyrolactones in general. A high-yield synthesis of endocyclic unsaturated methyl lactones is also available.

Experimental Section[44]

General Procedure for Preparation of Triphenylmethyllithium Solutions. In a flame-dried flask under N$_2$, triphenylmethane (distilled, recrystallized from anhydrous methanol, and dried under high vacuum for 24 hr) (1 mmol) was dissolved in dry THF or DME (1 ml). To the stirred solution, kept under a static atmosphere of dry nitrogen, was added dropwise through a serum cap a solution of *n*-butyllithium in hexane (0.95 mmol, Fluka or Merck). The solution, which became dark red immediately, was stirred for 1 hr at room temperature prior to further use.

c-2-Bromo-*r*-2′*H*,*c*-1′*H*,2(2′-hydroxycyclohexyl)propionic Acid Lactone (7). A solution of *cis*-α-methyl lactone **3**[12] (240 mg, 1.58 mmol) in dry THF (3 ml) was treated with excess triphenylmethyllithium (from 1 g of triphenylmethane, 1.7 ml of *n*-BuLi in hexane, and 6 ml of THF). The mixture was stirred for 2 hr at room temperature and treated with dry 1,2-dibromoethane (2 ml). After 2 hr of continued stirring the product was isolated with ether. The crude mixture was immediately chromatographed over 40 g of silica gel. Elution with benzene gave α-bromo lactone **7** (310 mg, 85%). Recrystallization from hexane gave an analytical sample: mp 107.5–109°; M·$^+$ *m/e* 232–234; ν_{max} (CCl$_4$) 2940, 2860, 1785, 1204, 1178, 1117, and 968 cm^{-1}; δ_{TMS} (CCl_4) 4.85 (t, *J* = 4 Hz, 1 H), 2.38 (m, 2 H), and 1.80 ppm (s, 3 H). *Anal.* Calcd for $C_9H_{13}BrO_2$: C, 46.37; H, 5.62; Br, 34.29. Found: C, 46.6; H, 5.5; Br, 34.0.

c-1′*H*-r-2′*H*,2-(2′-Hydroxycyclohexyl)propenoic Acid Lactone (5). A solution of 104 mg (0.445 mmol) of α-bromo lactone 7 in 2 ml of anhydrous toluene and 250 μl of 1,5-diazabicyclononene was refluxed under nitrogen for 45 min. The cooled solution was extracted with ether and washed with a cooled (~5°) 10% hydrochloric acid solution, which was back extracted with ether. The combined ether extracts were dried over potassium carbonate, evaporated, and short path distilled, affording 54 mg (78%) of the pure known[8c] methylene lactone **5**: bp 70° (bath temperature, 0.05 mm); M$\cdot^+$ *m/e* 152; ν_{max} (film) 2920, 2860, 1767, 1449, 1367, 1342, 1161, 1125, 1012, 977, and 963 cm^{-1}; δ_{TMS} ($CDCl_3$) 6.18 (d, *J* = 2, 5 Hz, 1 H), 5.52 (d, *J* = 2, 5 Hz, 1 H), 4.53 (q, *J* = 5, 5 Hz, 1 H), and 3.02 ppm (m, 1 H).

1,2-Dihydro-α-santonin[45] (9). Sims'[24] modified procedure was used in the preparation of **9**. To a solution of 5 g of (−)-α-santonin (8) (20 mmol) in 250 ml of a 1:1 mixture of benzene and 95% ethanol was added 110 mg of tris(triphenylphosphine(chlororhodium(I) (Fluka). The mixture was flushed with hydrogen and then very efficiently stirred under hydrogen. After 12 hr the theoretical amount of hydrogen was absorbed. The solvents were evaporated and the mixture was filtered over 50 g of neutral alumina (grade II–III). Elution with 10% ethyl acetate in benzene afforded a brown oil (5 g) which was crystallized from a 1:1 mixture of hexane–carbon tetrachloride, affording 4.95 g (98%) of 1,2-dihydro-α-santonin (**9**): mp 102° after a phase change at 95°; λ_{max} (EtOH) 244 nm (ε 16,200); ν_{max} (KBr) 1782, 1667, and 1619 cm^{-1}; δ_{TMS} ($CDCl_3$) 4.69 (d, *J* = 9 Hz, 1 H), 2.00 (d, *J* = 2 Hz, 3 H), 1.32 (s, 3 H), and 1.26 ppm (d, *J* = 7 Hz, 3 H). [lit.[45] mp 101–102°; λ_{max} 244 nm (ε 14,700); ν_{max} (CCl_4) 1795, 1680, and 1628 cm^{-1}].

1,2-Dihydro-6β-santonin[46] (10). A modified procedure of Piers and Cheng[25] was used for the preparation of **10**. A solution of 2.48 g of 1,2-dihydro-α-santonin (**9**, 10 mmol, dried under vacuum for one night) in 15 ml of dry dimethylformamide was treated with 7.5 ml of a solution of dimethylformamide containing 1.5 g of hydrogen chloride and was heated under nitrogen for 30 min at 85°. The yellow solution was evaporated at 70° (20 mm), the residue was taken up in 50 ml of a 1:1 mixture of benzene and ether, and this solution was washed with ether. The residue of the organic layer (2.55 g) was chromatographed over 100 g of silica gel and the desired product was eluted with a 4:1 mixture of benzene and ethyl acetate. It was obtained as a yellow syrup (2.41 g) which crystallized from benzene–hexane as colorless, compact prisms: mp 125°; λ_{max} (EtOH) 245 nm (ε 14,600), 327 (44); ν_{max} (KBr) 1772, 1668, and 1614 cm^{-1}; δ_{TMS} ($CDCl_3$) 5.49 (d, *J* = 6 Hz, 1 H), 1.96 (s, 3 H), 1.44 (d, *J* = 8 Hz, 3 H), and 1.33 ppm (s, 3 H) (lit.[46] mp 127°).

Thioketal of 1,2-Dihydro-6β-santonin (11). A solution of 5.28 g of 1,2-dihydro-6β-santonin (**10**, 2.12 mmol) in 450 ml of anhydrous benzene, 15 ml of ethanedithiol, and 400 mg of *p*-toluenesulfonic acid was heated at reflux under nitrogen for 10 hr. The cooled solution was extracted with chloroform, washed with a saturated solution of sodium bicarbonate, and dried under vacuum (0.01 mm) overnight. The crude mixture obtained was chromatographed over 100 g of silica gel and the thioketal **11** was eluted with chloroform and crystallized from hexane, affording 6.60 g (95%) of pure thioketal **11**: mp 163–164°; M$\cdot^+$ *m/e* 324; $[\alpha]_D$ −48° (*c* 0.11, $CHCl_3$); ν_{max} (KBr) 1772, 1615, 1455, 1277, 1236, 1212, 1200, 1185, 1165, 1012, 942, and 917 cm^{-1}; δ_{TMS} ($CDCl_3$) 5.36 (d, *J* = 5 Hz, 1 H), 3.33 (m, 4 H), 2.05 (s, 3 H), 1.38 (d, *J* = 7.5 Hz, 3 H), and 1.10 ppm (s, 3 H). *Anal.* Calcd for $C_{17}H_{24}S_2O_2$: C, 62.95; h, 7.45; S, 19.75. Found: C, 63.0; H, 7.4; S, 19.7.

(−)-11,12-Dihydro-11β$_H$-frullanolide (13). A solution of 2.00 g (6.17 mmol) of thioketal **11** in 95% ethanol was treated under nitrogen with 8.1 g of potassium hydroxide. After 90 min, the mixture was cooled to −40° and 20 ml (~12 g) of W-2 Raney nickel[47] in precooled 95% ethanol was rapidly added. The vigorously stirred mixture was kept for 2 hr between −25 and −30° under nitrogen. The cold mixture was filtered, washed with 95% ethanol, and acidified by slow addition of a 10% solution of hydrogen chloride. The green filtrate was extracted with a 1:1 mixture of benzene and ether, the organic phase was washed twice with a saturated solution of sodium bicarbonate, and the combined water phases were back extracted with ether. The combined organic phases were dried over magnesium sulfate and evaporated, affording 1.2 g of an oil which was chromatographed over 100 g of silica gel. Elution with benzene gave 590 mg (40%) of dihydrofrullanolide **13** and then 85 mg (6%) of its isomer **14**. The analytical sample of **13** was prepared by recrystallization from hexane: mp 119–121°; M$\cdot^+$ *m/e* 234; $[\alpha]_D$ −58° (c 0.12, $CHCl_3$); ν_{max} ($CHCl_3$) 1750, 1645, 1455, 1370, 1310, 1195, 1075, 1005, 940, and 910 cm^{-1}; δ_{TMS} ($CDCl_3$) 5.43 (d, *J* = 5 Hz, 1 H), 2.42 (q, *J* = 8 Hz, 1 H), 1.77 (s, 3 H), 1.33 (d, *J* = 8 Hz, 3 H), and 1.07 ppm (s, 3 H). *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.9; H, 9.45. The analytical sample of **5α,6α,11β$_H$-eudesm-3-en-6,13-olide (14)** was prepared by recrystallization from *n*-hexane: mp 102.5–103.5°; M$\cdot^+$ *m/e* 234; $[\alpha]_D$ −108° (c 0.14, $CHCl_3$); ν_{max} ($CHCl_3$) 1762, 1450, 1382, 1340, 1208, 1170, 1082, 1000, and 975 cm^{-1}; δ_{TMS} ($CDCl_3$) 5.42 (s, br, 1 H) 4.45 (dd, *J* = 6.5 Hz, 1 H), 1.82 (s, br, 3 H), 1.22 (d, *J* = 7 Hz, 3 H), and 0.91 ppm (s, 3 H). *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.9; H, 9.5.

11α-Bromo-11,12-dihydrofrullanolide (15). A cooled (0°) solution of 190 mg (0.82 mmol) of lactone **13** in anhydrous 1,2-dimethoxyethane (2 ml) was added to a cooled solution (0°) of triphenylmethyllithium (from 2.4 g of triphenylmethane, 6 ml of 1,2-dimethoxyethane, 1.5 ml of *N,N,N′,N′*-tetramethylenediamine, and 3.3 ml of *n*-butyllithium in hexane). The mixture, kept under nitrogen, was stirred for 3 hr, treated with 4 ml of 1,2-dibromoethane, and then stirred for an additional 75 min. The usual workup afforded a residue which was immediately chromatographed over 75 g of silica gel. Elution with benzene afforded 115 mg (48%) of bromide **15**: M$\cdot^+$ *m/e* 312, 314; ν_{max} ($CHCl_3$) 1775 and 1650 cm^{-1}; δ_{TMS} ($CDCl_3$) 5.68 (d, *J* = 4 Hz, 1 H), 1.92 (s, 3 H), 1.80 (s, 3 H), and 1.01 ppm (s, 3 H).

(−)-Frullanolide (1). A solution of 70 mg (0.22 mmol) of bromide **15** in 2 ml of anhydrous toluene and 150 μl of 1,5-diazabicyclononene was heated at reflux under nitrogen for 60 min. The cooled solution was extracted with ether and washed with a cold (~5°) 10% solution of hydrogen chloride and then with saturated brine. The combined water phases were back extracted with ether and the combined organic layers were dried over potassium carbonate and evaporated, affording a residue which was chromatographed over 10 g of silica gel. Elution with a 24:1 mixture of benzene–ethyl acetate afforded 41 mg (80%) of (−)-frullanolide. The analytical sample was recrystallized from *n*-hexane: mp 75.5–76° (no depression when mixed with authentic natural material); M$\cdot^+$ *m/e* 232; $[\alpha]_D$ −112° (*c* 0.155, $CHCl_3$); ν_{max} (CCl_4) 1765, 1667, 1644, 1264, 1143, 1122, 1006, 940, and 915 cm^{-1}; ν_{TMS} ($CDCl_3$) 6.17 (d, *J* = 1.5 Hz, 1 H), 5.58 (d, *J* = 1.5 Hz, 1 H), 5.27 (d, *J* = 6 Hz, 1 H), 2.95 (m, 1 H), 1.75 (s, 3 H), and 1.08 ppm (s, 3H). *Anal.* Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.4; H, 8.8 (lit.[3a,b] mp 76°, $[\alpha]_D$ −113°).

11,12-Dihydro-11β*H*-γ-cyclocostunolide (17). The procedure of Barton and coworkers[27] was modified affording lactone **17** *via* thioketal **16** in a substantially better yield. A solution of 2 g (6.17 mmol) of dihydrosantonin **9** in 20 ml of glacial acetic acid was cooled under nitrogen to ~5° and sirred with 4 ml of 1,2-ethanedithiol and 0.3 ml of freshly distilled boron trifluoride etherate. After 6 hr, an additional 0.3 ml of boron trifluoride was added and the mixture was stored at 5° for 15 hr. The product was isolated with ether and the residual ethanedithiol was removed under high vacuum, affording 2.57 g (98%) of thioketal **16**: mp 166–168°; M$\cdot^+$ *m/e* 324; ν_{max} ($CHCl_3$) 1772, 1665, 1460, 1382, 1330, 1315, 1280, 1242, 1170, 1140, 1030, and 985 cm^{-1}; δ_{TMS} ($CDCl_3$) 4.58 (d, br, 1 H), 3.30 (m, 4 H), 2.10 (d, *J* = 1.5 Hz, 3 H), 1.18 (d, *J* = 7 Hz, 3 H), and 1.14 ppm (s, 3 H).

A 2.50-g sample (7.72 mmol) of the above thioketal **16** in 250 ml of anhydrous methanol was stirred with 20 ml (*ca.* 12 g) of W-2 Raney nickel at room temperature for 15 min. The mixture was filtered through Celite, washed with methanol, and dried. The product was isolated with ether, affording 1.75 g of a clear oil. This oil was chromatographed over 150 g of silica gel. Elution with benzene gave 1.35 g (75%) of lactone **17** and 250 mg (14%) of an isomer **18**.

The analytical sample of **17** was obtained by crystallization from *n*-hexane: mp 89–90°; M$\cdot^+$ *m/e* 234; ν_{max} ($CDCl_3$) 1762, 1455, 1380, 1330, 1312, 1240, 1185, 1165, 1140, 1112, 1080, 1030, and 980 cm^{-1}; δ_{TMS} ($CDCl_3$) 4.55 (d, br, 1 H), 1.84 (s, br, 3 H), 1.22 (d, *J* = 6.5 Hz, 3 H), and 1.13 ppm (s, 3 H). The analytical sample of **11,12-dihydro-5β,11β*H*-α-cyclocostunolide (18)** was obtained by recrystallization from *n*-hexane: mp 119–121°; M$\cdot^+$ *m/e* 234; $[\alpha]_D$ −65° (c 0.100, $CHCl_3$); ν_{max} ($CHCl_3$) 1769, 1455, 1385, 1271, 1245, and 1005 cm^{-1}; δ_{TMS} ($CDCl_3$) 5.50 (m, 1 H), 4.34 (q, *J* = 5, 9 Hz, 1 H), 1.67 (s, br, 3 H), 1.19 (d, *J* = 7 Hz, 3 H), and 1.11 ppm (s, 3 H). *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.7; H, 9.4.

11β-Bromo-11,12-dihydro-γ-cyclocostunolide (19). A solution of 54 mg (0.23 mmol) of dihydro-γ-cyclocostunolide 17 in 1 ml of anhydrous 1,2-dimethoxyethane kept under nitrogen was added dropwise to a solution of triphenylmethyllithium (from 300 mg of triphenylmethane and 0.45 ml of *n*-butyllithium in hexane in 1.2 ml of 1,2-dimethoxyethane) at room temperature. After 15 min the stirred solution was cooled to 0° and stirring was continued for 75 min. The mixture was then treated with 0.5 ml of 1,2-dibromethane and stirred for 45 min at 0°. Extraction with ether afforded a mixture which was immediately chromatographed over 15 g of silica gel. Elution with benzene gave 55 mg (77%) of α-bromo lactone **19**. The analytical sample was recrystallized from *n*-hexane: mp 139–141°; $M\cdot^+$ *m/e* 312–314; $[\alpha]_D$ −2° (*c* 0.12 $CHCl_3$); ν_{max} ($CHCl_3$) 1780, 1455, 1381, 1293, 1130, 1065, 1032, and 980 cm^{-1}; δ_{TMS} ($CDCl_3$) 4.87 (d, br, 1 H), 1.89 (s, 3 H), 1.84 (d, *J* = 1.5 Hz, 3 H), and 1.15 ppm (s, 3 H). *Anal.* Calcd for $C_{15}H_{21}BrO_2$: C, 57.56; H, 6.76; Br, 25.23. Found: C, 57.7; H, 6.6; Br, 25.4.

4βH-Eudesma-5,7(11)-dien-6,13-olide (20). A solution of 78 mg (0.27 mmol) of α-bromo lactone **19** in 1.5 ml of anhydrous toluene or benzene was treated under nitrogen at reflux with 150 μl of 1,5-diazabicyclononene for 30 min. The cooled mixture was extracted with ether, washed with a cooled (~5°) hydrogen chloride solution and then with saturated brine, dried over potassium carbonate, and evaporated. The crude oil was chromatographed over 10 g of silica gel. The product was eluted with a 98:2 mixture of benzene and ethyl acetate, affording 47 mg (78%) of diene lactone **20**. The analytical sample was recrystallised as long needles from *n*-hexane: mp 114–115° (with beginning of sublimation); $M\cdot^+$ *m/e* 232; $[\alpha]_D$ − 206° (*c* 0.14, $CHCl_3$); λ_{max} (EtOH) 289 nm (ε 14,500); ν_{max} ($CHCl_3$) 1738, 1650, 1283, 1108, 1070, 1025, 998, 943, and 905 cm^{-1}; δ_{TMS} ($CDCl_3$) 2.60 (m, 3 H), 1.84 (s, br, 3 H), 1.42 (d, *J* = 6.5 Hz, 3 H), and 1.18 ppm (s, 3 H). *Anal.* Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.6; H, 8.7.

2-Benzoyloxy-*r*-2′*H*,*t*-1′*H*,2-(2′-hydroxycyclohexyl)propionic Acid Lactone (22). A solution of 290 mg (0.019 mmol) of *trans*-α-methyllactone 4[12] in 4 ml of anhydrous 1,2-dimethoxyethane was treated under nitrogen at room temperature for 2 hr with a solution of triphenylmethyllithium (from 1.2 g of triphenylmethane, 2.1 ml of *n*-butyllithium in hexane, and 10 ml of 1,2-dimethoxyethane). The enolate solution was added dropwise (behind a safety screen) with a hypodermic syringe to a cooled (~5°) solution of 2 g of recrystallized dibenzoyl peroxide in 10 ml of 1,2-dimethoxyethane. A white salt precipitated instantaneously. The stirring was maintained for 45 min. The excess peroxide was destroyed with a solution of 2 g of potassium iodide in 5 ml of water and 0.5 ml of acetic acid. Usual work-up afforded a residue which was immediately chromatographed over 50 g of silica gel. Elution with a 97:3 mixture of benzene and ethyl acetate afforded 330 mg (60%) of α-benzoyloxylactone **22** as an oil which could not be induced to crystallize, but was shown by tlc to be a single product: ν_{max} ($CHCl_3$) 1785, 1725, 1450, 1382, 1280, 1108, 1030, and 710 cm^{-1}; δ_{TMS} ($CDCl_3$) 8.01 (m, 2 H), 7.43 (m, 3 H), 4.25 (m, 1 H), and 1.74 ppm (s, 3 H).

***t*-1′*H*,*r*-2′*H*,2-(2′-Hydroxycyclohexyl)propenoic Acid Lactone (6).** The apparatus for vapor-phase pyrolysis used was almost identical with the one described by DePuy and King.[34]

A solution of 540 mg (2 mmol) of benzoyloxylactone **22** in 2 ml of anhydrous ether was introduced dropwise with a syringe on top of a vertical 30-cm Pyrex column, which was packed with 4-mm Pyrex beads, preequilibrated at 550° for 4 hr, and flushed with a 20 ml/min nitrogen stream. The products resulting from the pyrolysis were trapped in a flask at −78°, appearing after a contact time of about 20 sec. The cooled apparatus was washed with dry ether and the ether solution was washed with a 5% sodium hydroxide solution and then dried over potassium carbonate. Evaporation of the solvent led to 217 mg of an oil which was distilled and chromatographed over 15 g of silica gel. Elution with benzene afforded 125 mg (45%) of the known[8c] methylene lactone **6** and elution with a 4:1 mixture of benzene and ethyl acetate afforded 25 mg (~15%) of the known[39] α,β-unsaturated lactone **23**.

The methylene lactone **6** was distilled, bp 65° (0.01 mm), to give a sample identical in all respects with the one described by Marshall and Cohen.[8c]

Pure 2-(2′-hydroxycyclohexylidene)propionic acid lactone (23) was obtained by distillation and was identical with the previously prepared sample (*cf.* ref 33): bp 65–68° (bath temperature, 0.05 mm); mp ~20°; $M\cdot^+$ *m/e* 152; $n^{25}D$ 1.5069; λ_{max} (EtOH) 217 nm (ε 13,100); ν_{max} ($CHCl_3$) 1745, 1678, 1450, 1095, 1038, and 1027 cm^{-1}; δ_{TMS} ($CDCl_3$) 4.58 (m, 1 H) and 1.78 ppm (s, br, 3 H) [lit.[39] bp 121–124° (3 mm); $n^{25}D$ 1.5060; λ_{max} (EtOH) 217 nm (ε 14,150)].

11β-Benzoyloxy-11,12-dihydro-γ-cyclocostunolide (24). A solution of 700 mg (3 mmol) of dihydro-γ-cyclocostunolide **17** in 7 ml of 1,2-dimethoxyethane was rapidly added at room temperature to a solution of triphenylmethyllithium (from 4 g of triphenylmethane and 6 ml of *n*-butyllithium in hexane in 20 ml of 1,2-dimethoxyethane). After 15 min, the stirred solution was cooled to 0° for 2 hr and then added dropwise (behind a safety screen) with a hypodermic syringe to a cooled (5°) solution of 5 g of dibenzoyl peroxide in 20 ml of 1,2-dimethoxyethane. A white solid precipitated almost instantaneously. The stirring was maintained for 1 hr and then the excess peroxide was destroyed with a solution of 4 g of potassium iodide in 10 ml of water and 1 ml of acetic acid. Formation of iodine was immediate. The mixture was stirred for another 15 min at 0° followed by the usual work-up, which gave a residue which was chromatographed over 150 g of silica gel. Elution with benzene gave 550 mg of α-benzoyloxylactone **24** and 150 mg of starting material (yield 67%). The analytical sample of **24** was obtained by recrystallization from *n*-hexane: mp 139–140°; $M\cdot^+$ *m/e* 354; $[\alpha]_D$ +17° (*c* 0.29, $CHCl_3$); ν_{max} ($CHCl_3$) 1780, 1725, 1605, 1382, 1300, 1280, 1180, 1140, 1115, 1095, 1040, 985, and 705 cm^{-1}; δ_{TMS} ($CDCl_3$) 8.00 (m, 2 H), 7.50 (m, 3 H), 5.10 (d, *J* = 10 Hz, 1 H), 1.79 (s, br, 3 H), 1.68 (s, 3 H), and 1.01 ppm (s, 3 H). *Anal.* Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.6; H, 7.6.

(+)-Arbusculin B (2). A solution of 60 mg (0.17 mmol) of α-benzoyloxylactone **24** in 1 ml of anhydrous ether was added dropwise onto the pyrolysis apparatus described earlier preequilibrated at 450° and flushed with a nitrogen stream of 30 ml/min. The apparatus was washed with ether and the ethereal solution obtained was washed with a 5% sodium hydroxide solution, dried over potassium carbonate, and evaporated. The residue was chromatographed over 10 g of silica gel. Elution with benzene afforded 14 mg of (+)-arbusculin B and then 5 mg of starting material **24** (yield 35%, 40% based on consumed **24**). The analytical sample of (+)-arbusculin B was obtained by crystallization from *n*-pentane: mp 86–88°; $M\cdot^+$ *m/e* 232; $[\alpha]_D$ +46° (*c* 0.104, $CHCl_3$); ν_{max} ($CHCl_3$) 1763, 1665, 1452, 1290, 1254, 1146, 1133, 1034, 978, 941, and 907 cm^{-1}; δ_{TMS} ($CDCl_3$) 6.12 (d, *J* = 3 Hz, 1 H), 5.44 (d, *J* = 3 Hz, 1 H), 4.52 (d, br, *J* = 12 Hz, 1 H), 2.53 (m, 1 H), 1.85 (s, 3 H), and 1.11 ppm (s, 3 H) [lit.[10a] mp 86.5–88°; $[\alpha]_D$ +47.3° ($CHCl_3$)]. *Anal.* Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.6; H, 8.75.

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Registry No. **1**, 27579-97-1; **2**, 24164-19-0; **3**, 2205-25-6; **5**, 16822-06-3; **7**, 42807-10-3; **8**, 481-06-1; **9**, 42807-12-5; **10**, 25645-13-0; **11**, 37720-27-7; **13**, 37720-28-8; **14**, 42807-16-9; **15**, 37720-29-9; **16**, 20482-46-6; **17**, 42807-19-2; **18**, 42807-20-5; **19**, 42807-21-6; **20**, 42807-22-7; **22**, 38602-10-7; **23**, 15174-78-4; **24**, 38602-09-4; 1,2-dibromoethane, 106-93-4; 1,5-diazabicyclononene, 3001-72-7; 1,2-ethanedithiol, 540-03-6.

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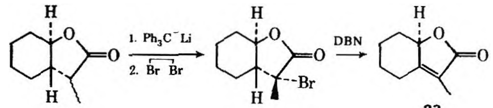

4 i 23

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Photosensitive Protecting Groups of Amino Sugars and Their Use in Glycoside Synthesis. 2-Nitrobenzyloxycarbonylamino and 6-Nitroveratryloxycarbonylamino Derivatives[1]

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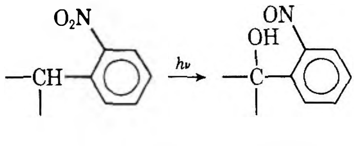
2-Nitrobenzyloxycarbonyl and 6-nitroveratryloxycarbonyl derivatives of 2-amino-2-deoxy-D-glucose and of 2-amino-2-deoxy-D-galactose were prepared and characterized. 2-Deoxy-2-(2-nitrobenzyloxycarbonyl)amino-1,3,4,6-tetra-*O*-acetyl-D-glucopyranose was prepared by acetylation in pyridine and was converted by hydrogen chloride in acetic acid to the 1-chloro derivative (under the same conditions a benzyloxycarbonyl group is removed). The latter compound was condensed with methanol, using mercuric cyanide, to yield methyl 2-deoxy-2-(2-nitrobenzyloxycarbonyl)amino-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside. Irradiation of the 2-nitrobenzyloxycarbonyl and the 6-nitroveratryloxycarbonyl derivatives afforded the free amino derivatives in high yields. Polymer-bound aldehyde reagents were used in some of these photochemical reactions.

The use of photosensitive protecting groups is of potential importance to many areas of synthetic chemistry and especially in syntheses involving polyfunctional molecules such as peptides and saccharides. These groups should be stable to a variety of chemical treatments and cleaved readily by irradiation.

Nitro aromatic compounds containing benzylic hydrogens ortho to the nitro group are light sensitive.[3] The primary photochemical reaction that occurs in such compounds is the internal redox reaction shown in Scheme I.

Scheme I



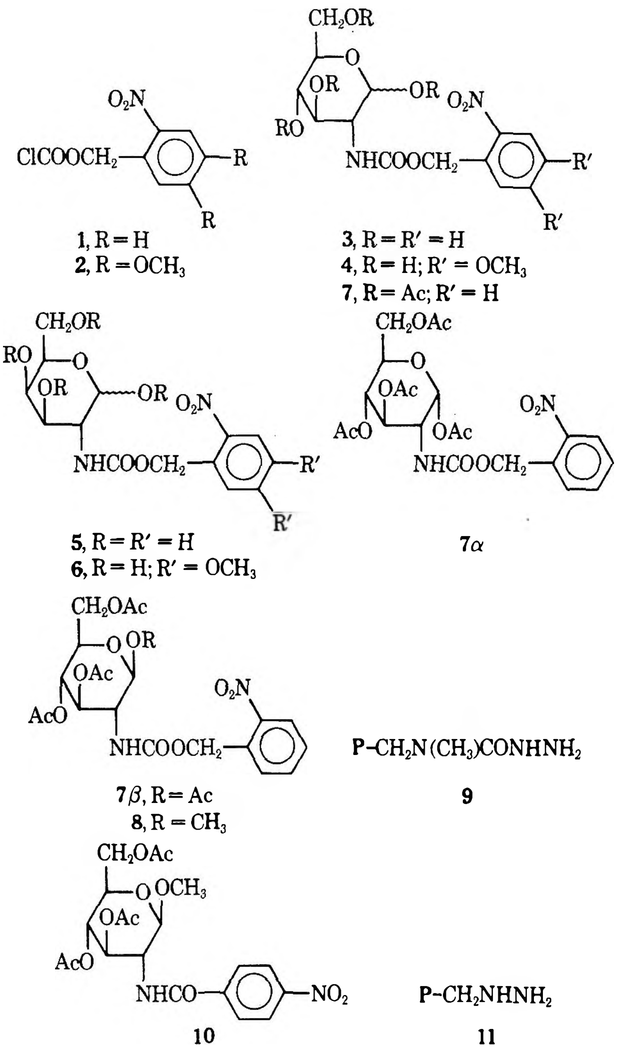
This reaction was used in our laboratory for designing light-sensitive protecting groups for the amino, carboxyl, and sulfhydryl functions in amino acids and peptides.[4] Recently we have also prepared light-sensitive glycosides[5] and ethers.[1b,6] Such glycosides were even used for oligosaccharide synthesis on a solid support.[7]

In the present work we describe the use of 2-nitrobenzyloxycarbonyl (NBOC) and 6-nitroveratryloxycarbonyl (NVOC) as protecting groups for the amino function in amino sugars.

Results and Discussion

2-Nitrobenzyloxycarbonyl chloride (NBOCCl, 1) and 6-nitroveratryloxycarbonyl chloride (NVOCCl, 2) were prepared by bubbling phosgene through dioxane solutions of 2-nitrobenzyl alcohol or 6-nitroveratryl alcohol (Scheme II).

Scheme II



The two reagents that are quite stable in storage and react with 2-amino-2-deoxy-D-glucose under Schotten-Baumann conditions to give compounds 3 and 4, respectively. NBOCCl (1) and NVOCCl (2) reacted in the same fashion with 2-amino-2-deoxy-D-galactose, yielding compounds 5 and 6. Compound 3 was totally acetylated in pyridine, yielding the α,β mixture 7 that could be further separated on silica gel. The difference in specific rotation between the two is not particularly great (probably owing to the presence of the aromatic nitro chromophore). The nmr spectrum of compound 7α, however, has the expected $J_{1,2}$ value of 3.5 Hz while that of 7β has a $J_{1,2}$ value of 8.5 Hz. The ratio of compound 7α to compound 7β in the mixture 7 obtained by acetylation was found to be 2.1:1 by examination of the optical rotation and the uv absorbancy of the isomers after resolution on silica gel as described in the Experimental Section.

We have compared the stability of NBOC, NVOC, and benzyloxycarbonyl (Z) groups in 2-amino-2-deoxy-D-glucose and in alanine derivatives using hydrogen chloride in acetic acid or (when the solubility was low) hydrogen chloride in acetic acid–trifluoroacetic acid (Table I). As expected, under these conditions the order of increasing stability of these derivatives is Z < NVOC < NBOC, which may be explained by the effect of the aromatic

Scheme III

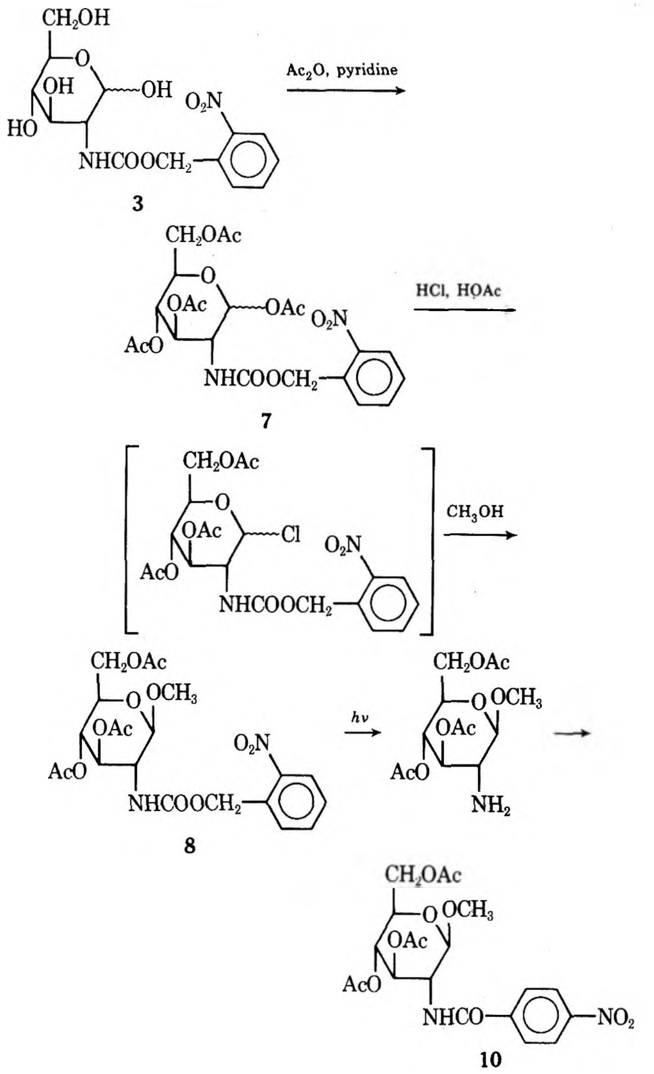


Table I
Splitting of 2-Nitrobenzyloxycarbonyl (NBOC), 6-Nitroveratryloxycarbonyl (NVOC), and Benzyloxycarbonyl (Z) Groups by Hydrogen Chloride

Reactant	Product	Yield, %
NBOC-L-Ala[a]	Alanine	0.5
NVOC-L-Ala[a]	Alanine	8
Z-L-Ala[a,b]	Alanine	55
3[c]	2-Amino-2-deoxy-D-glucose	53
4[c]	2-Amino-2-deoxy-D-glucose	80
2-(Benzyloxycarbonyl)-amino-2-deoxy-D-glucose[c,d]	2-Amino-2-deoxy-D-glucose	98

[a] The reactant (30 mg/ml) dissolved in hydrogen chloride (1.4 *N*) in acetic acid was kept under seal at room temperature for 48 hr. [b] M. Hunt and V. du Vigneaud, *J. Biol. Chem.*, **124,** 699 (1938). [c] The reactant (30 mg/ml) dissolved in hydrogen chloride (1.4 *N*) in acetic acid–trifluoroacetic acid (1:3) was kept sealed at room temperature for 1 hr. [d] E. Chargaff and M. Bovarnick, *J. Biol. Chem.*, **118,** 421 (1937). Yields of products were determined by the amino acid analyzer (±3% error).

nitro or methoxy substituents on an intermediate benzylium ion. The NBOC grouping is, thus, an urethane type of protecting group, quite stable under strong acidic conditions, which permit the use of the NBOC group during the preparation of 1-chloro derivatives, necessary for Königs–Knorr condensations. Similar treatment of Z derivatives will remove the protecting group.

The mixture 7 was treated with hydrogen chloride in acetic acid, giving the chloro derivative that was not isolated but was treated immediately with methanol in the presence of mercuric cyanide, yielding methyl 2-deoxy-2-(2-nitrobenzyloxycarbonyl)amino-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (8) in 56% yield, based on the mixture 7 (Scheme III). It is pertinent to note that no formation of 2-nitrobenzyl chloride was observed in this preparation and no evidence for the formation of an α anomer was obtained. This selectivity may be a result of a neighboring-group participation by the NBOC function and of the less hindered equatorial approach.

In a previous study[4] on NBOC and NVOC derivatives of amino acids and peptides it turned out that, although the photoremoval of the protecting groups from amino functions was judged to be quantitative by the release of carbon dioxide, the newly formed amino function further reacted with components of this irradiation mixture (*e.g.*, 2-nitrosobenzaldehyde). In order to achieve quantitative yield of the amino derivative it was found necessary to add aldehyde reagents or sulfuric acid. As the result, it became subsequently difficult to isolate the desired product from the colored reaction mixture. In the present work, sulfuric acid was occasionally used during the photoremoval of NBOC or NVOC derivatives or, alternately, we have introduced polymeric carriers of aldehyde reagents. We have found that these polymeric reagents were the most suitable aldehyde reagents. They increase the yield of the free amino derivative, and will react with colored by-products in the reaction mixture. They could be filtered off following the photochemical reaction, thus affording the relatively pure amino product in solution.

The NBOC was cleaved photochemically from compound 8 in the presence of sulfuric acid or P–$CH_2N(CH_3)CONHNH_2$ (9),[8] giving the free amino derivative, as suggested by its chromatographic behavior and staining properties and the preparation of its 2-(4-nitrobenzoyl) derivative (10).[9] Although the optical rotation of this compound is rather high for a β anomer (+34.7°), the nmr supports the proposed structure and in particular $J_{1,2} = 8.0$ Hz corresponds to the axial–axial interaction present in the β anomer.

Furthermore, we have photochemically split the NVOC or NBOC groupings in compounds 4 and 3 to yield 2-amino-2-deoxy-D-glucose (Table II, Figure 1). The isolation of 2-amino-2-deoxy-D-glucose from the irradiated solution of compound 4 required, however, ion-exchange column fractionation[10] and afforded a low yield of product. The use of a hydrazine polymer (11) in the reaction mixture eliminated the need for column fractionation and increased the yield of 2-amino-2-deoxy-D-glucose isolated.

In conclusion, NBOC and NVOC derivatives of amino sugars are easily prepared. These protecting groups withstand a series of reactions during glycoside synthesis. They are photolyzed in high yield at wavelengths higher than 320 nm to give the free amino derivatives without affecting other functional groups in the molecule including acetates, glycoside, and hydroxy. The addition of polymeric aldehyde reagents to the reaction mixture did not affect the above functional groups and increased the yields of free amino derivatives. We have also demonstrated that using this approach one can obtain, very conveniently, a free amino function adjacent to the glycosidic bond, a situation present in many natural products.

Experimental Section

All melting points are corrected. Optical rotations were determined with a Bendix or a Perkin-Elmer Model 141 polarimeter. Nmr spectra were recorded on a Varian A-60 or a Bruker HFX-10

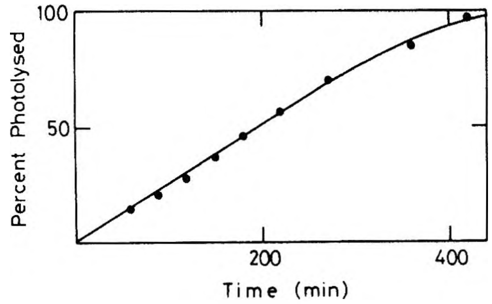


Figure 1. Photolysis of **4**. **4** (59.2 mmol) in water (40 ml) was irradiated (see Experimental Section) under a stream of nitrogen. The evolved carbon dioxide was absorbed in benzylamine and titrated: A. Patchornik and Y. Shalitin, *Anal. Chem.*, **33**, 1887 (1961).

Table II
Splitting of 2-Nitrobenzyloxycarbonyl (NBOC) and 6-Nitroveratryloxycarbonyl (NVOC) Groups by Irradiation

Reactant[a]	Product	Yield, %	Yield in presence of sulfuric acid acid (5 equiv), %
3	2-Amino-2-deoxy-D-glucose	82	96
5	2-Amino-2-deoxy-D-galactose	80	97
4	2-Amino-2-deoxy-D-glucose	89	100
6	2-Amino-2-deoxy-D-galactose	91	98

[a] Reactants (10^{-3} *M* in water–ethanol, 2:1) were irradiated for 10 hr as described in the Experimental Section. Yields were determined by the amino acid analyzer (±3% error).

instrument with tetramethylsilane as an internal standard. The uv spectra were taken on a Cary Model 14 spectrophotometer. Thin layer chromatography was carried out on fluorescent silica gel plates SIF or on aluminum oxide plates AlF (Reidel-de-Haën, Hannover), and the spots were observed under a uv lamp. Thick layer chromatography was carried out on plc plates silica gel F_{254} supplied by Merck. Plates were viewed after development under a uv lamp. The band of the desired material was extracted with ethyl acetate or methylene chloride, filtered, and evaporated. 2-Nitrobenzyl alcohol was purchased from Fluka, Switzerland. NBOC and NVOC derivatives were kept in the dark. Irradiations were carried out in an RPR-100 apparatus (Rayonet the Southern Co., Middletown, Conn.) using 3500-Å lamps and Pyrex equipment.

2-Nitrobenzyloxycarbonyl Chloride (NBOCCl, 1). 2-Nitrobenzyl alcohol (50 g) was dissolved in 1,4-dioxane (400 ml), and phosgene (200 g) was bubbled through the solution at such a rate that the temperature of the reaction mixture was kept below 40°. The reaction mixture was left at room temperature overnight, the excess of phosgene was then removed by bubbling nitrogen through, and the solution was evaporated *in vacuo* at a bath temperature under 40°. The residual oil (70 g, quantitative yield) constituted the pure product **1**. Compound **1** was clean by tlc (silica gel, developed with dichloromethane), d^{25} 1.32. The neutralization equivalent of this compound was determined[11] to be 217 (theoretical 215.5) by dissolving a sample of compound **1** (*ca.* 30 mg) in hot ethanol (5 ml) and titrating the released hydrochloric acid with 0.1 *N* sodium methoxide in methanol-benzene (3:7) using Thymol Blue as an indicator (color change from red to yellow). Little decomposition was observed when the solution was kept at 0° for 1 month.

6-Nitroveratryloxycarbonyl Chloride (NVOCCl, 2). 6-Nitroveratryl alcohol (50 g) was dissolved in dioxane (700 ml) with gentle heating. The solution was treated as described for compound **1**, yielding 64 g (quantitative yield) of yellow solid **2** that was kept for long periods at 0°. The neutralization equivalent, 283 (theoretical 275.5) was determined as described for compound **1**. A sample was recrystallized from benzene, mp 125–127° dec.

Anal. Calcd for $C_{14}H_{18}N_2O_9 \cdot \frac{1}{2}H_2O$: C, 45.78; H, 5.21; N, 7.63. 5.08. Found: C, 43.38; H, 3.59; Cl, 13.03; N, 5.01.

2-Deoxy-2-(2-nitrobenzyloxycarbonyl)amino-D-glucose (NBOC Glucosamine, 3). 2-Amino-2-deoxy-D-glucose hydrochloride (7.0 g, 32.5 mmol) and sodium bicarbonate (7.0 g, 83 mmol) were dissolved in water (140 ml). The reaction mixture was mechanically stirred and a solution of compound **1** (7.0 g, 32.5 mmol) in dioxane (200 ml) was added. The stirring was stopped after 6 hr, 1 *N* hydrochloric acid (18 ml) was added, and the solution was concentrated to one-third of its original volume. The precipitate was collected by suction and crystallized from ethanol–water (7:3): yield 10 g (83%); mp 202–204°; $[\alpha]^{24}\mathrm{D}$ +59.6° (3 min) → +64.6° (20 hr, final, c 2.5, pyridine).

Anal. Calcd for $C_{14}H_{18}N_2O_9 \cdot \frac{1}{2}H_2O$: C, 45.78; H, 5.21; N, 7.63. Found: C, 46.00; H, 5.18; N, 7.46.

A sample was heated to 110° for 5 hr under high vacuum.

Anal. Calcd for $C_{14}H_{18}N_2O_9$: C, 46.93; H, 5.06; N, 7.82. Found: C, 46.72; H, 4.94; N, 7.70.

2-Deoxy-2-(6-nitroveratryloxycarbonyl)amino-D-glucose (NVOC Glucosamine, 4). 2-Amino-2-deoxy-D-glucose hydrochloride (431 mg, 2 mmol) and sodium bicarbonate (420 mg, 5 mmol) were dissolved in water (50 ml). The reaction mixture was mechanically stirred and a solution of compound **2** (1.1 g, 4 mmol) in dioxane (70 ml) was added. The stirring was stopped after 6 hr, water (200 ml) was added, and the reaction mixture was washed with ethyl acetate (5 × 50 ml). The aqueous layer was concentrated to one-fourth of its original volume. The resulting precipitate was collected by suction and crystallized from ethanol–water (7:3): yield 575 mg (70%); mp 199–201°; $[\alpha]^{24}\mathrm{D}$ +64.5° (4 min final, c 1.2, pyridine).

Anal. Calcd for $C_{16}H_{22}N_2O_{11} \cdot \frac{1}{2}H_2O$: C, 44.96; H, 5.42; N, 6.56. Found: C, 45.07; H, 5.69; N, 6.74.

A sample was heated to 135° for 5 hr under high vacuum.

Anal. Calcd for $C_{16}H_{22}N_2O_{11}$: C, 45.93; H, 5.30; N, 6.70. Found: C, 45.75; H, 5.58; N, 6.78.

2-Deoxy-2-(2-nitrobenzyloxycarbonyl)amino-D-galactose (NBOC Galactosamine, 5). This compound was prepared as described for compound **4** but using 2-amino-2-deoxy-D-galactose hydrochloride (300 mg, 1.39 mmol) and compound **1** (430 mg, 2 mmol): yield 350 mg (70%); mp 165–166°; $[\alpha]^{24}\mathrm{D}$ +103° (7 min) → 74.2° (24 hr, final c 0.9, pyridine).

Anal. Calcd for $C_{14}H_{18}N_2O_9$: C, 46.93; H, 5.06; N, 7.82. Found: C, 46.79; H, 4.97; N, 7.71.

2-Deoxy-2-(6-nitroveratryloxycarbonyl)amino-D-glactose (NVOC Galactosamine, 6). This compound was prepared as described for compound **4** but using 2-amino-2-deoxy-D-galactose hydrochloride (430 mg, 2 mmol): yield 580 mg (70%); mp 193–195°; $[\alpha]^{24}\mathrm{D}$ +114° (10 min) → +98.5° (24 hr, final c 1.2, pyridine).

Anal. Calcd for $C_{16}H_{22}N_2O_{11} \cdot \frac{1}{2}H_2O$: C, 44.96; H, 5.42; N, 6.56. Found: C, 44.98; H, 5.59; N, 6.36.

A sample was heated to 135° for 5 hr under high vacuum.

Anal. Calcd for $C_{16}H_{22}N_2O_{11}$: C, 45.93; H, 5.30; N, 6.70. Found: C, 46.10; H, 5.55; N, 6.80.

2-Deoxy-2-(2-nitrobenzyloxycarbonyl)amino-1,3,4,6-tetra-*O*-acetyl-α- and -β-D-glucopyranose (7). Compound **3** (7.34 g) was dissolved in pyridine (70 ml) and acetic anhydride (15 ml) was added. The reaction mixture was left at room temperature overnight. Water (10 ml) was then added and the mixture was evaporated *in vacuo* after an additional 30 min. The oily residue was dissolved in chloroform (100 ml) and washed sequentially with 0.1 *N* hydrochloric acid, water, 5% sodium bicarbonate, and water. The solution was then dried over sodium sulfate and evaporated to yield 10 g (95%) of oil that solidified after being kept under petroleum ether (bp 30–60°) at −20° for 72 hr, $[\alpha]^{20}\mathrm{D}$ +50.9° (*c* 3.3, chloroform). Mixture **7** (80 mg) was resolved by preparative tlc using ether–methylene chloride (1:9) for development. The uv-absorbing bands were extracted with methylene chloride, evaporated to dryness, and dissolved in ethanol. The proportion of **7α** and **7β** was determined to be 2.1:1 by the absorbance at 260 nm of the extraction solutions and by the optical rotation of mixture **7**. Compound **7α** (52 mg) was crystallized from ether–ethyl acetate: mp 107°; $[\alpha]^{20}\mathrm{D}$ +69.0° (*c* 1.5, chloroform); $\lambda_{\max}$ (ethanol) 262 nm (ϵ 6200); nmr (90 MHz, $CDCl_3$) τ 1.89–2.73 (m, 4, aromatic), 3.84 (d, 1, H-1, $J_{1,2}$ = 3.5 Hz), 4.36–5.08 (m, 5, including benzylic CH_2 at τ 4.58, d, J = 3.0 Hz), 5.63–6.20 (m, 4), 7.80 (s, 3, $OCOCH_3$), 7.93 (s, 3, $OCOCH_3$), 7.97 (s, 3, $OCOCH_3$), 7.99 (s, 3, $OCOCH_3$).

Irradiation at τ 4.82 causes the collapse of the H-1 signal into a singlet.

Anal. Calcd for $C_{22}H_{26}N_2O_{13}$: C, 50.19; H, 4.98; N, 5.32. Found: C, 50.07; H, 5.27; N, 5.45.

Compound 7β (25 mg) was crystallized from 2-propanol: mp 151–152°; $[\alpha]^{20}\mathrm{D}$ +13.0° (c 2.2, chloroform); λ_{max} (ethanol) 262 nm (ϵ 6120); nmr (90 MHz, $CDCl_3$) τ 1.93–2.70 (m, 4, aromatic), 4.33 (d, 1, H-1, $J_{1,2}$ = 8.5 Hz), 4.48–5.20 (m, 5, including benzylic CH_2 at τ 4.59, s, 2, and at τ 4.91, t, 1, J = 8.5 Hz), 7.95 (s, 6, two $OCOCH_3$), 8.00 (s, 3, $OCOCH_3$), 8.02 (s, 3, $OCOCH_3$).

Anal. Calcd for $C_{22}H_{26}N_2O_{13}$: C, 50.19; H, 4.98; N, 5.32. Found: C, 50.18; H, 5.24; N, 5.40.

Methyl 2-Deoxy-2-(2-nitrobenzyloxycarbonyl)amino-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (8). A solution of mixture 7 (3.5 g) in 70 ml of 1.5 *N* hydrogen chloride in acetic acid was stored in a stoppered flask at room temperature for 48 hr. Chloroform (600 ml) was then added and the solution was rapidly washed with cold 5% sodium bicarbonate solution and cold water to neutrality. The chloroform layer was dried over sodium sulfate and concentrated *in vacuo* at room temperature to 30 ml. Mercuric cyanide (2 g), crushed calcium sulfate (2 g), and methanol (2 ml) were added and the reaction mixture was left under reflux overnight and then filtered. The filtrate was examined by tlc (silica gel, chloroform) and found to contain one major product. It was then evaporated to dryness and the residual oil solidified upon trituration with 2-propanol. The crude product was recrystallized from 2-propanol to give 1.9 g (57%) of chromatographically pure product: mp 163°; $[\alpha]^{24}$n −4.3° (c 0.7, methanol); λ_{max} (chloroform) 262 nm (ϵ 6280); nmr (60 MHz, $CDCl_3$) τ 1.80–2.65 (m, 4, aromatic), 4.3–6.4 (unresolved m, 10), 6.48 (s, 3, OCH_3), 7.93 (s, 3, $OCOCH_3$), 7.99 (s, 6, two $OCOCH_3$).

Anal. Calcd for $C_{21}H_{26}N_2O_{12}$: C, 50.60; H, 5.26; N, 5.62. Found: C, 50.70; H, 5.56; N, 5.92.

$P-CH_2N(CH_3)CONHNH_2$ (9). This compound was prepared according to Rubinstein, *et al.*,[12] in the following way. Chloromethylated 2% cross-linked styrene–divinylbenzene copolymer ($P-CH_2Cl$, 10 g) containing 3 mmol/g of chlorine was swelled for 5 hr in dioxane (100 ml). The mixture was cooled to 0° and methylamine was bubbled through to saturate the solution, and the solution was subsequently left with stirring at room temperature overnight. The polymer was collected by filtration, washed with a solution of triethylamine in dioxane, water, and methanol, and dried at high vacuum.

Anal. Found: N, 3.90.

The polymer from the last stage was swelled once again in dioxane (100 ml), and phosgene (15 g) was bubbled into the stirred mixture. The stirring was continued overnight. The excess of phosgene was removed by a stream of nitrogen, and the polymer was collected by filtration and washed with anhydrous ether and petroleum ether. The resulting polymer was suspended overnight in hydrazine hydrate (50 ml). The polymer 9 was filtered, washed with water and methanol, and dried *in vacuo*.

Anal. Found: N, 7,85.

The increase in nitrogen content corresponds to 1.41 mmol/g of hydrazide groups.

Methyl 2-Deoxy-2-(4-nitrobenzoyl)amino-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (10).[9] A. Compound 8 (122 mg) was dissolved in anhydrous dioxane (30 ml), and a solution of 1 *N* sulfuric acid in dioxane (1.25 ml) was added. The mixture was irradiated for 6 hr at room temperature. The resulting dark red solution that contained a major ninhydrin-positive spot when checked by tlc (silica gel, chloroform–ethanol, 19:1) was treated with charcoal, filtered, and evaporated under high vacuum at room temperature. The resulting red oil was dissolved in pyridine (5 ml), 4-nitrobenzoyl chloride (226 mg) was added, and the mixture was left with stirring overnight. Water (2 ml) was then added and the stirring was continued for an additional 30 min. The solution was diluted with chloroform (50 ml) and the chloroform solution was washed with 0.1 *N* hydrochloric acid, water, 5% sodium bicarbonate solution, and water. It was then dried over sodium sulfate and evaporated. The residual solid was purified by preparative tlc (chloroform–ethanol, 19:1). The product was eluted with ethyl acetate, the extract was evaporated, and the residue was recrystallized from 2-propanol: yield 57 mg (50%); mp 227°: $[\alpha]^{20}\mathrm{D}$ +34.7° (c 0.3, chloroform) [lit.[9] mp 227–228°, $[\alpha]^{19}\mathrm{D}$ +35.1° (c 0.77, chloroform)].

Anal. Calcd for $C_{20}H_{24}N_2O_{11}$: C, 51.28; H, 5.16; N, 5.98. Found: C, 51.25; H, 5.10; N, 6.00.

B. Polymer 9 (2 g) was suspended in a solution of compound 8 (100 mg) in chloroform (200 ml) and the mixed suspension was irradiated for 50 hr at ambient temperature (mixing the two in the dark did not affect compound 8). The polymer was filtered off and the colorless filtrate was evaporated to dryness, giving a crude yellowish residue of methyl 2-amino-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (63 mg) possessing a major ninhydrin-positive spot in tlc (silica gel, chloroform–ethanol, 19:1). No aromatic and benzylic protons were detected in the nmr (60 MHz, $CDCl_3$); the compound had an OCH_3 resonance at τ 6.43 and acetate resonances at τ 7.92 (6 protons) and 7.97 (3 protons). The crude amino derivative was acylated and processed as described in part A: yield 75 mg (80%); mp 227°; $[\alpha]^{20}\mathrm{D}$ +30.5° (c 0.7, chloroform); nmr (90 MHz, $CDCl_3$) τ 1.71 (d, 2, aromatic, J = 9.0 Hz), 2.06 (d, 2, aromatic, J = 9.0 Hz), 3.33 (d, 1, NH, J = 9.0 Hz), 4.57 (t, 1, H-3, $J_{2,3}$ = $J_{3,4}$ = 10 Hz), 4.84 (t, 1, H-4, $J_{4,5}$ = 9.5 Hz), 5.31 (d, 1, H-1, $J_{1,2}$ = 8.0 Hz), 5.60–5.94 (unresolved m, 3, H-2 and CH_2), 6.19 (m, 1, H-5), 6.46 (s, 3, OCH_3), 7.87 (s, 3, $OCOCH_3$), 7.92 (s, 3, $OCOCH_3$), 7.98 (s, $OCOCH_3$). Irradiation at τ 1.71 caused the collapse of the doublet at τ 2.06 into a singlet. Irradiation at τ 4.84 affected H-3 and narrowed H-5. Irradiation at τ 5.89 caused the collapse of the NH signals into singlets, H-3 into a doublet (J = 10 Hz), and H-5 into a doublet (J = 9.5 Hz). Irradiation at τ 6.19 changed the H-4 triplet to a doublet (J = 10 Hz). An Indor effect, affecting the multiplet τ 5.60–5.94, was observed when irradiating any of the NH or the H-1 lines. The NH signal disappeared after prolonged mixing with D_2O.

Anal. Calcd for $C_{20}H_{24}N_2O_{11}$: C, 51.28; H, 5.16; N, 5.98. Found: C, 51.34; H, 5.06; N, 6.02.

Photolysis of Compound 4 and the Isolation of 2-Amino-2-deoxy-D-glucose. Compound 4 (312 mg) was dissolved in water (800 ml) and the solution was irradiated for 12 hr at ambient temperature. The dark reaction mixture was concentrated to 10 ml and applied to a Dowex 50 × 8 (H^+ form) column (2.5 × 30 cm). The elution was carried out according to Gardell[10] with 0.3 *N* hydrochloric acid. The initial volume of 320 ml was discarded and the next 240 ml was collected, treated with active charcoal, and evaporated almost to dryness. White crystals formed on the addition of acetone. The material was recrystallized by dissolving it in water–methanol and acetone was added till turbidity, yield 109 mg (70%), mp 190–195° dec, $[\alpha]^{23}\mathrm{D}$ +77.5° (30 min) → 72.5° (7 hr, c 2.4, water). The product was indistinguishable from 2-amino-2-deoxy-D-glucose hydrochloride when examined by descending paper chromatography on Whatman No. 1 paper using 1-butanol–acetic acid–water (25:6:25, upper phase) or ethyl acetate–pyridine–water (2:1:2, upper phase) as the solvent and a ninhydrin on a silver nitrate stain.

$P-CH_2NHNH_2$ (11). Chloromethylated 2% cross-linked styrene–divinylbenzene copolymer ($P-CH_2Cl$, 10 g) containing 3 mmol/g of chlorine was suspended in ethanol (100 ml) containing hydrazine hydrate (16 g) and the mixture was kept under reflux for 6 hr. The product 11 was filtered off, washed with water, methanol, and ether, and dried *in vacuo*.

Anal. Found: N, 8.00.

The nitrogen analysis corresponds to 2.85 mmol/g of bound hydrazine.

Photolysis of Compound 3 and the Isolation of 2-Amino-2-deoxy-D-glucose. Polymer 11 (4 g) was suspended in a solution of compound 3 (157 mg) in water–ethanol (3:2, 250 ml) and the mixed suspension was irradiated at ambient temperature for 16 hr. The polymer was filtered off and the filtrate was treated with active charcoal, filtered again, evaporated almost to dryness, and treated with acetone. The solid residue was pure by paper chromatography (1-butanol–acetic acid–water, 25:6:25, upper phase) and was recrystallized by dissolving it in dilute hydrochloric acid–methanol and adding acetone till turbidity, yield 88 mg (95%), mp 190° dec, $[\alpha]^{24}\mathrm{D}$ +80.0° (10 min) → +73.8° (7 hr, final, *c* 1.6, water).

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Registry No. 1, 42854-99-9; **2,** 42855-00-5; **3,** 42855-01-6; **4,** 42855-02-7; **5,** 42855-03-8; **6,** 42855-04-9; 7α isomer, 42855-05-0; 7β isomer, 42855-06-1; **8,** 42855-07-2; **10,** 42854-51-3; **10** amine, 42854-52-4; 2-nitrobenzyl alcohol, 612-25-9; 6-nitroveratryl alcohol, 1016-58-6; 2-amino-2-deoxy-D-galactose hydrochloride, 1772-03-8; 2-amino-2-deoxy-D-glucose, 3416-24-8; 2-amino-2-deoxy-D-glucose hydrochloride, 66-84-2.

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Solution and Solid-State Photodimerization of Some Styrylthiophenes

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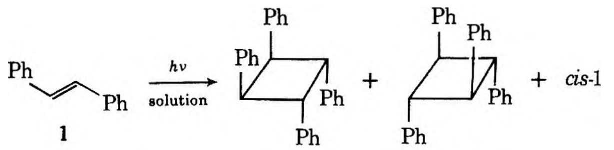
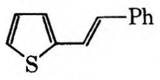
The Pyrex-filtered uv irradiation of *trans*-1-phenyl-2-(2-thienyl)ethene (4), *trans*-1-(2,4-dichlorophenyl)-2-(2-thienyl)ethene (7), and *trans*-1-(3,4-dichlorophenyl)-2-(2-thienyl)ethene (8) has been performed in the crystalline state and in benzene solution. The solid-state behavior is crystal lattice controlled: 4 and the two crystal modifications of 8 are light stable; 7 yields the topochemically expected mirror-symmetric dimer 9. Contrary to a previous report, 4 undergoes photodimerization in solution and one of the photoproducts has been assigned the centrosymmetric structure 23. The two dichloro derivatives also afforded solution photodimers and there is a striking substituent effect on their solution photobehaviors. The 2,4-dichloro isomer, 7, yields only the two dimers 9 and 11, both of cis,anti,cis stereochemistry. By contrast, the 3,4-dichloro isomer, 8, yields all four cyclobutane isomers possible from the union of trans monomers: two all-trans isomers, 16 and 17, and two cis,anti,cis isomers, 14 and 15. The photodimerization rates in benzene solution of 7, 4, 8, and *trans*-stilbene were in the ratio 1.0:2.1:2.4:15. Attention is drawn to a correlation between the monomer crystal structures and their solution photodimerization.

In the solid state *trans*-stilbene (1) is unreactive when irradiated[1] but in solution it yields the two photodimers, 2 and 3.[2] The absence of reaction in the solid can be ascribed to the lack of short intermolecular C=C double bond contacts in the crystal,[3] since substituted stilbenes whose crystal structures have such short spacings (parallel double bonds separated by 3.7–4.2 Å) do undergo solid-state photodimerization, affording the dimers predicted on the basis of the monomer lattices.[4] Irradiation of substituted stilbenes in solution generally yields mixtures of photodimers, although the stereochemistries of the products have been unambiguously established in only a few cases.[5]



1 2 3

In contrast to the above, it has been reported that irradiation of saturated benzene solutions of the thiophene analogs of 1, namely 4, 5, and 6, does not yield photodimers, although these molecules, like stilbene, photoisomerize to the cis isomers which, in turn, undergo photocyclization to unstable dihydrophenanthrene-like intermediates.[6] In the course of our investigation of the packing characteristics and photobehavior of dichloro-substituted molecules[7] we prepared 1-(2,4-dichlorophenyl)-2-thienyl-*trans*-ethene (7) and 1-(3,4-dichlorophenyl)-2-thienyl-*trans*-ethene (8). The solid-state photobehavior of 7 and 8, reported herein, conformed to topochemical expectations and we therefore investigated their solution photobehavior, as well as that of the previously investigated unsubstituted styrylthiophene, 4.



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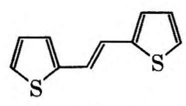

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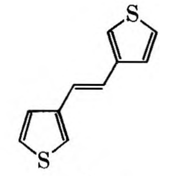

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In addition, this research sought to inquire into the possible correlation of solid-state photobehavior with solution photobehavior. There may well be such correlation in a photodimerization reaction in which the approach of two molecules in solution may be governed by intermolecular forces similar to those operative in the crystal. If preformed aggregates are important in the solution reaction we might also anticipate such a correlation. Evidence supporting a nonbonded *attractive* interaction between halogen atoms in organic molecules[7] made the dichloro derivatives 7 and 8 especially suitable subjects for this study.

Results and Discussion

Solid State. The crystallographic constants of the three stylthiophenes investigated are presented in Table I. The 2,4-dichloro derivative, 7, crystallizes in needles having a 4-Å axis and it was therefore expected to yield, on irradiation, the mirror-symmetric photodimer, 9; indeed, exposure (Westinghouse sun lamps, Pyrex filter) of solid 7 afforded 9 in high yield. The structure of 9 was suggested by spectral data and confirmed by oxidative degradation to the known tetrachloro-β-truxinic acid, **10a**,[8] whose dimethyl ester, **10b**, was identical with an authentic sample.

In addition to 9 the centrosymmetric dimer **11** was formed in small quantities on irradiation of crystalline 7, even at −20°. The presence of this nontopochemical product may be due to "local melting" and disruption of lat-

Table I
Crystallographic Constants of Styrylthiophenes and Their Centrosymmetric Photodimers

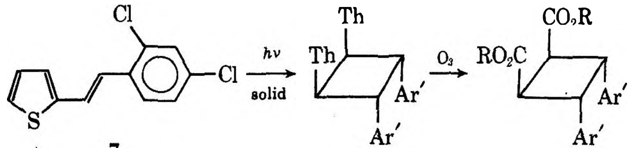
Compd	a, Å	b, Å	c, Å	β, deg	d_{calcd}, g/cm³	Z	Space group
1[a]	15.68	5.70	12.35	112		4	$P2_1/c$
4[b]	31.28	12.27	10.90		1.18	16	
7	10.74	3.98	27.15		1.50	4	$P2_12_12_1$
8 (form 1)	14.3	6.05	26.7		1.45	8	$Pbca$
8 (form 2)	12.86	11.5	7.72	94.5	1.48	4	$P2_1/c$
11	10.44	15.30	15.37	104.5	1.43[c]	4	$P2_1/c$
15	10.55	15.00	16.02	108	1.41	4	$P2_1/c$
23	16.30	6.1	20.45	102.8	1.25[d]	4	Cc or $C2/c$

[a] Reference 3a. [b] d_m = 1.23. The space group has not been established. The intensity data, according to the Weissenberg and precession photographs, show an orthorhombic symmetry *mmm*. The photographs however, exhibit a set of diffuse reflections. General conditions governing the diffraction data follow: *hkl*, for $k = 2n$, $h = 4n$; for $k = 2n + 1$ all reflections are present except for $4n + 2$; $0kl$, $l = 2n$ except for a small number of diffuse spots; $h0l$, $h = 8n$. These conditions suggest some kind of superstructure. [c] d_m = 1.42. [d] d_m = 1.28.

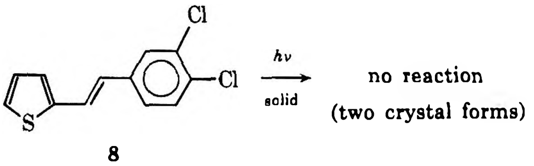
tice control with subsequent formation of the same products as derived from solution (see below). Alternatively, a stacking fault may be present in crystalline **7**, whose geometry allows formation of **11**; the reaction may then promote further propagation of such a dislocation.[4,9]

The 3,4-dichloro derivative, **8**, was found to be dimorphic, neither modification having a 4-Å axis. In the absence of full crystal-structure analyses one cannot make rigorous predictions of photobehavior; however, both forms may be expected either to give a photodimer of other than mirror symmetry or to be light stable; irradiation of both crystal modifications of solid **8** led to little reaction under conditions where **7** is largely converted to **9**. When solid **7** and **8** were irradiated at temperatures at which they gradually melted, the same photoproducts were obtained as described below for the solution experiments.

Exposure of solid **4** induces no detectable dimeric material, and we would therefore expect that there are no short, parallel C=C separations in the crystal of **4**; the cell constants of **4** do not reveal any short lattice-repeat distance.



7 **9** **10a**, R = H; **b**, R = CH₃



8

$4 \xrightarrow[\text{solid}]{h\nu}$ no reaction

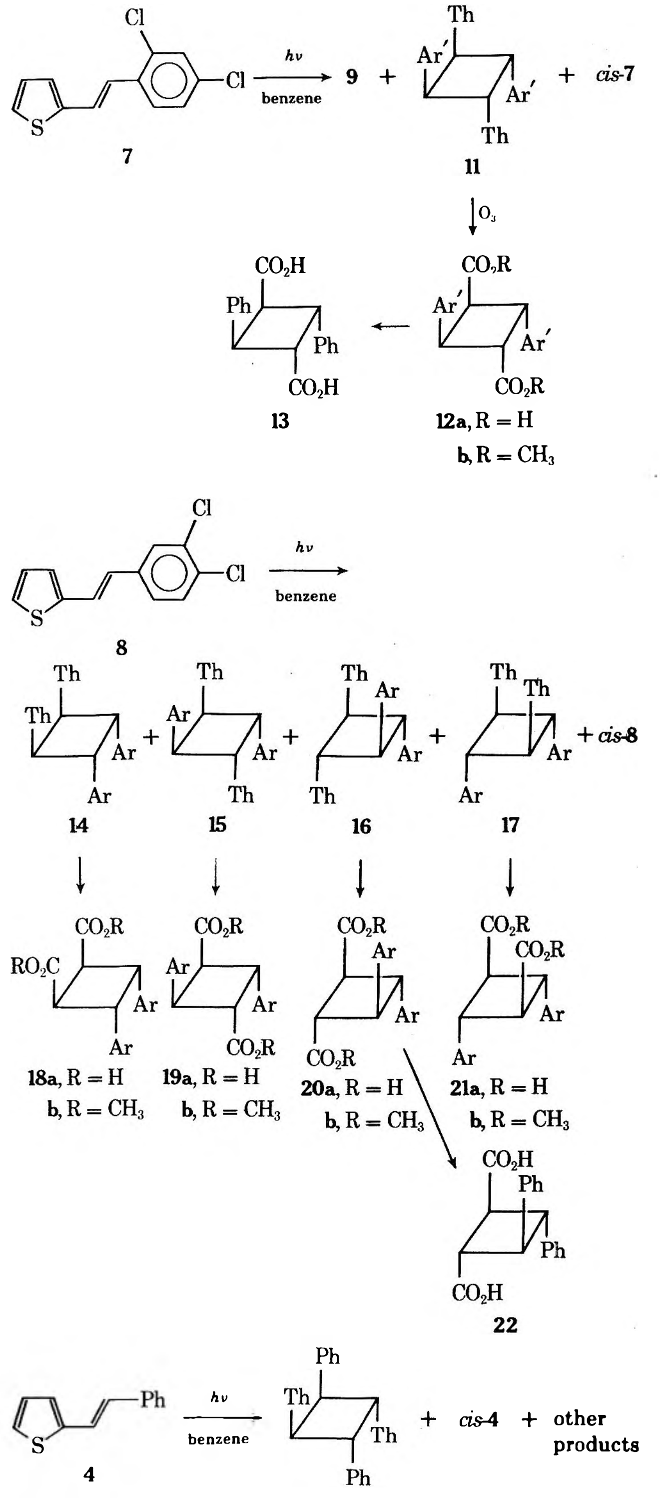
Solution. Irradiation of 2-styrylthiophene (**4**) in benzene solution through Pyrex led to photodimer formation. The nmr spectrum of the irradiated mixture contained a multiplet, δ 4.05–4.7, and a singlet, δ 3.72, in the cyclobutane region. One of the compounds responsible for the multiplet was isolated by column chromatography as a crystalline photodimer and, in view of the absence of a significant dithienyl ethene peak in the mass spectrum and because it matched, on tlc analysis, a sample obtained by the hydrogenative dechlorination of **11**, this dimer was assigned the structure **23**. The singlet at δ 3.72 is, by comparison with the cyclobutane signals in the spectra of the stilbene cis,anti,cis dimer **2** (δ 4.40) and the all-trans dimer **3** (δ 3.63), indicative of an isomer of all-trans configuration.

Since the styryl thiophene **4** does afford photodimers, its photobehavior is at least qualitatively analogous to that of trans-stilbene (**1**). The photodimerization of **4** is, however, considerably less efficient than that of the phenyl compound **1**. This rate difference, and the difference of the rates of the solution photodimerizations of the dichloro compounds **7** and **8**, cannot be discussed until a variety of additional information is available. Even the multiplicity(ies) of the excited state(s) responsible for dimerizations remains to be established for the thiophene compounds discussed herein; *trans*-stilbene has been shown to photodimerize *via* its lowest singlet state.[1a]

Irradiation through Pyrex of **7** in benzene solution led to the formation of the same mirror dimer **9** obtained in the solid and a second dimer, having the centrosymmetric configuration **11** on the basis of its nmr spectrum; the same cis,anti,cis geometry as in **9** is indicated, since the midpoints of the symmetrical cyclobutane AA′BB′ multiplets in both compounds fall at almost the same point in the spectrum,[4a,10] and the aromatic signals in both are shifted upfield owing to mutual shielding of the cis 1,2-diaryl groups, a feature that would be lacking in a dimer of all-trans configuration.

The structure of **11** was confirmed by ozonolysis of the dimer to give the tetrachloro-α-truxillic acid **12a**, which was hydrogenatively dechlorinated to give α-truxillic acid (**13**), identical (melting point, ir) with an authentic sample.

However, the irradiation of the isomeric 3,4-dichloro derivative, **8**, under identical conditions to those used for **7** resulted in the formation of *four* dimeric photoproducts whose nmr spectra all displayed symmetrical cyclobutane signals; these products are assigned structures **14**, **15**, **16**, and **17**. The formation in comparable yield of all four possible cyclobutane-type photodimers that can result without isomerization from 1,2-disubstituted trans ethenes is uncommon.[4a,5,11] The four nmr spectra fall into two groups, those of **14** and **15** having their symmetrical cyclobutane AA′BB′ multiplets centered at δ 4.41, while those of **16** and **17** have multiplets centered at δ 3.60–3.63; the spectra of the former show similar characteristics to the pair **9** and **11**. The assignment of head-to-head and head-to-tail constitution is provided by the mass spectra of the four, all of which show molecular ions, *m/e* 508, and, as base peaks, half molecular ions, *m/e* 254, all containing the characteristic isotope pattern expected for a species containing four chlorine or two chlorine atoms, respectively. The head-to-head configuration of **14** and **16** is appar-



Th = 2-C_4H_3S; Ar′ = 2,4-$C_6H_3Cl_2$; Ar = 3,4-$C_6H_3Cl_2$

ent from the peaks in their mass spectra due to cleavage perpendicular to the direction of monomerization, m/e 316 ($C_6H_3Cl_2CH{=}CHC_6H_3Cl_2$) and 192 ($C_4H_3SCH{=}CHC_4H_3S$); these signals are absent in the mass spectra of 15 and 17.

An interesting stereochemical point with regard to the direction of ring splitting of the cyclobutane is revealed by comparison of the fragmentation patterns of the two head-to-head dimers 14 and 16. In the dimer of all-trans configuration, 16, the intensity ratio of the dithienylethene to the half-molecular ion is 0.32, whereas in the cis,anti,cis dimer 14, this ratio is only 0.04. This can be explained both by the greater aryl-aryl repulsion in 14 relative to 16 as well as by the greater stability of the expected trans species from 16 compared to the cis species from 14.

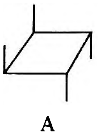
The structure assignments were corroborated by degradation of all four dimers of 8. Ozonolysis of 14 led to the known tetrachloro-β-truxinic acid 18a[8] while ozonolysis of 15 led to the tetrachloro-α-truxillic acid 19a whose dimethyl ester 19b showed a single $-OCH_3$ signal at δ 3.42 characteristic of methyl esters of α-truxillic acid derivatives.[12] The ozonolysis of 16 and 17 afforded two new diacids, 20a and 21a, respectively, whose dimethyl esters, 20b and 21b, displayed OCH_3 signals at δ 3.77 and 3.75, respectively. Confirmation of the stereochemical assignment of 16 was obtained by hydrogenative dechlorination of 20a to give δ-truxillic acid 22.[11b]

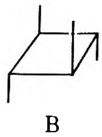
The crystallographic constants of the centrosymmetric dimers were measured in the hope that crystallographic and molecular centers of symmetry would coincide, as is often observed,[2a,13] and would therefore prove or confirm structure assignments. However, the results, presented in Table I, do not allow any structural conclusions to be drawn.

In order to obtain a quantitative estimate of the relative dimerizing efficiencies of these materials as well as a comparison to the hydrocarbon analog, *trans*-stilbene (1), degassed solutions, 0.3 M in benzene, of each were irradiated in a rotating turntable apparatus for varying periods and the total amount of dimer formed was estimated by integration of the cyclobutane proton signals in the nmr spectra using a known quantity of *n*-octadecane as a standard. The initial rates, relative to the slowest reaction, are as follows: 7:4:8:1 = 1.0:2.1:2.4:15.

To summarize the photochemical results, we find that styrylthiophenes do photodimerize in solution and, if the molecular juxtaposition within the crystal lattice is appropriate, in the solid as well. The photoproduct structures have been established, but additional work is called for in order to identify the electronic multiplicity of each dimer precursor and to compare the rates of competing process (*e.g.*, trans → cis isomerization, deactivation) with photodimerization. Although evidence for aggregation has not yet been sought, we anticipate that photodimerization in these materials will be strongly aggregation dependent.[11a] The only evidence of concentration or solvent effects which we can present so far is the change in product ratio when 3,4-dichlorostyrylthiophene is irradiated in the melt and in 0.4 M benzene solution (the ratio of cis,anti,cis dimers, 14 and 15, to all-trans dimers, 16 and 17, changes from *ca.* 1:1 in the melt to 2.5:1 in solution).

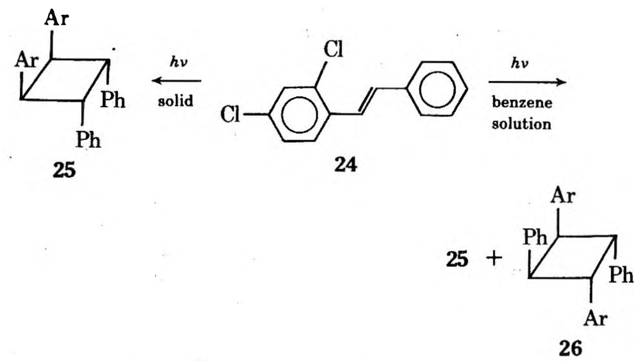
The most striking aspect of this investigation is the dramatic substituent effect on the photobehavior of the 2,4-dichloro- and 3,4-dichloro derivatives of *trans*-styrylthiophene. The 2,4-dichloro isomer 7 yields only *two* dimers, both of the cis,anti,cis geometry (A), while the 3,4-dichloro isomer 8 affords all four of the possible cyclobutane photoproducts resulting from union of two trans olefins, two isomers of all-trans configuration (geometry B) and two of cis,anti,cis configuration (geometry A).

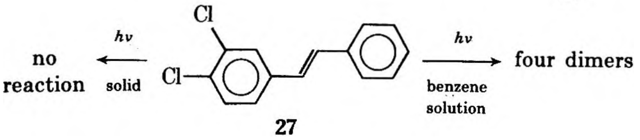

A


B

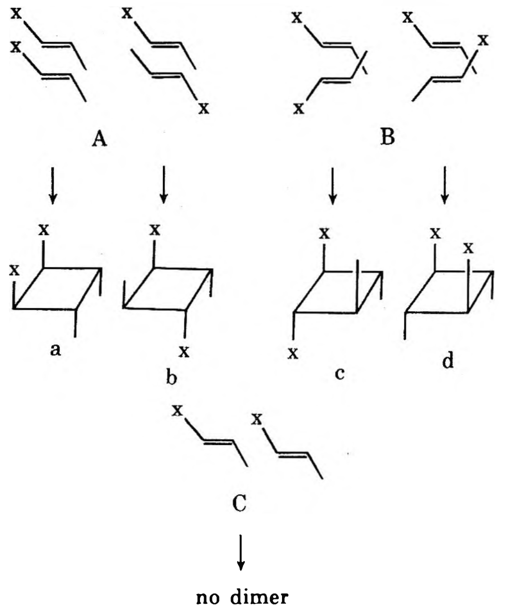
It is interesting to recall that 2,4-dichloro-*trans*-stilbene (24) behaves analogously to the corresponding thiophene compound 7 both in its solid-state and in its solution photobehavior. Irradiation of the solid (short 4-Å axis as in 7) affords the topochemical dimer 25, while irradiation in solution yields the two cis,anti,cis photodimers 25 and 26.[4a]

The suggestion that this similarity between the identically substituted thiophene and phenyl compounds is indeed due to the substitution pattern is strongly supported by our preliminary results on the solution and solid-state photobehavior of 3,4-dichloro-*trans*-stilbene (27). This material is exactly analogous in behavior to 3,4-dichlorostyrylthiophene. Solid 27 lacks a 4-Å axis and is light stable, while irradiation of 27 in solution affords *four* photodimers all having symmetrical nmr spectra and assigned structures analogous to **14**–**17**.





At the outset of this paper we suggested that it might be possible in such systems as are here described to find a correlation between the crystal lattice of the monomers and their solution photodimerization. We consider first three kinds of solution precrystal aggregate geometries. (Alternatively, these can be considered as approach geometries of an excited-state species with a ground-state monomer): (i) a highly overlapped molecular juxtaposition A, either parallel or antiparallel; (ii) an arrangement with only close double bond overlap B, also of either head-to-head or head-to-tail; and (iii) arrangements C in which double bond–double bond overlap is not present. Cycloaddition from geometry A affords the two cis,anti,cis cyclobutane isomers a and b while B affords the all-trans dimers c and d. Geometry C cannot lead to dimer formation.



No crystalline arrangements corresponding to B have been found in any of the more than 100 solid trans olefins whose crystallographic properties or solid-state photochemistry have been studied.[14] However, the intermolecular arrangements A are very common, as are the arrangements C. Thus, we can ask whether materials which crystallize with a parallel or antiparallel A structure will differ in their solution photobehavior from those which crystallize in one of the C-type structures. In the admittedly limited number of materials which have been studied thus far, the following correlation emerges: 1,2-diaryl-*trans*-ethenes crystallizing in photoreactive A-type lattices afford two solution photodimers, of structure a and b, while materials crystallizing in the light-stable C-type lattices afford, on irradiation in solution, four photodimers, a, b, c, and d.

This correlation presently rests on the six compounds **1**,[15] **4**, **7**, **8**, **24**, and **27**, and we await further examples before judging its validity and defining the scope of its applicability. A reasonable interpretation is that materials which favor crystal structures with highly overlapped molecules will tend to aggregate in this fashion in solution as well (or, alternatively, will favor molecular approaches, of the A type). Compounds for which good molecular overlap is not a high-priority requirement in their crystal structures, C-type lattices, will in solution show no distinct preference for any particular intermolecular geometry and afford all four possible photodimers.

Experimental Section

Melting points, measured on a Fisher-Johns apparatus, are uncorrected. Ir spectra were determined on a Perkin-Elmer Infracord spectrophotometer in KBr pellets, unless otherwise indicated. The nmr spectra were recorded on a Varian A-60 spectrometer in deuteriochloroform. Chemical shifts are reported in δ units downfield from internal tetramethylsilane (TMS); the multiplicity, number of hydrogens, coupling constants, and proton assignments are given in parentheses. When accurate integration was required the average of four to six readings on a digital integrator attachment was made. The mass spectra were recorded on an Atlas MAT CH4 mass spectrometer at 70 eV. The mass spectral data are presented using the following format: m/e (relative abundance), fragment assignment, molecular formula. All chlorine-containing fragments show the expected isotope patterns corresponding to the number of chlorine atoms present.

Solids were irradiated, unless otherwise stated, in Petri dishes with Pyrex covers using Westinghouse sun lamps at a distance of *ca.* 30 cm. Samples were irradiated at 40 or 8°, the latter by placing the irradiation apparatus in a cold room. Solutions were irradiated in benzene (Fluka, for uv spectroscopy) in Pyrex ampoules, after being deaerated by passing a stream of benzene-saturated argon through and then sealing under argon. Thin layer chromatographic (tlc) analyses were performed on silica gel HF_{254} using methylcyclohexane as eluent. Spots were indicated by fluorescence (Mineral-light UVS-12) and/or iodine vapor. Column chromatography was performed using the dry-column method[16] with Merck 0.05–0.20-mm silica gel in a ratio of 20–30 times the weight of the sample. Ozonolyses were performed with a Welsbach ozonator Model T-408. Powder photographs were taken with a "Guinier" Nonius camera using Cu Kα radiation.

Preparation of phosphonates was accomplished (Michaelis–Arbuzov reaction[17]) in 80–90% yield by heating the benzyl chlorides and triethyl phosphite for 16 hr. Diethyl benzylphosphonate had bp 110–118° (0.5 mm); diethyl 3,4-dichlorobenzylphosphonate had bp 142° (0.5 mm); diethyl 2,4-dichlorobenzylphosphonate was used directly without distillation.

Preparation of 1-Aryl-2-thienylethenes. *trans*-1-Phenyl-2-(2-thienyl)ethene (4) was prepared, as were compounds 7 and 8, by the method of Seus and Wilson.[18] The product was purified by sublimation, mp 113–115° (lit.[18] mp 112–113°) (monomorphic from methylcyclohexane, ethyl acetate, or ethanol and by sublimation), ir (Nujol) 975, 965 cm^{-1} (trans HC=CH). ***trans*-1-(2,4-Dichlorophenyl)-2-(2-thienyl)ethene** (7) was prepared from diethyl 2,4-dichlorobenzylphosphonate and 2-thienoaldehyde. The product separated as an oil and was extracted from the aqueous DMF solution with n-hexane (2 × 100 ml). The hexane extract was dried (sodium sulfate) and evaporated to give a 45% yield of crude product which was purified by crystallization (75% recovery) from ethanol-methanol to give colorless needles; mp 61.5-62°; ir 948, 958 cm^{-1} (trans HC=CH); uv λ_{max} (MeOH) 330 nm (ϵ 2.5 × 10^4).

Anal. Calcd for $C_{12}H_8Cl_2S$: C, 56.48; H, 3.16; Cl, 27.79; S, 12.57. Found: C, 56.28; H, 3.02; Cl, 27.95; S, 12.75.

Single crystals of 7 were grown from ethanol and placed in sealed Lindemann glass capillaries coated with Mercurochrome to prevent photoreaction while taking X-ray photographs. ***trans*-1-(3,4-Dichlorophenyl)-2-(2-thienyl)ethene (8)** precipitated from the reaction of diethyl 3,4-dichlorobenzylphosphonate and 2-thienoaldehyde in 60% yield and was crystallized from 2-propanol to give colorless crystals (45% overall yield): mp 96-97°; ir 955, 970 cm^{-1} (trans CH=CH); nmr δ 6.9-7.6; mass spectrum: *m/e* 254 (rel intensity) (100, molecular ion, $C_{12}H_8Cl_2S$), 218 (36, M − HCl, $C_{12}H_7ClS$), 184 (66, M − Cl_2, $C_{12}H_8S$), 139 (22), 109 (16).

Anal. Calcd for $C_{12}H_8Cl_2S$: C, 56.48; H, 3.16; Cl, 27.79; S, 12.57. Found: C, 56.57; H, 3.16; Cl, 27.64; S, 12.73.

Compound 8 is dimorphic; form I, shiny, colorless plates, was grown from carbon tetrachloride, 2-propanol, or 1-butanol; form II, colorless needles, was obtained from ethyl acetate, methylcyclohexane, acetone, acetic acid, or methanol.

Irradiation of *trans*-1-Phenyl-2-(2-thienyl)ethene (4). Solid State. The sample remained solid and no dimerization was observed after 1 month of exposure at 40° or 8°; however, the upper, exposed layer gradually darkened. (This process is faster at 40°).

Solution. A 0.85 *M* benzene solution of 4 was irradiated for 1 month. Nmr analysis showed cyclobutane signals at δ 4.05-4.7 (m), corresponding to a cis,anti,cis structure, and 3.72 (s) due to an all-trans structure, in the ratio 2.5:1. A second sample of 4, 1.5 g (8.0 mmol), in 15 ml of benzene, was irradiated as above and then chromatographed with petroleum ether (bp 40-60°) containing increasing amounts of ethyl acetate as eluent. First 750 mg (50%) of *cis*-1-phenyl-2-(2-thienyl)ethene (colorless oil) was eluted followed by 330 mg (22%) of a mixture of *cis*- and *trans*-4. The next component to elute was 150 mg (10%) of yellow oil which, upon treatment with aqueous ethanol, deposited 40 mg of **1,*trans*-3-diphenyl-*trans*-2,*cis*-4-dithienylcyclobutane (23)** as colorless crystals: mp 110°; nmr δ 6.7-7.37 (m, 16 H, aromatic) and 4.90-4.15 (AA'BB', 4 H, cyclobutane); mass spectrum *m/e* (rel intensity) 372 (0.016, molecular ion, $C_{24}H_{20}S_2$), 188 (6), 187 (15), 186 (100, monomer, $C_{12}H_{10}S$), 185 (25), 184 (10). The oily residue (100 mg) showed several nmr signals in the cyclobutane region: δ 3.75 (s, all-trans dimer), 4.15-4.65 (m) (peak shape suggests more than one dimer). The last component to elute was an unidentified dark oil (50 mg) having no cyclobutane nmr signals.

Irradiation of *trans*-1-(2,4-Dichlorophenyl)-2-(2-thienyl)ethene (7). Solid State. Irradiation at 8° using a Corning filter (color specification no. 3-73, code no. 5543, for λ > 405 nm, or color specification no. 5-60, code no. 5543, for 520 > λ > 350 nm) led to formation of a strong tlc spot corresponding to 9 (see below) and weak spots corresponding to *cis*-7, 11, and "polymer" (R_f 0). Irradiation at 8° through a Pyrex filter caused darkening of the product and a considerable increase in the amount of "polymer;" irradiation at 40° or exposure to sunlight caused the sample to turn brown and melt after 1 day. Tlc analysis of these samples revealed spots corresponding to *cis*-7, *trans*-7, 9, 11, and "polymer" (R_f 0). A 2.5-g sample of 7, irradiated in sunlight for 2 days, was chromatographed and eluted with *n*-hexane; 20-ml fractions were collected. Fractions 6-12 afforded 550 mg (22%) of *cis*-7 [nmr δ 6.4 (1 H, cis HC=CH, *J* = 12 Hz), 6.75-7.55 (aromatic multiplet, 7 H)] followed by a mixture of *cis*- and *trans*-7, 400 mg (16%). Fractions 35-60 gave, upon concentration, 560 mg (22%) of colorless crystals, mp 189-191°. Recrystallization from ethyl acetate afforded pure **1,*trans*-3-di(2,4-dichlorophenyl)-*trans*-2,*cis*-4-dithienylcyclobutane (11):** mp 194°; nmr δ 6.75-7.5 (m, 12 H, aromatic) and 4.45-5.0 (AA'BB', 4 H, cyclobutane); mass spectrum *m/e* (rel intensity) 508 (0.014, molecular ion, $C_{24}H_{16}Cl_4S_2$), 254 (100, M/2, $C_{12}H_8Cl_2S$), 218 (20, M/2 − HCl, $C_{12}H_7ClS$), 184 (30, M/2 − Cl_2, $C_{12}H_8S$).

Anal. Calcd for $C_{24}H_{16}Cl_4S_2$: C, 56.48; H, 3.16; Cl, 27.79; S, 12.57. Found: C, 56.45; H, 2.95; Cl, 27.68; S, 12.68.

Fractions 64-72 contained 440 mg (18%) of a yellow oil from which, **1,*cis*-2-di(2,4-dichlorophenyl)-*trans*-3,*trans*-4-dithienylcyclobutane (9)** crystallized upon standing. Two recrystallizations from ethanol gave a colorless solid: mp 196-197°; nmr δ 6.85-7.3 (m, 12 H, aromatic) and 4.30-5.0 (AA'BB', 4 H, cyclobutane); mass spectrum *m/e* (rel intensity) 508 (0.02, molecular ion, $C_{24}H_{16}Cl_4S_2$), 316 (0.6, ArCH=CHAr, $C_{14}H_8Cl_4$), 254 (100, M/2, $C_{12}H_8Cl_2S$), 218 (11, M/2 − HCl, $C_{12}H_7ClS$), 192 (4.6, ThCH=CHTh, $C_{10}H_8S_2$), 184 (82, M/2 − Cl_2, $C_{12}H_8S$).

Anal. Calcd for $C_{24}H_{16}Cl_4S_2$: C, 56.48; H, 3.16; Cl, 27.79; S, 12.57. Found: C, 56.28; H, 3.36; Cl, 27.52; S, 12.61.

Dehalogenation of 11. A solution of 11 (200 mg) in 80 ml of methanol containing 200 mg of KOH and 160 mg of 10% Pd/C was warmed to gentle reflux while passing through a stream of hydrogen gas. Periodic tlc analysis indicated that the reaction was proceeding very slowly and was still incomplete after 4 weeks. At this point tlc analysis (benzene-methylcyclohexane, 1:4) showed traces of starting material and four additional, less mobile spots, the final one having an R_f value identical with that of 23. Additional attempts at reaction shifted the product distribution in the direction of this spot, implying that the intermediate three spots were tri-, di-, and monochloro derivatives, but in no case was 23 isolated.

Solution. A 0.1 *M* solution of 7 in benzene or in *n*-hexane was irradiated for 18 days. Tlc analysis showed *cis*-7 as the major component in addition to dimers 9 and 11, in approximately equal quantities, 7, and a spot with R_f 0.

Ozonolysis of 9. A 180-mg sample of 7, irradiated at 8° using a blue Corning filter, code no. 5543, was dissolved in 30 ml of acetic acid, and 1% ozone was bubbled through the ice-cooled solution for 12 min followed by an oxygen stream for 30 min. One milliliter of 30% H_2O_2 was added and the mixture was kept for 24 hr and then warmed with 5% Pd/C to destroy the peroxides present. After filtration, the solvents were evaporated to give 2,2',4,4'-tetrachloro-β-truxinic acid (**10a**), which was esterified (diazomethane) and the product was passed over a short column of silica, using benzene as eluent, to afford pure dimethyl 2,2',4,4'-tetrachloro-β-truxinate (**10b**), mp 111-113°, identical (melting point and ir) with an authentic sample.

Ozonolysis of 11. Dimer 11 (400 mg), was dissolved in 40 ml of methylene chloride and cooled to −45°. Ozone (1%), was bubbled in for 25 min followed by oxygen for 0.5 hr. The solution was allowed to warm to room temperature and then 50 ml of acetic acid and 10 ml of 50% H_2O_2 were added. The mixture was kept for 24 hr and then warmed with 5% Pd/C to decompose the excess peroxides. Filtration and evaporation to dryness left 230 mg (68%) of 2,2',4,4'-tetrachloro-α-truxillic acid (**12a**), mp >290°, ir 1695 cm^{-1} COOH. The methyl ester was prepared by refluxing overnight a solution of 40 mg of **12a** in 30 ml of methanol containing two drops of thionyl chloride. Evaporation of volatile material left dimethyl 2,2',4,4'-tetrachloro-α-truxillate (**12b**): mp 175-176°; nmr δ 7.3-7.5 (m, 6 H, aromatic), 3.95-4.95 (AA'BB', 4 H, cyclobutane), and 3.4 (s, 6 H, methyl).

Dehalogenation of 12a. A solution of **12a** (120 mg) in 50 ml of 4% aqueous NaOH containing 50 mg of 10% Pd/C was hydrogenated at atmospheric pressure for 20 hr. The catalyst was filtered off and the solution was acidified with HCl to precipitate α-truxillic acid (**13**), ir identical with that of an authentic sample.

Irradiation of *trans*-1-(3,4-Dichlorophenyl)-2-(2-thienyl)ethene (8). Solid State. Both crystalline forms of 8 show identical behavior on irradiation. After 1 month of exposure at 8° the surface layer darkens slightly, but tlc analysis shows no dimer spots, only a spot with R_f 0. On irradiation at 40° both forms darken and gradually melt; after 20 days both forms have melted entirely and display three strong tlc spots corresponding to the four dimers [**14** (R_f 0.095); **15** (R_f 0.13); **16** and **17** appear together (R_f 0.17)] as well as *trans*-8 (R_f 0.32) and traces of *cis*-8 (R_f 0.38). Based on nmr analysis, the ratio of all-trans configurated dimers, **16** and **17**, to the cis,anti,cis configurated dimers, **14** and **15**, in such a melt-irradiated sample is *ca.* 1:1. The photodimers were isolated from a melt-irradiated sample of 8 because of the small quantity of cis monomer present and because of the larger dimer content compared to a sample irradiated in benzene solution.

Form I (4.9 g) was irradiated at 40° for 1 month and then chromatographed (*n*-hexane elution) to give the following fractions: (a) the cis isomer of 8 as an oil, nmr δ 6.4 (d, 1 H, *J* = 12 Hz, cis HC=CH); (b) mixture of *cis*- and *trans*-8; (c) 1.4 g (28%) of *trans*-8; (d) dimers 16 and 17, 1.4 g (28%), which upon treatment with *n*-hexane gave 900 mg (18%) of **1,*trans*-2-di(3,4-dichlorophenyl)-*cis*-3,*trans*-4-dithienylcyclobutane (16)** which was recrystallized from CH_2Cl_2-EtOH to give colorless crystals [mp 142-143°; nmr δ 6.83-7.50 (m, 12 H, aromatic) and 3.42-3.85 (AA'BB', midpoint at 3.63, 4 H, cyclobutane); mass spectrum *m/e* (rel intensity) 508 (0.036, molecular ion, $C_{24}H_{16}Cl_4S_2$), 316 (0.27, ArCH=CHAr, $C_{14}H_8Cl_4$), 254 (100, M/2, $C_{12}H_8Cl_2S$), 218 (8.6, M/2 − HCl, $C_{12}H_7ClS$), 192 (32, ThCH=CHTh, $C_{10}H_8S_2$), 184 (15, M/2 − Cl_2, $C_{12}H_8S$), 139 (2.8), 109 (1.3)].

Anal. Calcd for $C_{24}H_{16}Cl_4S_2$: C, 56.48; H, 3.16; Cl, 27.79; S, 12.57. Found: C, 56.60; H, 3.25; Cl, 27.87; S, 12.38.

The filtrate, after chromatography and several crystallizations from MeOH and EtOH, gave 170 mg of **1,*cis*-3-di(3,4-dichlorophenyl)-*trans*-2,*trans*-4-dithienylcyclobutane (17)**: mp 102–103.5°; nmr δ 6.83–7.58 (m, 12 H, aromatic) and 3.55–3.75 (A_2B_2, midpoint at 3.63, 4 H, cyclobutane); mass spectrum *m/e* (rel intensity) 508 (0.0054, molecular ion, $C_{24}H_{16}Cl_4S_2$), 254 (100, M/2, $C_{12}H_8Cl_2S$), 218 (14, M/2 − HCl, $C_{12}H_7ClS$), 184 (25, M/2 − Cl_2, $C_{12}H_8S$), 139 (6), 109 (2.3). Fraction e was a mixture of **15**, **16**, and **17**, 650 mg (13%). Fraction f was **1,*trans*-3-di(3,4-dichlorophenyl)-*trans*-2,*cis*-4-dithienylcyclobutane (15)**, 160 mg (~3%), which crystallized from MeOH: mp 84–86.5°; nmr δ 6.67–7.45 (m, 12 H, aromatic) and 4.00–4.83 (AA′BB′, midpoint at 4.41, 4 H, cyclobutane); mass spectrum *m/e* (rel intensity) 508 (0.15, molecular ion, $C_{24}H_{16}Cl_4S_2$), 254 (100, M/2, $C_{12}H_8Cl_2S$), 218 (21, M/2 − HCl, $C_{12}H_7ClS$), 184 (36, M/2 − Cl_2, $C_{12}H_8S$), 139 (8.6), 109 (33). Fraction g was a mixture of photodimers **14** and **15**, 460 mg (9%). Fraction h was **1,*cis*-2-di(3,4-dichlorophenyl)-*trans*-3,*trans*-4-dithienylcyclobutane (14)**, 270 mg (5.5%), an almost colorless oil which failed to crystallize: nmr δ 6.67–7.73 (m, 12 H, aromatic) and 4.20–4.65 (AA′BB′, midpoint at 4.41, 4 H, cyclobutane); mass spectrum *m/e* (rel intensity) 508 (0.022, molecular ion, $C_{24}H_{16}Cl_4S_2$), 316 (0.31, ArCH=CHAr, $C_{14}H_8Cl_4$), 254 (100, M/2, $C_{12}H_8Cl_2S$), 218 (15, M/2 − HCl, $C_{12}H_7ClS$), 192 (3.8, ThCH=CHTh, $C_{10}H_8S_2$), 184 (23, M/2 − Cl_2, $C_{12}H_8S$), 139 (5.6), 109 (4.2).

Solution. After irradiation of a 0.4 *M* benzene solution of 8 for 1 month at 40° *ca.* one-third had been transformed to the cis isomer and *ca.* 15% had undergone dimerization; the ratio of cis,anti,cis dimers (14 and 15) to all-trans dimers (16 and 17) was *ca.* 2.5:1.

Ozonolysis of 14. The dimer (70 mg) was treated as in the case of **9** above. Work-up afforded diacid **18a**, which was esterified (methanol, thionyl chloride) to give dimethyl 3,3′,4,4′-tetrachloro-β-truxinate (**18b**): mp 107–108° (lit.[8] mp 106.5–107°); ir identical with that of an authentic sample; nmr δ 6.6–7.35 (m, 6 H, aromatic), 3.75–4.45 (AA′BB′, midpoint at 4.1, 4 H, cyclobutane), and 3.75 (s, 6 H, methyl).

Ozonolysis of 15. Ozonolysis as above afforded **19a**, which was directly esterified to give dimethyl 3,3′,4,4′-tetrachloro-α-truxillate (**19b**): mp 191–193° (from methanol); nmr δ 7.0–7.5 (m, 6 H, aromatic), 3.6–4.6 (AA′BB′, midpoint at 4.1, 4 H, cyclobutane), and 3.42 (s, 6 H, methyl).

Ozonolysis of 16. The dimer (380 mg), ozonolyzed according to the procedure used for **11**, gave 175 mg (50%) of **20a**, mp 255–261°. A portion of **20a** was esterified (MeOH–$SOCl_2$) and afforded dimethyl 3,3′,4,4′-tetrachloro-δ-truxinate (**20b**): nmr δ 7.0–7.6 (m, 6 H, aromatic), 3.25–3.8 (AA′BB′, midpoint at 3.53, 4 H, cyclobutane), and 3.77 (s, 6 H, methyl). The remainder of **20a** was hydrogenated, as described for **12a**, and afforded δ-truxinic acid **22**, which was crystallized from benzene–acetic acid, mp 175–177° (lit.[11b] mp 175°). The dimethyl ester of **22** was prepared and crystallized from methanol, mp 76–77° (lit.[11b] mp 76°).

Ozonolysis of 17. The dimer was ozonolyzed by the method used for **9** and gave **21a** which was directly esterified (MeOH–$SOCl_2$) to give dimethyl 3,3′,4,4′-tetrachloro-ϵ-truxillate (**21b**): mp 166–167.5° (methanol); nmr δ 7.0–7.55 (m, 6 H, aromatic), 2.85–4.25 (A_2B_2, midpoint at 3.55, 4 H, cyclobutane), and 3.75 (s, 6 H, methyl).

Determination of Rates. Solutions (3.0 ml) of **1**, **4**, **7**, and **8**, respectively, in benzene (Fluka, for uv spectroscopy) in identical Pyrex tubes were degassed by three freeze–evacuate–thaw cycles on a vacuum line and then flame sealed *in vacuo.* The tubes were exposed for varying times to identical radiation conditions in a Rayonet type RS Merry-Go-Round photochemical reactor equipped with lamps having maximum emission at 350 nm. The tubes were opened, the solvent was evaporated, and a weighed quantity of *n*-octadecane was added to the residue. Integration of the cyclobutane region, δ 3.5–5, and *n*-octadecane region, δ 1.4–0.7, allowed calculation of the total dimer content by the following relationship: milligrams of dimer = (milligrams of *n*-octadecane)(area of cyclobutane signals/area of *n*-octadecane signals)(38/4)(molecular weight of cyclobutane/molecular weight of *n*-octadecane).

Results obtained were (compound, molarity of solution, milligrams of material irradiated, irradiation time in hours, milligrams of dimer formed, rate in mmol $l.^{-1}min^{-1}$): *trans*-stilbene (**1**), 0.30, 162, 3.83, 10.8, 0.087; **1**, 0.30, 162, 9.6, 22.2, 0.071; **1**, 0.30, 162, 27.3, 38.2, 0.043; *trans*-styrylthiophene (**4**), 0.29, 163, 61.3, 24.7, 0.012; **4**, 0.29, 163, 90.0, 32, 0.0106; **7**, 0.29, 218, 61.3, 15.8, 0.0057; **8**, 0.29, 218, 27.3, 25.2, 0.020; **8**, 0.29, 218, 61.3, 37.8, 0.0135.

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Registry No. 1, 103-30-0; *cis*-**4**, 23516-73-6; *trans*-**4**, 26708-50-9; *cis*-**7**, 42829-18-5; *trans*-**7**, 42829-19-6; *cis*-**8**, 42829-20-9; *trans*-**8**, 42829-21-0; **9**, 42829-22-1; **11**, 42829-23-2; **12a**, 42829-24-3; **12b**, 42829-25-4; **14**, 42829-26-5; **15**, 42829-27-6; **16**, 42829-28-7; **17**, 42829-29-8; **18b**, 42903-89-9; **19b**, 42829-30-1; **20a**, 42829-31-2; **20b**, 42829-32-3; **21b**, 42829-33-4; **23**, 42829-34-5; diethyl benzylphosphonate, 2768-31-2; diethyl 3,4-dichlorobenzylphosphonate, 42822-50-4.

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Dihydrothiophenes. II. Preparation and Properties of Some Alkylated 2,5-Dihydrothiophenes[1a]

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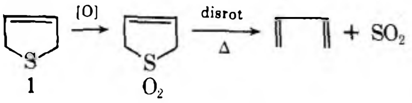
A new general preparation of alkylated 2,5-dihydrothiophenes **1** is reported. Reaction of α-mercapto ketones with vinylphosphonium salts leads to compounds of type **1** in excellent yield. The preparation of substituted vinylphosphonium salts is also described. The synthetic utility of **1** in the preparation of dienes has been demonstrated by the formation of **29** and **33** from **18** and **15**.

The wide applicability of the Diels-Alder reaction to the synthesis of complex molecules is well known.[2] While the common dienophiles can be obtained in a variety of ways, in many cases the preparation of the required diene is not so straightforward. Isomerically and stereoisomerically pure materials are required if the stereochemical integrity of the reaction is to be maximally utilized.

The formation of conjugated dienes can be effected in a number of diverse ways. In addition to the classical methods,[3] newer methods, including the addition of vinyl organometallic reagents to acetylenic bonds[4a] and those related to the Wittig reaction,[4b] have recently been developed. While some of these reactions are completely or partially stereospecific, the stereochemistry of the newly formed double bond is in many cases quite difficult to predict.[5] Another difficulty encountered is the lack of stability of many functional groups to the reaction conditions. Furthermore, one of the chief drawbacks to the use of the Wittig reaction is the low yield frequently obtained in the preparation of tri- and tetrasubstituted double bonds,[2,3b,6,7] although Wittig's method for "directed aldol condensations"[6] has provided a useful alternative. Therefore, the development of a new method for the regiospecific and stereospecific formation of conjugated double bonds under mild reaction conditions would be desirable.

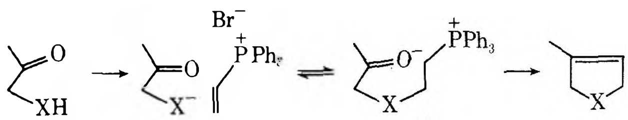
The thermal decomposition of 2,5-dihydrothiophene sulfones (**2**) to sulfur dioxide and dienes has frequently been used as the final step in the purification of diene mixtures.[8] This reaction invariably proceeds at an easily accessible temperature and in a completely regiospecific and stereospecific disrotatory manner.[9] While the most common preparation of compounds of type **2** involves the cycloaddition of sulfur dioxide to conjugated dienes,[8] a method which clearly does not fit our requirements, an alternate approach involves the oxidation of 2,5-dihydrothiophenes (**1**).[10] Thus a general synthesis of compounds of type **1** would constitute a method for the preparation of dienes and our attention was focused on this problem.



1 2

Results and Discussion

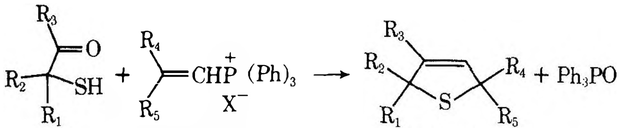
Vinyltriphenylphosphonium bromide[11a] (**10**) has been used extensively by Schweizer in the preparation of a large variety of carbocyclic, heterocyclic, and acyclic molecules.[11] In particular the preparations of 2,5-dihydropyrroles[12] and furans[13] have been reported. Initial addition of a nucleophile to the vinyl salt affords an intermediate ylide (**3**) which undergoes an intramolecular or intermolecular Wittig reaction leading to the desired product with the concomitant loss of triphenylphosphine oxide. As we have reported,[14] the use of **10** and α-mercapto ketones as the nucleophilic species leads to the required 2,5-dihydrothiophenes (Scheme I, Table I).



X = N, O

3

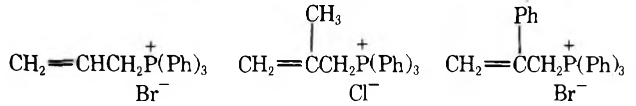
Scheme I



4-9

10, $R_4 = R_5 = H$
11, $R_4 = H$; $R_5 = Me$
12, $R_4 = R_5 = Me$
13, $R_4 = Me$; $R_5 = Ph$

14-24



$CH_2{=}CHCH_2\overset{+}{P}(Ph)_3\ Br^-$ **11a**

$CH_2{=}C(CH_3)CH_2\overset{+}{P}(Ph)_3\ Cl^-$ **12a**

$CH_2{=}C(Ph)CH_2\overset{+}{P}(Ph)_3\ Br^-$ **13a**

It should be noted that several groups have commented[15,16] on the lack of addition of alcohols and amines to β-substituted vinylphosphonium salts. We were aware of these reports, but one publication[15b] indicated that the more nucleophilic mercaptans would add to salt **11** in the presence of a catalytic amount of base. Based on this, we proceeded to investigate the preparation of dihydrothiophenes utilizing substituted vinyl salts.

Schweizer has reported preparation[17] and reactions[11,17] of a number of α-substituted vinylphosphonium salts. The interference of an alkyl group attached to phosphorus in the usual reaction has been noted.[11] Also, previous investigations[15] of the base-catalyzed isomerization of allylic phosphonium salts to their vinyl isomers showed that the presence of aromatic groups attached to phosphorus facilitated the reaction.[15a] Since we wished to prepare the substituted vinyl salts **11**, **12**, and **13** by isomerization of the appropriate allyl salts, we decided to restrict our present investigation to the salts derived from triphenylphosphine which bore no substituents in the α position.

We have verified the isomerization by nmr. While pyridine solutions of the allyl salts **11a**, **12a**, and **13a** were stable at room temperature, addition of a catalytic amount of triethylamine caused complete and rapid disappearance of the methylene absorption at δ 5-6. We have used this solvent system to prepare vinyl salts **11**, **12**, and **13** in high yields. In cases where the reaction medium used for the formation of the dihydrothiophenes contained

Table I
Products and Yields of 2,5-Dihydrothiophenes[a]

Ketone	Salt	Product	R_1	R_2	R_3	R_4	R_5	Time, hr	Yield, %
4[b]	**10**	**14**[c]	H	H	Me	H	H	24	60
5[d]	**10**	**15**	Me	Me	Me	H	H	30	95
5	**11**	**16**	Me	Me	Me	Me	H	20	80
5	**12**	**17**	Me	Me	Me	Me	Me	30	30
6[e]	**10**	**18**	H	$-(CH_2)_4-$		H	H	18	74
6	**11**	**19**	H	$-(CH_2)_4-$		Me	H	18	91
6	**12**	**20**	H	$-(CH_2)_4-$		Me	Me	55	61
7[d]	**10**	**21**	H	$-(CH_2)_3-$		H	H	18	76
8[f]	**10**	**22**	H	Ph	Me	H	H	168	65[g]
9[h]	**10**	**23**	Me	Me	*i*-Pr	H	H	48	20
9	**11**	**24**	Me	Me	*i*-Pr	Me	H	72	6

[a] Satisfactory analytical data were recorded for all new compounds in the table. [b] L. Field, W. S. Hanley, and I. McVeigh, *J. Org. Chem.*, **36**, 2731 (1971). [c] S. F. Birch and D. T. McAllan, *J. Chem. Soc.*, 3411 (1951). [d] F. Ansinger, M. Thiel, and G. Esser, *Justus Liebigs Ann. Chem.*, **610**, 33 (1953). [e] G. Gieseler and F. Stache, *Chem. Ber.*, **94**, 337 (1961). [f] A. von Wacek, K. Kratzl, and A. von Bezard, *ibid.*, **75**, 1348 (1942). [g] By-product of phenylacetone also present. [h] F. Ansinger, M. Thiel, and V. Tesar, *Justus Liebigs Ann. Chem.*, **619**, 169 (1958).

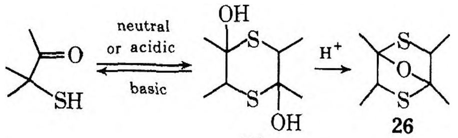
triethylamine (*vide post*), the allyl salts **11a**, **12a**, and **13a** could be substituted with no decrease in yield.

Investigations by other workers of the reactions of allyl salts have led to the formation of materials which could be envisaged as proceeding by initial isomerization followed by the same Michael addition–Wittig cyclization, but which, on closer scrutiny, proved to proceed by initial Wittig reaction followed by cyclization.[12a,16] Although we have no direct evidence for either mechanism, we favor the former sequence because the decreased basicity of the mercaptide ion relative to the alkoxide ion should inhibit the proton exchange leading to the phosphorane and thus to the initial Wittig reaction.

We were intrigued by the report[18] of the isolation of the vinyl salt 11 ($X^- = Cl$) when allyl chloride and triphenylphosphine were heated together in benzene, while the use of allyl bromide led to the expected allyl salt **11a**. We have found that the same situation obtains when methallyl chloride is treated under the same conditions. The vinyl salt **12** obtained has the same physical properties as those reported[19] for the expected allyl salt **12a**, and clearly the earlier reports are in error. In analogy with the previous report,[18] when a large excess of methallyl chloride is heated in the presence of the phosphine in the absence of added solvent, a 5:1 mixture (nmr) of **12a** and **12** is obtained. The suggestion has been made that the increased nucleophilicity of chloride relative to bromide ion was responsible for this result.[18] We have found that refluxing a benzene slurry of bromide salt **11a** with lithium chloride effects complete isomerization (nmr) into vinyl salt **11**, but we attribute this result to the difference in basicity of the two halide ions. Other workers have reported the isolation of vinyl salts from reactions of allylic halides.[20]

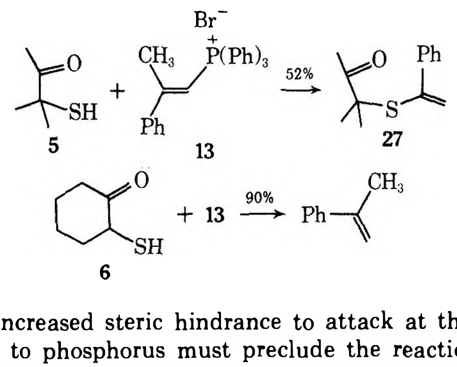
In order to attain generality for the synthesis, a reliable preparation of the α-mercapto ketones or the α-halocarbonyl precursors is required. The regiospecific halogenation of carbonyl compounds has been reviewed[21] and a recent method[22] appears to offer a completely regiospecific synthesis. The replacement of halogen by the sulfhydryl group is a facile reaction. It is worthy of note that the stereochemistry of halogenation is unimportant as the eventual fate of the carbon atom being substituted is sp^2 hybridization and thus any stereochemistry is destroyed.

The α-mercaptocarbonyl compounds typically exist as dimeric dihydroxy-1,4-dithianes,[23,24] (**25**), many of which are highly insoluble in the usual organic solvents and which are easily dehydrated to transannular ethers **26** by traces if acid,[23a] In basic medium, an equilibrium is established between monomer and dimer and the material becomes much more soluble.[24] However, under these conditions, protonic solvents readily add to the vinyl salts, forming β-substituted compounds which are inactive in the desired reaction. The ability of pyridine to dissolve both reactants, serve as the base, and provide a solvent which could easily be removed by acid extraction suggested its use. While some reactions did indeed proceed satisfactorily under these conditions, the addition of some triethylamine to the reaction system speeded the reaction and allowed the use of either the vinyl or allyl salt as the starting material. Simple chromatography eliminated all phosphorus-containing and colored impurities and afforded the dihydrothiophenes listed in Table I in the generally excellent yields shown.



25 26

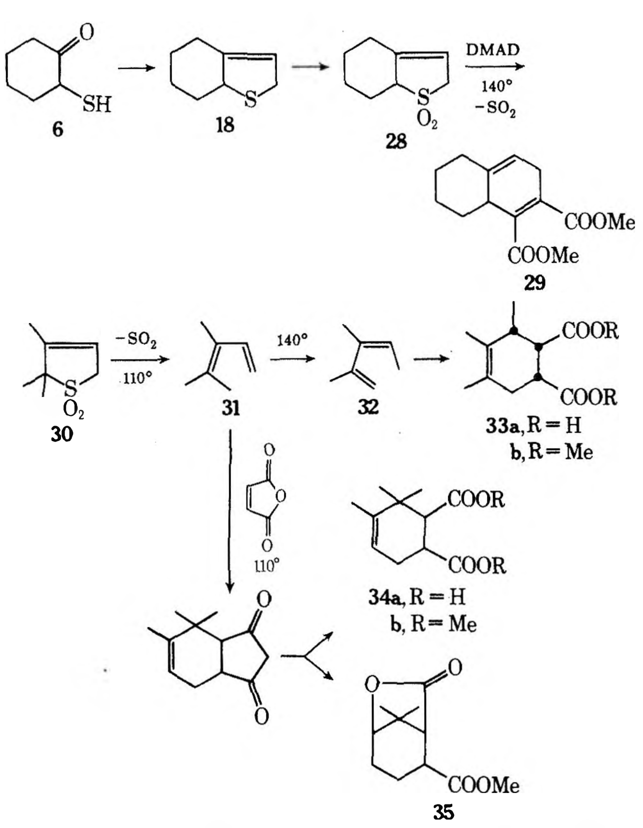
Anomalous results were obtained using salt **13** and ketones **5** and **6**. In the first case, the product (**27**) formed was derived by attack of the sulfur nucleophile on the equilibrium concentration of the allylic isomer of the salt.



The increased steric hindrance to attack at the carbon atom β to phosphorus must preclude the reaction of the nucleophile at this point. Substitution, with or without allylic rearrangement, will lead to the observed product.

The product isolated in high yield from the reaction between **13** and **6** was identified as α-methylstyrene. This may be formed by attack of sulfur at phosphorus, but we have no further information on this reaction at the present time. Finally, when mercapto ketone **8** was used, an additional peak in the glc appeared which was identified as phenylacetone, a product of desulfurization of **8**. Desulfurization of aromatic mercapto ketones under basic conditions also has been observed by other workers.[25]

Scheme II



The synthetic utility of the overall scheme is illustrated by the oxidation–cycloelimination–cycloaddition sequences outlined in Scheme II. Oxidation of 18 with *m*-chloroperbenzoic acid afforded the known[26] sulfone 28 in quantitative yield. Refluxing a xylene solution of this material in the presence of 1 equiv of dimethyl acetylenedicarboxylate led to 29[27] in an isolated yield of 78%. Thus the overall conversion of 6 to 29 occurs in 58% yield in three simple steps. Similarly, the oxidation of 15 under the same reaction conditions afforded sulfone 30, again in quantitative yield. In refluxing xylene solution in the presence of maleic anhydride, a rapid evolution of sulfur dioxide occurred, but the product isolated in 58% yield after hydrolysis was the diacid 33a[28] derived from rearranged diene 32. Reducing the reaction temperature to 110° reduced the rate of reaction drastically, but, after prolonged reaction, a quantitative yield of three products was obtained. Hydrolysis and esterification of these materials led to the isolation of rearranged adduct 33b (11%), unrearranged diester 34b,[28,29] and the known lactone ester 35[28] derived from diacid 34a. The unambiguous synthesis of diene 31 from ketone 5 thus proceeds in 74% overall yield in three steps. The only previous synthesis of this diene involved a multistep reaction sequence starting from a complex starting material and proceeding in 8% overall yield.[29]

We are currently engaged in an investigation of the stereochemistry of formation of the dihydrothiophenes by this method, in its extension to functionalized reactants and intermolecular examples. Work is also in progress on other reactions of compounds of type 1 and the results of these investigations will be reported at a later date.

Experimental Section

Unless otherwise noted, infrared spectra were recorded on a Beckman IR-20A spectrometer in carbon tetrachloride solution and nmr spectra were obtained on a JEOLCO C60HL spectrometer in deuteriochloroform and are reported in parts per million from TMS as internal standard. Glc analyses were carried out on an F & M Model 720 gas chromatograph utilizing an 8 ft × 0.375 in. 20% SE-30 on Chromosorb W column. The flow rate of the helium carrier gas was 1 ml/sec. Mass spectra were obtained on a Varian MAT CH5-DF instrument. Unless otherwise noted, the drying agent used was anhydrous sodium sulfate and solvents were removed on a rotary evaporator at reduced pressure. Chromatography was performed using Fisher acidic alumina, 80–200 mesh, Brockman activity grade I. Microanalyses were performed by A. B. Gygli, Microanalysis Laboratory, Toronto, Ontario, Canada.

Preparation of Salts 10, 11, 12, 13, and 13a. Vinyltriphenylphosphonium bromide[11a] (10) was purchased from the Aldrich Chemical Co.

2-Methylvinyltriphenylphosphonium bromide[15a] (11) was prepared by stirring a solution of 5 g of salt 11a in 40 ml of dry pyridine containing 6 drops of triethylamine at room temperature for 18 hr. After removal of solvent, purification was effected by adding 50 ml of boiling benzene, adding enough methylene chloride to effect solution, cooling to room temperature, and precipitating the salt with 20 ml of ethyl acetate. The yield was 96%, mp 210–212° (lit.[15a] mp 213–214°).

2,2-Dimethylvinyltriphenylphosphonium chloride (12) was prepared by refluxing equimolar amounts of triphenylphosphine and methallyl chloride in benzene solution, removing the solvent, and recrystallizing the residue in the same manner as for 11: mp 211–213° (lit.[19a] mp 214–216° reported as 12a); nmr δ 7.80–7.38 (m, 15), 6.48 (d, 1, J = 20 Hz), 2.42 (br s, 3), 1.76 (d, 3, J = 2 Hz). An alternate procedure whereby a large excess of methallyl chloride was used as the reaction solvent afforded a crude product whose nmr spectrum showed it to be a 5:1 mixture of salts 12a and 12.

Bromination of α-Methylstryene. α-Methylstryene (94.4 g, 0.8 mol) and 90 g (0.5 mol) of *N*-bromosuccinimide were mixed under a nitrogen atmosphere in a 1000-ml flask fitted with a magnetic stirrer, a reflux condenser, and an addition funnel containing 400 ml of carbon tetrachloride. The stirrer was started and the flask was heated with a Meker burner until the solid started to melt. An exothermic reaction started and the flask was cooled in an ice bath to moderate the reaction. After the reaction had subsided, the mixture was stirred for 2 hr, the carbon tetrachloride was added, and the insoluble material was removed by filtration. The residue was washed with solvent and the filtrate was evaporated to afford 95 g of a dark oily lachrymator[30] which was used without further purification.

2-Phenyl-1-propen-3-yltriphenylphosphonium Bromide (13a). Crude α-bromomethylstryene (80 g, 0.4 mol) was dissolved in 50 ml of methylene chloride, and 107 g (0.41 mol) of triphenylphosphine was added. The solution was heated at reflux for 24 hr. The cooled solution was filtered, and the filtrate was diluted with 50 ml of ethyl acetate and refiltered. The combined residues were washed with ethyl acetate and dried to yield 59 g of salt 13a: mp 224–226°; nmr δ 8.0–6.8 (m, 20), 5.5–5.1 (m, 4).

Anal. Calcd for $C_{27}H_{24}PBr$: C, 70.57; H, 5.27. Found: C, 70.71; H, 5.40.

2-Phenyl-2-methylvinyltriphenylphosphonium Bromide (13). Salt 13a (60 mg) was dissolved in pyridine-d_5 in an nmr tube and 2 drops of triethylamine was added. After 30 min, the absorption at δ 5–6 had completely disappeared. Repeating the procedure on a preparative scale led to the isolation of salt 13a and an oil which could not be crystallized, but whose nmr spectrum was consistent with structure 13, nmr δ 7.9–7.35 (m, 20), 7.1–6.3 (m, 1), 2.20 (d, 3, J = 3.5 Hz). This salt was normally prepared *in situ* from 13a.

Preparation of Dihydrothiophenes. All the dihydrothiophenes listed in Table I were prepared by the following procedure.

The appropriate phosphonium salt (0.01 mol) was dissolved in 50 ml of dry pyridine in a 100-ml flask fitted with magnetic stirring, a reflux condenser, and a nitrogen inlet. Triethylamine was added (0.015 mol) and the mixture was stirred at room temperature for 30 min. The appropriate mercapto ketone (0.01 mol) was added, the system was purged with nitrogen, and the solution was heated at reflux for the time indicated in Table I. The cooled solution was poured into 600 ml of water and extracted twice with 100 ml of ether and twice with 100 ml of pentane. The combined organic layers were washed with two 100-ml portions of 10% hydrochloric acid and dried. The solution was reduced in volume to *ca.* 10 ml and chromatographed on alumina using pentane as the eluent. This removed all phosphorus-containing and colored materials. The solvent was removed to yield the dihydrothiophene, which glc analysis showed to be greater than 95% pure. Analyti-

Table II
Indices of Refraction and Nmr Spectra

Compd	$n^{25}D$	Nmr spectral data[a]
14	1.5192	5.40 (s, 1), 3.57 (s, 4), 1.81 (s, 3)
15	1.4912	5.32 (m, 1), 3.60 (t, 2, J = 2 Hz), 1.72 (d, 3, J = 1.5 Hz), 1.51 (s, 2)
16	1.4860	5.22 (m, 1), 4.02 (m, 1), 1.69 (t, 3, J = 1.8 Hz), 1.50 (s, 3), 1.47 (s, 3), 1.35 (d, 3, J = 6 Hz)
17	1.4701	5.15 (d, 1, J = 1 Hz), 1.67 (d, 3, J = 1 Hz), 1.50 (s, 12)
18	1.5476	5.35 (m, 1), 3.70 (m, 3), 2.80–1.01 (m, 8)
19	1.5272	5.26 (d, 1, J = 2 Hz), 4.48–3.70 (m, 2), 2.72–1.10 (m, 8), 1.40 (d, 3, J = 6.5 Hz)
20	1.5129	5.10 (t, 1, J = 1.5 Hz), 3.70 (m, 1), 2.65–1.10 (m, 8), 1.48 (s, 3), 1.44 (s, 3)
21	1.5408	5.35 (br s, 1), 4.26 (m, 1), 4.00 (m, 2), 2.5–1.2 (m, 6)
22	1.5186	7.12 (s, 5), 5.50 (m, 1), 4.85 (m, 1), 3.71 (m, 2), 1.51 (m, 3)
23	1.4732	5.40 (t, 1, J = 2 Hz), 3.53 (d, 2, J = 2 Hz), 2.22 (m, 1), 1.45 (s, 3), 1.12 (d, 6, J = 7 Hz)
24	*b*	5.23 (d, 1, J = 2 Hz), 3.99 (m, 1), 2.13 (m, 1), 1.45 (s, 3), 1.41 (s, 3), 1.27 (d, 3, J = 7 Hz), 1.07 (d, 6, J = 7 Hz)

[a] Tabulation follows the order chemical shift (δ), multiplicitly, number of protons, coupling constant. Spectra run in $CDCl_3$. [b] Insufficient sample available.

cal samples were collected by glc. Indices of refraction and nmr spectra are shown in Table II. Except for the lack of carbonyl absorption, the infrared spectra were uninformative.

Keto Sulfide 27. When salt **13** and mercapto ketone **5** were allowed to react under the conditions given for the preparation of the dihydrothiophenes, elution of the chromatography column with pentane afforded a 52% yield of **27** as a pale yellow oil: nmr δ 7.20 (s, 5), 5.28 (d, 1, J = 1 Hz), 5.15 (m, 1), 3.32 (d, 2, J = 1 Hz), 2.10 (s, 3), 1.37 (s, 6); ir 1720 cm^{-1}.

2,4,5,6,7,7a-Hexahydrobenzo[*b*]thiophene 1,1-Dioxide (28).[26] The reaction was carried out in the same manner as for **30** using 1.4 g (0.01 mol) of **18** and 3.96 g (0.022 mol) of *m*-chloroperbenzoic acid. Evaporation of the dried solution afforded 1.67 g (98%) of a colorless liquid: nmr δ 5.57 (t, 1, J = 2 Hz), 3.8–3.3 (m, 3), 2.7–1.1 (m, 8).

Dimethyl 3,5,6,7,8,8a-Hexahydronaphthalene-1,2-dicarboxylate (29).[27] Sulfone **28** (1 g, 0.0058 mol) was dissolved in 5 ml of xylene and 0.28 g of dimethyl acetylenedicarboxylate and a small amount of hydroquinone were added. The solution was heated at reflux for 6 hr and the xylene was removed by distillation at atmospheric pressure. Glc analysis of the residue showed only one peak which was collected and proved to be **29**. The yield was calculated to be 78%: nmr δ 5.35 (br s, 1), 3.80 (s, 3), 3.75 (s, 3), 2.97 (br s, 3), 2.32–1.10 (m, 8); ir 1730, 1660 cm^{-1}.

2,2,3-Trimethyl-2,5-dihydrothiophene 1,1-Dioxide (30). To a cold solution of 2 g (0.0156 mol) of **15** in methylene chloride was added 6.18 g (2.15 equiv) of *m*-chloroperbenzoic acid in two equal portions. The exothermic reaction was moderated by use of an ice bath. The solution was stirred at 0° for 3 hr and at room temperature for 1 hr. The precipitate was removed by filtration and the filtrate was washed with two 75-ml portions of saturated sodium carbonate solution, dried, and evaporated. The residue solidified to give 2.5 g (100%) of a white solid: mp 64–65° which was not raised by recrystallization from benzene–pentane; nmr δ 5.70 (m, 1), 3.71 (m, 2), 1.81 (m, 3), 1.44 (s, 6); ir 3030, 2990, 2940, 1310, 1140, 1110 cm^{-1}.

Anal. Calcd for $C_7H_{12}O_{12}S$: C, 52.46; H, 7.51; S, 20.00. Found: C, 52.62; H, 7.72; S, 19.86.

3,4,5-Trimethyl-4-cyclohexene-1,2-dicarboxylic Acid (33).[28] Sulfone **30** (0.5 g, 3.12 mmol) and 0.31 g (3.13 mmol) of maleic anhydride were dissolved in 5 ml of xylene and a small amount of hydroquinone was added. The solution was refluxed for 6 hr, cooled, and evaporated to afford 0.5 g of a solid which was immediately hydrolyzed in boiling water for 1.5 hr. Evaporation and crystallization of the residue from water afforded 0.45 g (58%) of **30**, mp 173–174° (lit.[28] mp 173–174°).

Reaction of 30 with Maleic Anhydride in Toluene. The reaction was run as before except that toluene was used as solvent. The evolution of sulfur dioxide was much slower and the reaction was monitored by nmr. After 165 hr reflux, the reaction was worked up as before and a mixture of acids was obtained from which 65 mg of **33a** could be isolated by crystallization from water. Esterification of the evaporated mother liquors using diazomethane gave a mixture of three esters which were separated by glc. These proved to be diester **33b**, 3,3,4-trimethyl-4-cyclohexene 1,2-dicarboxylate (**34b**), and 2-carbomethoxy-5-hydroxy-5,6,6-trimethylcyclohexanecarboxylic acid lactone (**35**).[28]

Acknowledgment. The financial support of the National Research Council of Canada is most gratefully acknowledged.

Registry No. **4**, 24653-75-6; **5**, 42855-44-7; **6**, 42904-05-2; **7**, 42855-45-8; **8**, 42855-46-9; **9**, 42855-47-0; **10**, 5044-52-0; **11**, 7301-94-2; **12**, 42855-48-1; **13**, 42904-06-3; **13a**, 42855-49-2; **14**, 42855-50-5; **15**, 42855-51-6; **16**, 42855-52-7; **17**, 42855-53-8; **18**, 42855-54-9; **19**, 42855-55-0; **20**, 42854-41-1; **21**, 42854-42-2; **22**, 42854-43-3; **23**, 42854-44-4; **24**, 42854-45-5; **27**, 42854-46-6; **28**, 42854-47-7; **29**, 42854-48-8; **30**, 42854-49-9; triphenylphosphine, 603-35-0; 2-methallyl chloride, 563-47-3; α-bromomethylstyrene, 3360-54-1.

References and Notes

(1) (a) Presented in part at the annual meeting, Chemical Institute of Canada, Montreal, June 1973; (b) National Research Council of Canada Predoctoral Fellow, 1969–1973; (c) NRCC Predoctoral Fellow, 1973.

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A Photochemical Route to the Thieno[c]cyclobutene System

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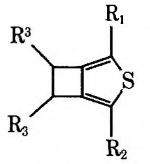
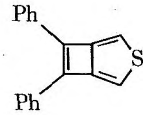
Photolysis of either of the cis or trans dihydrothienothiophene sulfones **15** and **16** affords primarily the thienocyclobutene **6**; similarly, the methoxy sulfone isomers **18** yield the methoxythienocyclobutene **19**. Both **6** and **19** undergo ready thermolysis to naphtho[c]thiophene derivatives. Evidence is presented which indicates that the thermolysis of **6** does not proceed *via* a tetravalent sulfur quinodimethane-type intermediate.

The first thieno[c]cyclobutenes have been reported only recently. These include the parent heterocycle **1**[1] and the tetrahalo derivatives **2** and **3**,[2] as well as the stable thienocyclobutadiene **4**.[3] Compounds **1** and **4** were prepared by constructing the thiophene nucleus by a Wittig synthesis; compounds **2** and **3** were prepared by a Finkelstein-type dehalogenation of an appropriate halo thiophene (**5**).



1, $R_1 = R_2 = R_3 = H$
2, $R_1 = R_2 = Cl$; $R_3 = Br$ (cis and trans)
3, $R_1 = Cl$; $R_2 = R_3 = Br$ (cis and trans)



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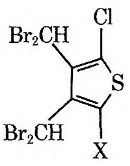

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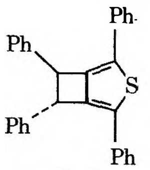
We now report the synthesis and properties of several 3,4-diphenylthieno[c]cyclobutenes (**6**, **7** and **8**), employing the photochemical decomposition of a sulfone precursor as the key synthetic step.



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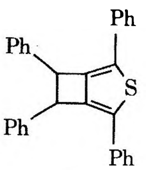

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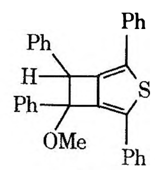
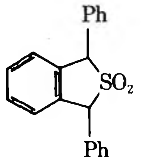


8

Results

The photochemical decomposition of the cyclic benzylic sulfones **9** and **10** affords a direct synthesis of the condensed cyclobutane aromatic hydrocarbons **11** and **12**.[4] Consequently, we decided to investigate the applicability of this type of reaction in the thiophene series. Thus, peracid oxidation of the known dihydrothienothiophenes **13** and **14**[5] gave the corresponding sulfone isomers **15** and **16**.



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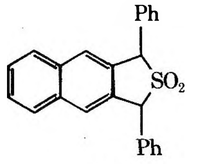

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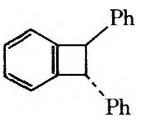

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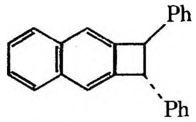

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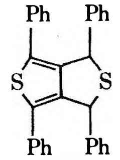
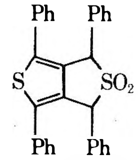


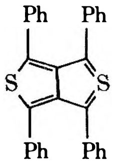
13, cis isomer
14, trans isomer



15, cis isomer
16, trans isomer

Both **15** and **16** lost sulfur dioxide cleanly upon irradiation in benzene-methanol in the presence of barium oxide to give, in good yield, the crystalline trans thienocyclobutene **6**. Careful chromatography of the photolysis residues afforded a very small amount of the corresponding cis isomer **7**. The nmr spectra of **6** and **7** showed benzylic singlets at δ 4.47 and 5.20, respectively; the corresponding reported values for *trans*-1,2-diphenylbenzocyclobutene (**11**) and its cis isomer are δ 4.42 and 5.20, respectively.[6]

A two-step conversion of tetraphenylthieno[3,4-c]thiophene (**17**) to the methoxy sulfone **18** has been reported.[5] We have now found that sulfone **18** can be separated into two stereoisomers, A and B (mp 234° dec and 210° dec, respectively), both of which lose sulfur dioxide upon irradiation to give the same methoxycyclobutene **19**. The nmr spectrum of **19**, which is probably the trans isomer, shows a single benzylic hydrogen at δ 4.72 as well as a methoxyl signal at δ 3.00.



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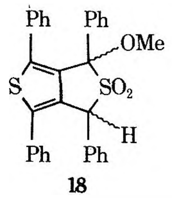

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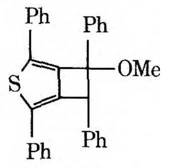
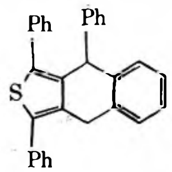


19

The thienocyclobutene **6** is quite stable in solution at temperatures up to about 60°. At 75°, however, an nmr study showed that it rearranged completely in hexachlorobutadiene solution within 45 min. The product, which was isomeric with **6** and which showed a one-proton singlet at δ 5.42 and a two-proton singlet at δ 3.98, was assigned structure **20**. Compound **20** was also obtained directly by the pyrolysis of sulfones **15** and **16** at their melting points (>200°). Palladium dehydrogenation of **20** afforded the bright red naphtho[*c*]thiophene derivative **21**.



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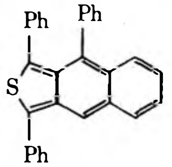
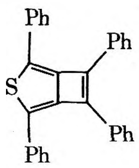


21

A number of unsuccessful attempts were made to carry out an acid-catalyzed elimination of methanol from the methoxy cyclobutene **19**, a reaction which we hoped would yield the thienocyclobutadiene **22**. The failure to achieve this conversion appears to be due to the thermal lability of **19**, which was completely converted to a complex mixture of products in a neutral deuteriobenzene solution in 30 min at 45°. Preparative decomposition of **19** in refluxing benzene, or in benzene containing *p*-toluenesulfonic acid at 25°, gave, after chromatographic separation, three isolable products. The major product was the red naphtho[*c*]thiophene **21**. The second product was also red and had spectral properties similar to those of **21**, although it contained a methoxyl group. It was therefore assigned structure **23**. The third product was colorless and contained a carbonyl group, and was assigned structure **24**, which is the expected acid hydrolysis product of **23**. It has been shown[7] that the parent ketone of **24**, namely **25**,



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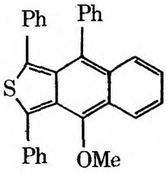


23

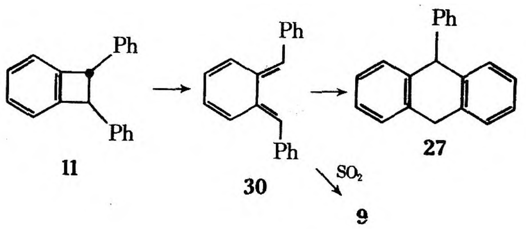
24, R = Ph
25, R = H

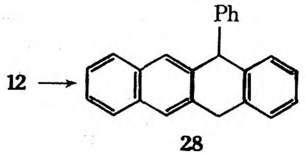
exists in the keto form rather than in the phenolic form. The pyrolysis of either of the stereoisomers of methoxy sulfone **18** also gave the naphtho[*c*]thiophene **21**.

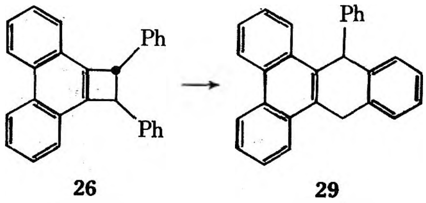
Discussion

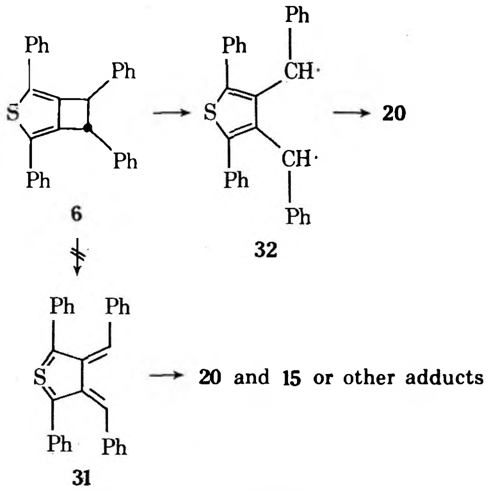
The thermal isomerization of the thienocyclobutene **6** to the isomeric dihydronaphtho[c]thiophene **20** is quite analogous to the thermolysis of the benzocyclobutene **11**,[8] the naphtho[*b*]cyclobutene **12**,[9] and the phenanthro[*l*]cyclobutene **26**[10] to give the corresponding rearrangement products **27**, **28**, and **29**. The rearrangements of **11**, **12**, and **26** all proceed by way of reactive *o*-quinodimethane intermediates (*i.e.*, **30**), which can be trapped either by olefinic dienophiles or by sulfur dioxide.[9,10,11] For example, the intermediate **30** from **11** is intercepted quantitatively by sulfur dioxide in boiling carbon tetrachloride,[11] or even in ether,[12] to give the sulfone **9**.

If the isomerization of **6** to **20** were to follow a similar pathway, the o-quinodimethane intermediate **31** would be an example of a new type of tetracovalent sulfur structure.[13] Attempts to intercept **31** during the thermolysis of **6** with either sulfur dioxide or *N*-phenylmaleimide were completely unsuccessful; only the isomer **20** was formed in the presence of these reagents. We conclude, therefore, that the tetravalent nature of the sulfur in quinomethane **31** destabilizes this species to a considerable extent relative to the diradical **32**, and that **32** is the actual intermediate in the conversion of **6** to **20**. Concerted addition of sulfur dioxide or a dienophile to **32** would not be expected on the basis of electrocyclic reaction theory.[14] Finally, it may be pointed out that the conversion of **6** to **20** represents the first case of *any* condensed cyclobutane aromatic compound which decomposes thermally without the generation of an *o*-quinonoid intermediate.









The ultraviolet spectra of both benzocyclobutene and naphtho[*b*]cyclobutene show practically no effect of ring strain on the positions of the aromatic maxima.[15,16] In contrast, a β,β-fused four-membered ring causes a considerable bathochromic shift in the thiophene series. Thus, the thieno[*c*]cyclobutene **6** has as its band of longest wavelength a triplet of maxima centered at 343 nm. Its thermal rearrangement product **20**, in which an unconjugated six-membered ring has replaced the cyclobutene ring, has a corresponding unresolved band centered at 310 nm. Since the analogous band of sulfide **13** is observed at 317 nm, it is clear that the major electronic distortion of the 2,5-diphenylthiophene chromophore occurs only when a four-membered ring is condensed to the heterocyclic nucleus.

Experimental Section

General. Melting points are uncorrected. Infrared spectra were determined in KBr, on a Perkin-Elmer Model 137 spectrophotometer. Ultraviolet and visible spectra were determined in cyclohexane solution, unless otherwise noted, using a Perkin-Elmer Model 202 instrument. Nmr spectra were recorded on a Varian HA-100 MHz machine. Photolyses were carried out under nitrogen using a Hanovia medium-pressure lamp with a Vycor filter.

Oxidation of Sulfide 13 to Sulfone 15. A solution of 1.6 g of *cis*-1,3-dihydro-1,3,4,6-tetraphenylthieno[3,4-c]thiophene (**13**)[5] in 180 ml of benzene–methanol (2:1) was treated with 50 ml of 40%

peracetic acid. The mixture was refluxed for 1 hr. The crystalline cis sulfone 15 was filtered. The filtrate was cooled, cautiously treated with ammonia, and extracted (chloroform) to yield additional 15. Recrystallization of the total crude 15 from chloroform–ethanol afforded 1.3 g (76%) of pure 15: mp 290° dec; nmr ($CDCl_3$-DMSO) δ 5.86 (s); ir 7.55, 8.80 μ (SO_2); uv spectrum λ_{max} (EtOH) 310 nm (log ϵ 4.20); mass spectrum *m/e* (rel intensity) 478 (M^+, 5), 414 (M − 64, 100).

Anal. Calcd for $C_{30}H_{22}S_2O_2$: C, 75.31; H, 4.63. Found: C, 74.82; H, 4.87.

Oxidation of Sulfide 14 to Sulfone 16. The corresponding trans-dihydrothieno[3,4-c]thiophene (14),[5] upon peracetic acid oxidation in a similar manner, yielded sulfone 16, mp 225° dec, in 71% yield: nmr ($CDCl_3$-DMSO) δ 5.67 (s); ir 7.55, 8.65 μ (SO_2); uv spectrum λ_{max} (EtOH) 312 nm (log ϵ 4.20); mass spectrum *m/e* (rel intensity) 478 (M^+, 6), 414 (M − 64, 100).

Anal. Calcd for $C_{30}H_{22}S_2O_2$: C, 75.31; H, 4.63. Found: C, 74.62; H, 4.86.

Photolysis of Sulfone 15 to the Thienocyclobutenes 6 and 7. A solution of 140 mg of 15 in 450 ml of benzene and 100 ml of methanol containing 100 mg of barium oxide was irradiated for 4 hr. The pale yellow solution was concentrated under reduced pressure (<40°). Extraction of the residue with benzene, followed by chromatography (Woelm I alumina, benzene–hexane 1:1 eluent) and crystallization from methanol–ether gave 75 mg (62%) of 6: mp 145°; nmr ($CDCl_3$) δ 4.47 (s); mass spectrum *m/e* (rel intensity) 414 (M^+ 98); uv spectrum λ_{max} 245 nm (log ϵ 4.28), 328 (4.41), 343 (4.52), 360 (4.39).

Anal. Calcd for $C_{30}H_{22}S$: C, 86.93; H, 5.35. Found: C, 87.37; H, 5.53.

Elution of the alumina column with benzene gave traces of the isomeric cis cyclobutene 7. Accumulation of material from several such runs, followed by crystallization from methanol, gave pure 7: mp 155° dec; nmr ($CDCl_3$) δ 5.20; mass spectrum *m/e* (rel intensity) 414 (M^+, 77); uv spectrum λ_{max} 245 nm (log ϵ 4.18), 327 (4.34), 343 (4.44), 360 (4.37).

Photolysis of Sulfone 16. Photolysis of 100 mg of 16 in benzene–methanol solution containing 100 mg of barium oxide was carried out as described above for isomer 15 to give 60 mg of 6 (70%), mp 145° dec.

The absence of methanol and barium oxide in the reaction mixture led to a 54% yield of 6, with recovery of 34% of 16. No interconversion of sulfones 15 and 16 was observed under the reaction conditions.

Separation of the Isomers of Methoxy Sulfone 18. The methoxy sulfone 18 (908 mg), prepared as described earlier,[5] was boiled with chloroform (120 ml). After cooling, the insoluble crystalline material was filtered to give isomer A (514 mg): mp 234° dec; nmr (DMSO-d_6) δ 6.27 (s, 1 Hz), 3.63 (s, 3 H); ir 7.60, 8.75 μ (SO_2).

Anal. Calcd for $C_{31}H_{24}S_2O_3$: C, 73.23; H, 4.72. Found: C, 73.03; H, 5.13.

Chromatography (silica, benzene eluent) of the residue followed by crystallization gave 290 mg of isomer B: mp 210° dec; nmr (DMSO-d_6) δ 6.26 (s, 1 H), 3.35 (s, 3 H); ir 7.60, 8.75 μ (SO_2).

Anal. Calcd for $C_{31}H_{24}S_2O_3$: C, 73.23; H, 4.72. Found: C, 73.09; H, 5.00.

Photolysis of Isomeric Methoxy Sulfones 18. Photolysis of 100 mg of sulfone 18A was carried out as described for sulfone 15. Direct crystallization of the crude product from ether–hexane led to the isolation of 30 mg (33%) of 19: mp 137° dec; nmr ($CDCl_3$) δ 4.72 (s, 1 H), 3.00 (s, 3 H); mass spectrum *m/e* (rel intensity) 444 (M^+, 100); uv spectrum λ_{max} 230 nm (sh, log ϵ 4.40), 245 (sh, 4.25), 330 (4.40), 345 (4.45), 364 (4.31).

Anal. Calcd for $C_{31}H_{24}SO$: C, 83.76; H, 5.44. Found: C, 83.59; H, 5.17.

Photolysis of the isomeric sulfone 18B gave 19 in similar yield. When 18A was photolyzed at 0–10°, the yield of 19 rose to 69%.

Thermal Rearrangement of 6. The nmr spectrum of a solution of 17 mg of 6 in 0.3 ml of hexachlorobutadiene was unchanged after 30 min at 25, 30, 40, 50, and 60°, no aliphatic proton being observed in addition to the singlet at δ 4.47. At 75° new signals at δ 5.42 and 3.98 (1:2 ratio) soon appeared and within 45 min the signal at δ 4.47 had vanished completely.

A solution of 30 mg of 6 in 10 ml of carbon tetrachloride was refluxed for 1 hr. Evaporation of the solvent and crystallization of the residue (ether–hexane) yielded 20 mg of 20: mp 178°; nmr ($CDCl_3$) δ 5.42 (s, 1 H), 3.98 (s, 2 H); mass spectrum *m/e* (rel intensity) 414 (M^+ 100); uv spectrum λ_{max} 254 nm (log ϵ 4.15), 310 (4.29).

Anal. Calcd for $C_{30}H_{22}S$: C, 86.93; H, 5.35. Found: C, 87.35; H, 5.77.

Thermal Decomposition of Sulfone 15. The sulfone 15 (100 mg) was heated in a tube at 290–295° until gas evolution ceased. Chromatography (Woelm neutral I alumina, hexane eluent) of the residue followed by crystallization (benzene–hexane) gave 45 mg (52%) of 20, mp 178°.

From 48 mg of sulfone 16, proceeding in a similar fashion, 20 mg (45%) of 20 was obtained.

Pyrolysis of Methoxy Sulfone 18A. The sulfone 18A (100 mg) was heated at 235° until gas evolution ceased. Chromatography (Woelm neutral I alumina, hexane eluent) of the melt followed by crystallization gave 25 mg (31%) of 21 as red needles: mp 222°; uv–visible spectrum λ_{max} 255 nm (log ϵ 4.53), 270 (sh, 4.45), 287 (sh, 4.32), 315 (sh, 4.13), 485 (3.90), 505 (3.95); mass spectrum *m/e* (rel intensity) 412 (M^+, 100).

Anal. Calcd for $C_{30}H_{20}S$: C, 87.35; H, 4.89. Found: C, 86.70; H, 5.07.

Dehydrogenation of 20 to 21. An intimate mixture of 20 (20 mg) and 5% Pd/C (20 mg) was heated for 5 min over a free flame. The melt was dissolved in benzene, freed from catalyst, and chromatographed [silica, benzene–hexane (1:1) eluent] to yield 5 mg (25%) of 21, mp 220° (from ether–hexane).

Attempted Elimination of Methanol from 19. A solution of 20 mg of 19 in 10 ml of benzene was heated on the steam bath. Within a few minutes all of the starting material had disappeared. The solvent was evaporated and the residue was subjected to plc [silica gel, benzene–hexane (1:1)] to give two red compounds A and B and a colorless compound C. Compound A, mp 220°, was identical with 21 as shown by comparison of melting point and ir and uv spectra with an authentic sample.

Compound B (23), mp 152° (from ether–hexane), was orange: nmr ($CDCl_3$) δ 3.44 (s, 3 H); uv–visible spectrum λ_{max} 235 nm (log ϵ 4.92), 278 (sh, 4.15), 287 (sh, 4.13), 476 (3.37), 510 (3.45); mass spectrum *m/e* (rel intensity) 442 (M^+, 20).

A satisfactory elemental analysis of this compound could not be obtained, probably because of the ease with which it undergoes photooxidation.

Compound C (24) had mp 178° (ether–hexane); nmr δ 5.52 (1 H, s); uv spectrum λ_{max} 220 nm (sh, log ϵ 4.58), 262 (sh, 4.37), 279 (4.40), 340 (3.84); ir 6.0 μ (C=O); mass spectrum *m/e* (rel intensity) 428 (M^+, 100).

Anal. Calcd for $C_{30}H_{20}SO$: C, 84.11; H, 4.67. Found: C, 84.11; H, 4.85.

Conversion of 23 to 24. A solution of 23 (5 mg) in moist benzene (10 ml) was refluxed for 1 hr after the addition of a trace of *p*-toluenesulfonic acid. The solution was evaporated to dryness. The residue was worked up by plc (silica–benzene) to yield 24 (3 mg, 61%), mp 178°.

Rearrangement of 6 to 20 in the Presence of Trapping Agents. A. In the Presence of Sulfur Dioxide. Sulfur dioxide was bubbled through a solution of 10 mg of 6 in 20 ml of ether at room temperature, taking care to maintain the solvent level. After 3 hr, evaporation of the ether gave unchanged 6 (7 mg). No trace of either sulfone 15 or 16 could be detected. The use of benzene or dimethylformamide at room temperature also led to recovery of 6. The sulfur dioxide addition was then attempted in boiling solvents, such as carbon tetrachloride, benzene, and xylene. Again no trace of 15 or 16 was detected, the only product isolated being 20, formed in good yield.

B. In the Presence of *N*-Phenylmaleimide. Solutions of 6 (10 mg) and *N*-phenylmaleimide (10 mg) in (a) benzene and (b) chloroform were stirred at room temperature for 24 hr. Evaporation followed by purification of the residue led to recovery of 6.

When a solution of 6 (20 mg) and *N*-phenylmaleimide (20 mg) in benzene (10 mg) was refluxed for 4 hr, the product obtained was 20 (13 mg). No other product could be detected.

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Registry No. 6, 42962-82-3; 7, 42962-83-4; 13, 40953-23-9; 14, 40953-24-0; 15, 42880-82-0; 16, 42880-83-1; *cis*-18, 42880-84-2; *trans*-18, 42962-84-5; 19, 42880-85-3; 20, 42893-99-2; 21, 42894-00-8; 23, 42894-01-9; 24, 42894-02-0.

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Urylenediphosphonates. A General Method for the Synthesis of α-Ureidophosphonates and Related Structures

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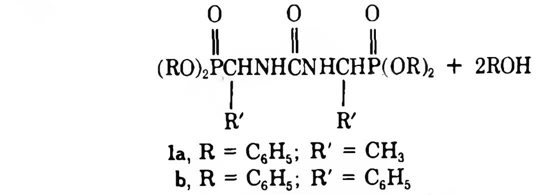
Urea and many mono- and disubstituted ureas and their thio analogs react with aldehydes and certain esters of trivalent phosphorus acids, providing a route to numerous new α-ureidophosphonates, $(RO)_2P(O)CHR'NHCONH_2$, and related products. Surprisingly, triphenyl phosphite is more readily converted to phosphonates in this process than are trialkyl phosphites, a reversal of the normal order of reactivity of phosphite esters. Acid catalysis is beneficial in some cases. Urylenediphosphonates, $(RO)_2P(O)CHR'NHCONHCHR'P(O)(OR)_2$, as well as monophosphonates are obtained when unsubstituted urea is used, whereas mono- and disubstituted ureas give only monophosphonates. Phosphonite and phosphinite esters react similarly, giving ureaphosphinates and -phosphine oxides, respectively. Cyclic 1,4,2-diazaphospholidins are the major products when 1,3-dimethylurea is used. Many of the products can be readily hydrolyzed to the corresponding ureidophosphonic and -phosphinic acids.

While the synthesis and properties of many types of nitrogen-containing organophosphorus compounds have been widely investigated,[1] for example, aminophosphonates in biochemical[2] and in chelation[3,4] studies, ureaphosphonates have received little attention. In connection with our interests in new biologically active structures and in permanent fire retardancy of polymers,[5] a search was made for routes to urea derivatives having organophosphorus substituents. The resulting investigation led to the discovery that urea and many mono- and disubstituted ureas and their thio analogs will react with certain esters of trivalent phosphorus acids and aldehydes to give α-ureidophosphonates and related products. Numerous compounds can be synthesized by this process, since the structures of all three reactants are subject to broad variation.

The application of this new reaction to the preparation of urylenediphosphonates (**1a–d**) from urea, phosphite esters, and aldehydes is represented by the following equation.

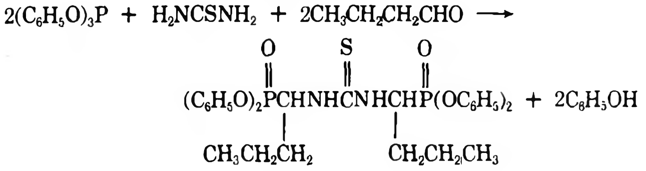


$$2(RO)_3P + H_2NCONH_2 + 2R'CHO \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}\underset{R'}{CH}NH\overset{O}{\overset{\|}{C}}NH\underset{R'}{CH}\overset{O}{\overset{\|}{P}}(OR)_2 + 2ROH$$

1a, $R = C_6H_5$; $R' = CH_3$
b, $R = C_6H_5$; $R' = C_6H_5$
c, $R = CH_2CH_2Cl$; $R' = CH_3$
d, $R = CH_2CH_2Cl$; $R' = CH(CH_3)_2$

Generally, the reaction is initiated when a mixture of the three reactants is warmed to about 60–70°; it is usually complete after 10–15 min at 70–100°. Alternatively, the aldehyde may be added gradually to a mixture of urea and the phosphite ester at this temperature. Since the crude products are mixtures of isomers, resulting from formation of two asymmetric centers in each diphosphonate molecule, crystallization is usually slow. Yields of crystalline diphosphonates isolated have consequently been limited to 60% or less even though ^{31}P nmr measurements have indicated that some of the crude reaction mixtures contained considerably more material.

Although thiourea is less reactive than urea in this process, results are satisfactory when it is used with triphenyl phosphite and an alkyl aldehyde. Tetraphenyl (thiourylenedibutyl)diphosphonate (**2**) was obtained from thiourea, triphenyl phosphite and *n*-butyraldehyde in nearly a quantitative yield according to ^{31}P nmr measurements.

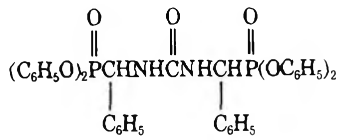


$$2(C_6H_5O)_3P + H_2NCSNH_2 + 2CH_3CH_2CH_2CHO \longrightarrow (C_6H_5O)_2\overset{O}{\overset{\|}{P}}\underset{CH_3CH_2CH_2}{CH}NH\overset{S}{\overset{\|}{C}}NH\underset{CH_2CH_2CH_3}{CH}\overset{O}{\overset{\|}{P}}(OC_6H_5)_2 + 2C_6H_5OH$$

2

In a few cases two fractions, presumably *dl* and meso forms, were isolated. Tetraphenyl (urylenedibenzyl)diphosphonate (**1b**), for example, was separated into fractions I and II.

The observed ^{31}P and ^1H nmr multiplets for I and II were consistent with the expected phosphorus–hydrogen and hydrogen–hydrogen spin couplings for structure **1b**. Conversion of the ^1H nmr doublet of doublets for each fraction to a simple doublet, $J_{CHNH} = 10$ Hz, by heteronuclear ^{31}P spin decoupling provided further evidence of the



$(C_6H_5O)_2\overset{O}{\overset{\|}{P}}\underset{C_6H_5}{CH}NH\overset{O}{\overset{\|}{C}}NH\underset{C_6H_5}{CH}\overset{O}{\overset{\|}{P}}(OC_6H_5)_2$

1b

Fraction I

Mp 189-191 °C
$\delta^{31}P$ −14.7 (d, J_{PCH} = 22 Hz)
$\delta^{1}H$ 5.98 (d of d, J_{CHP} = 22 Hz, J_{CHNH} = 10 Hz)
Ir 5.88 (C═O), 8.38 μ (P═O)

Fraction II

Mp 181-183 °C
$\delta^{31}P$ −15.5 (d, J_{PCH} = 22 Hz)
$\delta^{1}H$ 6.06 (d of d, J_{CHP} = 22 Hz, J_{CHNH} = 10 Hz)
Ir 5.88 (C═O), 8.38 μ (P═O)

presence of the PCHNH moiety. Infrared spectra, elemental analyses, and molecular weight measurements (see Experimental Section) also were in agreement with **1b**. A sharply depressed mixture melting point for I and II, as well as small but real nmr chemical shift differences, confirmed that these fractions were isomers.

Surprisingly, triaryl phosphites are markedly more reactive in this process than are trialkyl phosphites. For example, when a mixture of triphenyl phosphite, *n*-butyraldehyde, and urea (2:2:1 molar ratio) in toluene was warmed, reaction was initiated at 70°, and cooling was needed for several minutes to keep the temperature below 90° as the urea dissolved. The reaction was complete in less than 0.5 hr according to ^{31}P nmr. When triethyl phosphite was used under similar conditions, the urea did not dissolve, and there was no indication of reaction after 1 hr at 95-100°. Trimethyl and triisopropyl phosphites were similarly unreactive. Tris(2-chloroalkyl) phosphites, normally intermediate in reactivity in the phosphite series, reacted readily when alkyl aldehydes were used but only slowly with less reactive aryl aldehydes.

This may be the first known reaction in which triaryl phosphites are more readily converted to phosphonates than are low molecular weight trialkyl phosphites. The literature reports the synthesis of hundreds of phosphonates from the normally reactive trialkyl phosphites by the Michaelis-Arbuzov reaction and some of its variations[6-10] but gives comparatively few examples of phosphonates being prepared from triaryl phosphites. Triaryl phosphites usually form relatively stable intermediates that require drastic heating or treatment with aqueous alkali or alcohols for conversion to phosphonates.[6-10] It is thus unexpected that aryl phosphites should be converted to phosphonates under mild conditions in the present reaction whereas alkyl phosphites are unreactive under the same conditions.

Experimental observations that may explain this reversal of the normal order of reactivity of phosphite esters are listed below.

(1) Urea and *n*-butyraldehyde reacted readily and formed a polymer when a mixture was warmed to ~60°.

(2) Reaction of urea with *n*-butyraldehyde was inhibited when triethylamine was present.

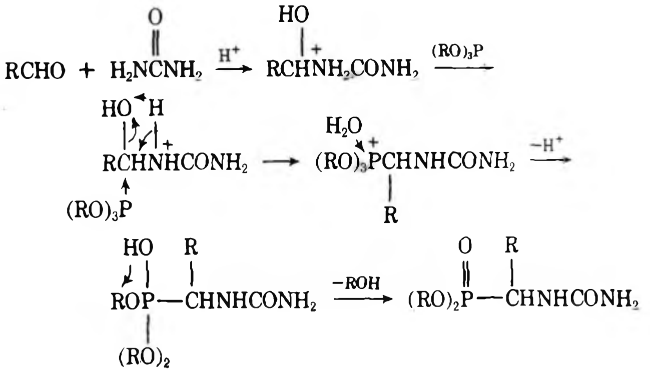
(3) Reaction of urea and *n*-butyraldehyde was also inhibited by triethyl phosphite.

(4) Reaction of triphenyl phosphite with urea and *n*-butyraldehyde was inhibited when triethyl phosphite was present.

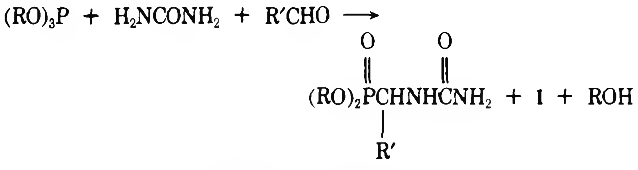
(5) The addition of acetic acid or boron trifluoride etherate to mixtures of triethyl phosphite, urea, and *n*-butyraldehyde or benzaldehyde promoted the formation of ureaphosphonates.

Evidently, the first step in the formation of ureaphosphonates is an acid-catalyzed reaction of urea and aldehyde as shown in Scheme I. Trialkyl phosphites, such as triethyl phosphite, are basic enough to inhibit this first step, whereas the less basic triphenyl phosphite[11] does not lower the acidity below the level needed for reaction of urea and aldehyde. Tris(2-chloroalkyl) phosphites, which are intermediate in nucleophilicity and probably in basicity,[12] are less reactive than triaryl phosphites but more reactive than unsubstituted trialkyl phosphites.

Scheme I

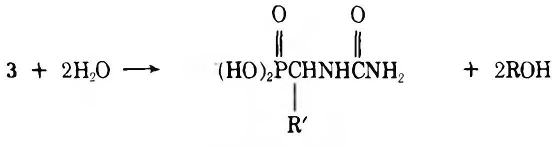


Since the formation of urea monophosphonates, such as **3a** and **3b**, is accompanied by formation of diphosphonates even when equimolar quantities of reactants are used, pure monophosphonates are usually difficult to isolate. Fortunately, the monophosphonates hydrolyze more readily than the diphosphonates, and the resulting phosphonic acids can be easily isolated. Pure ureaphosphonic acids **4a** and **4b** were obtained after crude mixtures of the phosphonates were warmed with distilled water. Presumably, the unsubstituted NH2 group, in a position that can allow formation of a five-membered ring with phosphorus, participates in the hydrolysis of the monophosphonates. The ureadiphosphonic acid **5a** was obtained only after **1d** was warmed with dilute hydrochloric acid for several hours.



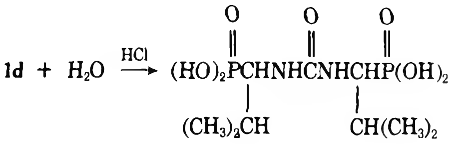
$(RO)_3P + H_2NCONH_2 + R'CHO \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}\underset{R'}{CH}NH\overset{O}{\overset{\|}{C}}NH_2 + 1 + ROH$

3a, R = CH_2CH_2Cl; R' = CH_2CH_3
b, R = CH_2CH_2Cl; R' = $CH(C_2H_5)\ (CH_2)_3CH_3$



$3 + 2H_2O \longrightarrow (HO)_2\overset{O}{\overset{\|}{P}}\underset{R'}{CH}NH\overset{O}{\overset{\|}{C}}NH_2 + 2ROH$

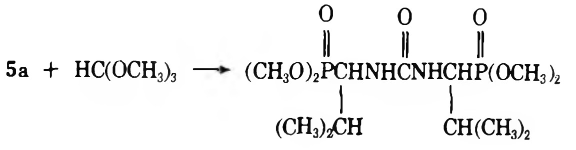
4a, R' = CH_2CH_3
b, R' = $CH(C_2H_5)(CH_2)_3CH_3$



$1d + H_2O \xrightarrow{HCl} (HO)_2\overset{O}{\overset{\|}{P}}\underset{(CH_3)_2CH}{CH}NH\overset{O}{\overset{\|}{C}}NH\underset{CH(CH_3)_2}{CH}\overset{O}{\overset{\|}{P}}(OH)_2$

5a

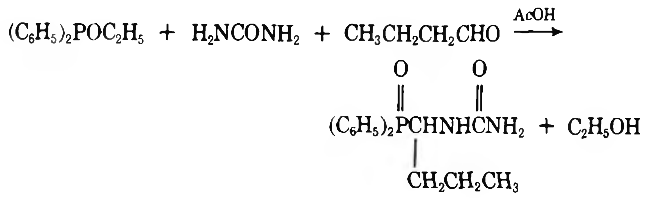
The tetramethyl ester of **5a** was synthesized by esterification of the acid with trimethyl orthoformate.



$$\mathbf{5a} + HC(OCH_3)_3 \longrightarrow (CH_3O)_2\overset{O}{\overset{\|}{P}}\underset{(CH_3)_2CH}{\underset{|}{C}}HNH\overset{O}{\overset{\|}{C}}NH\underset{CH(CH_3)_2}{\underset{|}{C}}H\overset{O}{\overset{\|}{P}}(OCH_3)_2$$

5b

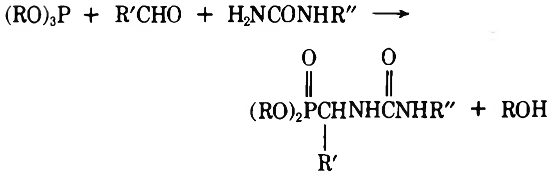
Aryl and 2-chloroalkyl esters of phenylphosphonous and diphenylphosphinous acids also react readily with urea and aldehydes. The alkyl ester, ethyl diphenylphosphinite, required the addition of an acid for reaction with urea and *n*-butyraldehyde. The monosubstituted product, diphenyl(1-ureidobutyl)phosphine oxide (6), was isolated in this case.



$$(C_6H_5)_2POC_2H_5 + H_2NCONH_2 + CH_3CH_2CH_2CHO \xrightarrow{AcOH} (C_6H_5)_2\overset{O}{\overset{\|}{P}}\underset{CH_2CH_2CH_3}{\underset{|}{C}}HNH\overset{O}{\overset{\|}{C}}NH_2 + C_2H_5OH$$

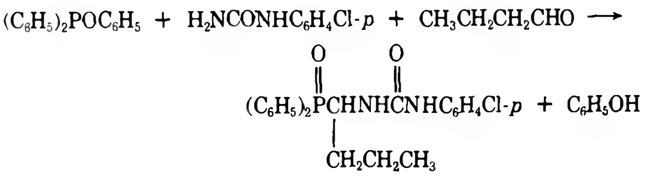
6

Ureidophosphonates **7a–c** were prepared from monosubstituted ureas. Acid catalysis again was needed for the formation of **7c** from triethyl phosphite. *p*-Chlorophenylurea, phenyl diphenylphosphinite, and *n*-butyraldehyde gave phosphine oxide **8**.



$$(RO)_3P + R'CHO + H_2NCONHR'' \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}\underset{R'}{\underset{|}{C}}HNH\overset{O}{\overset{\|}{C}}NHR'' + ROH$$

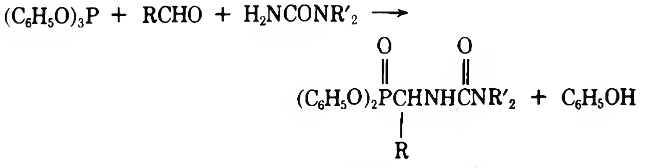
7a, R = C_6H_5; R′ = $CH_2CH_2CH_3$; R″ = $CH_2CO_2C_2H_5$
b, R = C_6H_5; R′ = 3-$CH_3OC_6H_3OH$-4; R″ = 4-ClC_6H_4
c, R = C_2H_5; R′ = C_6H_5; R″ = C_6H_5



$$(C_6H_5)_2POC_6H_5 + H_2NCONHC_6H_4Cl\text{-}p + CH_3CH_2CH_2CHO \longrightarrow (C_6H_5)_2\overset{O}{\overset{\|}{P}}\underset{CH_2CH_2CH_3}{\underset{|}{C}}HNH\overset{O}{\overset{\|}{C}}NHC_6H_4Cl\text{-}p + C_6H_5OH$$

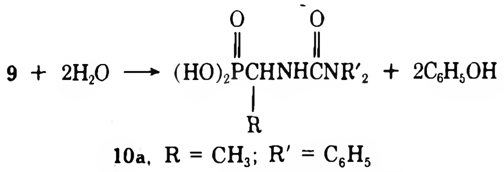
8

Similarly, ureidophosphonates **9a** and **9b** were prepared from 1,1-disubstituted ureas, and the esters were hydrolyzed to phosphonic acids **10a** and **10b**.



$$(C_6H_5O)_3P + RCHO + H_2NCONR'_2 \longrightarrow (C_6H_5O)_2\overset{O}{\overset{\|}{P}}\underset{R}{\underset{|}{C}}HNH\overset{O}{\overset{\|}{C}}NR'_2 + C_6H_5OH$$

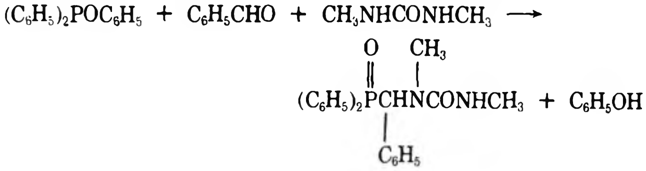
9a, R = CH_3; R′ = C_6H_5
b, R = $C_6H_4NO_2$-4; R′ = CH_3



$$\mathbf{9} + 2H_2O \longrightarrow (HO)_2\overset{O}{\overset{\|}{P}}\underset{R}{\underset{|}{C}}HNH\overset{O}{\overset{\|}{C}}NR'_2 + 2C_6H_5OH$$

10a, R = CH_3; R′ = C_6H_5
b, R = $C_6H_4NO_2$-4; R′ = CH_3

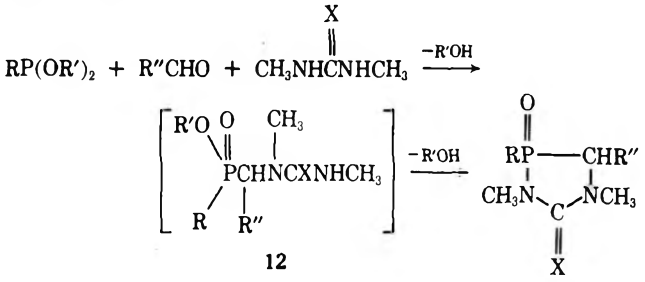
1,3-Dimethylurea gave two types of products, depending on the kind of phosphorus ester that was used. With phenyl diphenylphosphinite and benzaldehyde, a normal reaction occurred, and phosphine oxide **11** was obtained.



$$(C_6H_5)_2POC_6H_5 + C_6H_5CHO + CH_3NHCONHCH_3 \longrightarrow (C_6H_5)_2\overset{O}{\overset{\|}{P}}\underset{C_6H_5}{\underset{|}{C}}H\overset{CH_3}{\overset{|}{N}}CONHCH_3 + C_6H_5OH$$

11

However, when phosphite and phosphonite esters were used with 1,3-dimethylurea or its thio analog, cyclic 1,4,2-diazophospholidins (**13**) were the major products instead of linear structures such as those obtained in the preceding cases.



12

13

Some sulfamides, sulfonamides, and carbamates have also been found to react similarly to ureas with aldehydes and esters of trivalent phosphorus acids to give isolable crystalline products. Details of these results will be reported later. Moderate success with acid catalysis in several cases suggests that the process can probably be broadened in applicability by further study.

Experimental Section

Melting points were obtained in a Thomas-Hoover Unimelt instrument. Infrared spectra were determined in potassium bromide disks on a Beckman IR-4 spectrophotometer. Proton nuclear magnetic resonance (nmr) spectra were obtained at 60.0 or 100.0 MHz on Varian I-60 or HR-100 spectrometers with tetramethylsilane as an internal standard. Phosphorus nmr spectra were determined at 24.3 or 40.5 MHz on Varian HR-60 or HR-100 instruments and are reported with respect to 85% H_3PO_4 contained in a capillary. The nmr measurements were generally made on saturated solutions. Mass spectra were obtained on a Consolidated Engineering Corp. Type 21-104 spectrometer fitted with a probe for direct introduction of solids. Acid dissociation constants were determined from potentiometric titration data using the pH values at the midpoints of the titration curves.[13] Elemental analyses and molecular weights were determined by Galbraith Laboratories, Knoxville, Tenn.

Tetraphenyl (Urylenediethyl)diphosphonate (1a). A mixture of 60.0 g (1.0 mol) of powdered urea, 620.5 g (2.0 mol) of freshly distilled triphenyl phosphite, and 88.0 g (2.0 mol) of freshly distilled acetaldehyde in 600 g of 1,2-dichloroethane was stirred under nitrogen and warmed to 60° to initiate reaction. Cooling was used for a few minutes to keep the temperature below 80°, and the reaction mixture was then warmed at 80–84° for 0.5 hr to give a light tan solution having ^{31}P nmr signals at −19.7 (m) and −16.1 ppm (trace). The solution was washed three times with 10% sodium carbonate solution and three times with water, and it was then stripped to 130° (0.3 mm) to give 508.5 g (87.6%) of yellow, viscous oil having a ^{31}P nmr signal only at −19.9 ppm. A solution of 158 g of this oil in acetonitrile was refrigerated for 3 days to induce crystallization. It was then filtered, and the solid was washed with acetonitrile, giving 112.3 g (62%) of white solid, mp ~125–155°. Repeated recrystallizations from acetonitrile gave fractions I and II. Fraction I had mp 136–138°; ^{31}P nmr ($CDCl_3$) −19.7 ppm (m, $J \cong$ 18 Hz); ^1H nmr δ 7.21 (m, 20, C_6H_5), 6.46 (d, 2, J = 12 Hz, NH, collapsed to a singlet upon homonuclear decoupling), 4.86 (m, 2, CH), 1.30 (d of d, 6, J = 18 and 7.5 Hz, CH_3, collapsed to a doublet, J = 7.5 Hz, upon irradiation with 40.5 MHz at 750 Hz and to a doublet, J = 18 Hz, upon homonuclear decoupling): ir (KBr) 2.99 (m), 3.27 (w), 5.92 (s), 6.26 (m), 6.43 (s), 6.68 (s), 8.40 (vs), 10.6 μ (vs); mol wt ($CHCl_3$) 572 (theory 580).

Anal. Calcd for $C_{29}H_{30}N_2O_7P_2$: C, 59.98; H, 5.21; N, 4.82; P, 10.67. Found: C, 60.08; H, 5.05; N, 4.67; P, 10.71.

Fraction II had mp 156–161°; ^{31}P nmr −20.5 ppm (m, $J \cong 17.8$ Hz); ^{1}H nmr δ 7.20 (m, 20), 6.55 (d, 2, $J = 10$ Hz, NH), 4.86 (m, 2, CH), 1.37 (d of d, 6, $J = 18$ and 7.5 Hz, CH_3); ir essentially identical with that of I.

When the reaction was repeated without the use of a solvent, the results were essentially the same according to nmr measurements. In this run the by-product phenol (81%) of theory) was removed from **1a** by stripping to 120° (1 mm).

Tetraphenyl (Urylenedibenzyl)diphosphonate (1b). A mixture of 60.0 g (1.0 mol) of powdered urea, 620.5 g (2.0 mol) of freshly distilled triphenyl phosphite, and 212.2 g (2.0 mol) of benzaldehyde in 600 g of 1,2-dichloroethane was stirred under nitrogen and warmed. The heating mantle was removed at 70°, and a cooling bath was used as needed for 0.3 hr to keep the temperature below 83°. The reaction mixture was warmed at reflux (93°) for 0.7 hr and then allowed to cool. One pint of CCl_4 was added and the solution was washed once with 1 l. of 10% NaOH solution, three times with 500 ml of 5% NaOH solution, and three times with 500 ml of water. Stripping to 115° (0.2 mm) gave 498 g (71%) of pale yellow viscous oil: ^{31}P nmr −15 ppm (overlapping doublets). Two fractions, I and II, were separated by repeated recrystallizations from acetone and acetonitrile. Fraction I was a white solid: mp 189–191°; ^{31}P nmr ($CDCl_3$) −14.7 ppm (d, $J = 22$ Hz); ^{1}H nmr δ 6.66–7.66 (m, 32, aryl and NH), 5.98 (d of d, 2, $J = 22$, 10 Hz, CH, collapsed to doublet, $J = 10$ Hz, when decoupled from phosphorus); ir (KBr) 2.98 (m), 3.27 (w), 5.88 (s), 6.27 (m), 6.43 (s), 6.67 (s), 8.38 (vs), 10.6 μ (vs); mol wt (acetone) 731 (theory 704).

Anal. Calcd for $C_{39}H_{34}N_2O_7P_2$: C, 66.47; H, 4.86; N, 3.98; P, 8.79. Found: C, 66.35; H, 4.82; N, 3.99; P, 9.08.

Fraction II was a white solid: mp 181–183°; ^{31}P nmr −15.5 ppm (d, $J = 22$ Hz); ^{1}H nmr δ 6.66–7.75 (m, 32, aryl and NH), 6.06 (d of d, 2, $J = 22$, 10 Hz, CH, collapsed to doublet, $J = 10$ Hz, when decoupled from phosphorus); ir (KBr) essentially the same as that of I; mol wt (acetone) 692 (theory 704).

Anal. Found: C, 66.45; H, 4.83; N, 3.93; P, 8.71. The mixture melting point of I and II was 159–173°.

Tetrakis(2-chloroethyl) (Urylenediethyl)diphosphonate (1c). A 2-l., four-necked flask equipped with a thermometer, mechanical stirrer, dropping funnel, and Dry Ice cooled condenser was swept with nitrogen and charged with 539.0 g (2.0 mol) of *crude tris(2-chloroethyl)* phosphite, *60.0* g (*1.0* mol) of powdered urea, and one half of 94.6 g (2.15 mol) of freshly distilled acetaldehyde. When this mixture was warmed, refluxing began at 47° and the temperature gradually increased to 60° in 25 min. The mantle was removed, and heat of reaction raised the temperature to 82° in 15 min. The remainder of the acetaldehyde was then added below the surface of the reaction mixture in 11 min at 65–75°. Warming at 90–95° for 0.5 hr gave a clear, colorless solution, ^{31}P nmr −27.6 ppm. One pint of 1,2-dichloroethane was added, and the solution was washed five times with 400-ml portions of water and then stripped to 110° (0.2 mm) to give 469 g (89%) of colorless, viscous liquid: $n^{25}{}_D$ 1.4991; ^{31}P nmr −27.8 ppm; mol wt (acetone) 520 (calcd 526).

Anal. Calcd for $C_{13}H_{26}Cl_4N_2O_7P_2$: C, 29.67; H, 4.98; Cl, 26.95; N, 5.32; P, 11.77. Found: C, 29.75; H, 5.08; Cl, 27.00; N, 5.22; P, 11.63.

A solid formed after a portion of the viscous liquid was several times diluted with acetone and finally with ether and the solvent was allowed to evaporate each time. Recrystallization twice from acetonitrile–ether gave a white solid: mp 138–140°; ^{31}P nmr −27.8 ppm (m); ^{1}H nmr δ 6.45 (d, 2, $J = 10$ Hz, NH), 4.1–4.8 (m, 10, $POCH_2$ and PCH), 3.5–3.9 (m, 8, $ClCH_2$), 1.38 (d of d, 6, $J = 17$ and 7 Hz, CH_3); ir (KBr) 2.97 (m), 3.33 (w), 5.89 (s), 6.38 (s), 6.83 (m), 7.93 (s), 8.13 (s), 9.65 μ (vs); mol wt (DMF) 516.

Anal. Found: C, 29.97; H, 5.09; Cl, 26.99; N, 5.28; P, 11.71.

Tetraphenyl (Thiourylenedibutyl)diphosphonate (2). When a mixture of 11.4 g (0.15 mol) of thiourea, 93.0 g (0.30 mol) of triphenyl phosphite, and 22.7 g (0.32 mol) of *n*-butyraldehyde in 74 g of toluene was warmed to 100°, reaction was initiated, and the temperature increased to 105° within a few minutes without external warming. The reaction mixture was then warmed at 105–110° for 1 hr to give a light yellow solution having a ^{31}P nmr peak at −18.0 ppm, the only observable signal. Concentration to 120° (0.5 mm) to remove solvent and most of the by-product phenol gave 103.5 g (theory 97.5 g) of viscous liquid that completely solidified on standing. Recrystallization of a portion twice from acetone and once from acetonitrile gave a white solid (**2**): mp 138–143°; ^{31}P nmr −18.1 ppm; ^{1}H nmr δ 7.3 (d, 2, $J = 10$ Hz, NH), 7.1 (m, 20, aryl), 5.8 (m, 2, CH), 0.3–2.1 (m, 14, $CH_2CH_2CH_3$); ir 3.04 (w), 3.26 (w), 3.40 (w), 6.28 (m), 6.45 (m), 6.70 (m), 7.36 (m), 7.93 (m), 8.29 (m), 8.43 (s), 10.6–10.7 (vs), 13.0 (vs), 14.5 μ (s); mol wt (acetone) 630 (calcd 652).

Anal. Calcd for $C_{33}H_{38}N_2O_6P_2S$: C, 60.72; H, 5.87; N, 4.29; P, 9.49; S, 4.91. Found: C, 60.87; H, 6.09; N, 4.55; P, 9.56; S, 5.08.

1-Ureidopropylphosphonic Acid (4a). Freshly distilled propionaldehyde (58.0 g, 1.0 mol) was added dropwise in 1 hr to a stirred mixture of 60.0 g (1.0 mol) of powdered urea and 269.5 g (1.0 mol) of crude tris(2-chloroethyl) phosphite at 105–112°. Heat of reaction kept the temperature at this level without external warming during most of the aldehyde addition. The reaction mixture was warmed for 0.25 hr more, and then it was stripped to 122° (2 mm), giving a viscous, yellow residue (crude **3a**). This was dissolved in 100 ml of acetonitrile and 36 g (2.0 mol) of water, and the solution was warmed at reflux for 1 hr. A solid that formed during warming was separated by filtration of the warm reaction mixture, and then it was stirred and warmed in more acetonitrile and water, and the mixture was filtered while warm to give 76.2 g (42%) of white solid, mp 185–186° dec. A 5.0-g portion was recrystallized from acetic acid–water to give 3.2 g of **4a**: mp 189–191° dec; ^{31}P nmr (CD_3SOCD_3) −23.0 ppm (m); ^{1}H nmr δ 8.5 (broad, 4, OH and NH_2), 6.2 (broad, 1, NH), 3.7 (broad, 1, CH), 1.6 and 0.9 (broad, 5, CH_2CH_3); acidity 2.01 equiv/mol, $pK_1 = 2.70$, $pK_2 = 7.30$.

Anal. Calcd for $C_4H_{11}N_2O_4P$: C, 26.38; H, 6.09; N, 15.38; P, 17.01. Found: C, 26.50; H, 6.11; N, 15.26; P, 16.99.

2-Ethyl-1-ureidohexylphosphonic Acid (4b). This compound was prepared from tris(2-chloroethyl) phosphite, urea, and isobutyraldehyde by a procedure similar to that used for the preparation the preparation of 1-ureidopropylphosphonic acid. It was a white solid: mp 206° dec; ^{31}P nmr (CD_3SOCD_3) −23.2 ppm; ^{1}H nmr δ 8.5 (broad, 4, HO and NH_2), 6.2 (d, 1, $J = 8$ Hz, NH), 4.3 (d of d, 1, $J = 8$, 20 Hz, PCH), 1.3 and 0.9 (m, 15); acidity 2.00 equiv/mol, $pK_1 = 3.50$, $pK_2 = 9.08$.

Anal. Calcd for $C_9H_{21}O_4N_2P$: C, 42.85; H, 8.39; N, 11.11; P, 12.28. Found: C, 42.89; H, 8.29; N, 11.09; P, 12.23.

[Urylenedi(2-methylpropyl)]diphosphonic Acid (5a). Tetrakis(2-chloroethyl) [urylenedi(2-methylpropyl)]diphosphonate (**1d**) was prepared from tris(2-chloroethyl) phosphite, urea, and isobutyraldehyde by a procedure similar to that used for the preparation of **1c**. When a solution of 11.8 g (0.02 mol) of **1d**, mp 146–150°, and 2.9 g (0.16 mol) of distilled H_2O in 75 ml of acetonitrile was warmed at reflux for 7 hr, **1d** was recovered unchanged. The recovered **1d** was then stirred at reflux with 2.9 g of distilled H_2O and 1 ml of concentrated hydrochloric acid in 75 ml of acetonitrile for 6 hr. A solid, 4.4 g (67%), that separated during this warming period was recrystallized from CH_3CN-H_2O and then from CH_3CO_2H-H_2O to give white solid **5a** which appeared to melt at ~215°, resolidify, and then remelt at ~275–280° with foaming: ^{31}P nmr (DMSO-d_6) −22.8 ppm (m); ^{1}H nmr δ 8.6 (s, ~5, HO and NH?), 6.3 (broad, 1, NH), 3.8 (m, 2, CHP), 2.0 [m, 2, $CH(CH_3)_2$]; acidity by potentiometric titration 4.10 equiv/mol, $pK_1 = 2.71$, $pK_2 = 8.24$.

Anal. Calcd for $C_9H_{22}N_2O_7P_2$: C, 32.54; H, 6.68; N, 8.43; P, 18.64. Found: C, 32.64; H, 6.40; N, 8.35; P, 18.51.

Tetramethyl [Urylenedi(2-methylpropyl)]diphosphonate (5b). A mixture of 2.0 g of **5a** in 24 g of trimethyl orthoformate was warmed at reflux for 18 hr. Low boilers were removed by fractionation through a short column during the reflux period. The excess orthoformate was then distilled at reduced pressure, the residue was diluted with ether, and this mixture was filtered to give 0.5 g of solid. Recrystallization from acetone gave tetramethyl [urylenedi(2-methylpropyl)]diphosphonate (**5b**) as a white solid: mp 182–184.5°; ^{31}P nmr ($CDCl_3$) −27.7 ppm; ^{1}H nmr δ 6.61 (d, 2, $J = 10$ Hz, CHNH), 4.3 [four doublets, 2, J(CH-P) = 18, J(CH-NH) = 10, J(CH-CH) = 4 Hz, PCH(CH)NH], 3.76 [d, 6, $J(CH_3OP)$ = 10 Hz], 3.73 [d, 6, $J(CH_3OP)$ = 10 Hz], 2.06 [m, 2, $CH(CH_3)_2$], 1.03 [d, 12, $J = 7$ Hz, $CH(CH_3)_2$]; ir (KBr) 2.84 (w), 3.00 (m), 3.37 (m), 5.93 (s), 6.37 (s), 6.79 (m), 7.72 (m), 8.04 μ (vs).

Diphenyl(1-ureidobutyl)phosphine Oxide (6). After a mixture of 0.50 mol of ethyl diphenylphosphinite, 0.55 mol of *n*-butyraldehyde, and 0.25 mol of urea in 150 ml of chlorobenzene had been warmed at 110° for 3 hr, a ^{31}P nmr measurement showed a signal only for unreacted phosphite at −108.6 ppm. The mixture was cooled to room temperature and 0.25 mol of acetic acid was added dropwise in ~10 min. The temperature increased to 65° during this addition; the urea dissolved and then a white solid product separated. The addition of another 0.25 mol of acetic acid caused no additional heat of reaction. The reaction mixture was warmed at 65-80° for 1.5 hr and filtered, giving 44.4 g. Recrystallization from ethylene glycol gave 26.5 g of 6, a white solid: mp 241-244°; ^{31}P nmr (CF_3CO_2H) −44.4 ppm; mass spectrum M^+ 316 (theory 316).

Anal. Calcd for $C_{17}H_{21}N_2O_2P$: N, 8.85; P, 9.79. Found: N, 8.62; P, 9.94.

Ethyl [3-(1-Diphenoxyphosphinylbutyl)ureido]acetate (7a). When a mixture of 43.8 g (0.3 mol) of ethyl hydantoate, 93.0 g (0.3 mol) of triphenyl phosphite, and 21.6 g (0.3 mol) of *n*-butyraldehyde in 100 g of benzene was warmed to 65°, heat of reaction became sufficient to raise the temperature to 82° (reflux) without external warming. Warming at reflux was continued for 0.5 hr, giving a clear, colorless solution having a single ^{31}P nmr peak, −19.2 ppm. The solvent and most of the phenol were removed by stripping to 117° (1 mm). The crude product was diluted with an equal volume of ether, and this solution was cooled to 10° and filtered to give 87.6 g (68%) of white solid (7a): mp 114-116° (from CH_3CN); ^{31}P nmr −19.7 ppm; ^1H nmr δ 7.1 (m, 10, aryl), 6.5 (d, 1, J = 10 Hz, CHNH), 6.1 (broad, 1, $NHCH_2$), 4.8 (m, 1, CH), 4.1 (q, 2, J = 7 Hz, OCH_2CH_3), 3.8 (broad, 2, $NHCH_2$), 1.2 (t, 3, J = 7 Hz, OCH_2CH_3), 0.8-1.5 (m, 7, $CH_2CH_2CH_3$).

Anal. Calcd for $C_{21}H_{27}N_2O_6P$: C, 58.04; H, 6.26; N, 6.45; P, 7.13. Found: C, 57.82; H, 6.19: N, 6.24; P, 6.89.

Diphenyl α-[3-(4-Chlorophenyl)ureido]-4-hydroxy-3-methoxybenzylphosphonate (7b). A mixture of 34.1 g (0.2 mol) of 4-chlorophenylurea, 62.1 g (0.2 mol) of triphenyl phosphite, and 30.4 g (0.2 mol) of vanillin in 150 ml of benzene was warmed at reflux for 2.5 hr. The reaction mixture was cooled and filtered to give a light yellow solid which was twice recrystallized from acetonitrile-ethylene dichloride to give **7b:** mp 190-194° dec; ^{31}P nmr −15.8 ppm (d, J = 22 Hz); ^1H nmr δ 9.1 (s, 1, NHC_6H_4Cl), 8.7 (s, 1, OH), 6.7-7.8 (m, 18, aryl and CHNH), 5.7 (d of d, 1, J = 22, 10 Hz, PCHNH), 3.8 (s, 3, CH_3).

Anal. Calcd for $C_{27}H_{24}ClN_2O_6P$: C, 60.17; H, 4.48; Cl, 6.58; N, 5.19; P, 5.75. Found: C, 59.62; H, 4.36; Cl, 6.50; N, 5.13; P, 5.65.

Diethyl α-(3-Phenylureido)benzylphosphonate (7c). A ^{31}P nmr measurement indicated that there was no reaction when a mixture of 0.30 mol of triethyl phosphite, 0.30 mol of phenylurea, and 0.33 mol of benzaldehyde in 150 g of toluene was warmed at 95-100° for 0.5 hr. Boron trifluoride etherate (0.05 mol) was then added dropwise, causing a temperature rise. The reaction mixture was warmed at 95-100° for 1 hr and then stripped to a pot temperature of 120° (10 mm). The residue was diluted with ether, causing separation of a solid (75.7 g, including additional fractions from the filtrate). Recrystallization of a portion from acetonitrile gave a white solid: mp 150-151.5°; ^{31}P nmr ($CDCl_3$) −23.1 ppm; ^1H nmr δ 8.35 (s, 1, NHC_6H_5), 6.7-7.8 (m, 11, C_6H_5 and CHNH?), 5.6 [d of d, 1, J(H-P) = 22 Hz, J(HH) = 10 Hz, CHNH], 3.5-4.6 (m, 4, CH_2CH_3), 1.25 (overlapping triplets, 6, CH_2CH_3).

Anal. Calcd for $C_{18}H_{23}N_2O_4P$: C, 59.66; H, 6.40; N, 7.73; P, 8.55. Found: C, 59.60; H, 6.41; N, 7.65; P, 8.69.

Diphenyl {1-[3-(4-chlorophenyl)ureido]butyl}phosphine Oxide (8). A mixture of 0.15 mol each of *p*-chlorophenylurea, phenyl diphenylphosphinite, and *n*-butyraldehyde in 150 g of toluene was warmed at reflux for 5.5 hr, giving a reaction mixture having a ^{31}P nmr signal only at −36.8 ppm. When the toluene was removed at reduced pressure, the residue solidified. Recrystallization of a portion from benzene gave 8, a white solid: mp 257-258°; ^{31}P nmr −37.4 ppm; ^1H nmr δ 9.1 (s, 1, NHC_6H_4Cl), 6.4-8.1 (m, 15, aryl and CHNH?), 5.1 (m, 1, PCH), 0.6-2.0 (m, 7, $CH_2CH_2CH_3$).

Anal. Calcd for $C_{23}H_{24}ClN_2O_2P$: C, 64.70; H, 5.67; N, 6.56; Cl, 8.30; P, 7.25. Found: C, 65.45; H, 5.62; N, 6.55; Cl, 8.59; P, 7.20.

1-(3,3-Diphenylureido)ethylphosphonic Acid (10a). Freshly distilled acetaldehyde (0.22 mol) was added during 0.5 hr to a stirred solution of 0.1 mol each of 1,1-diphenylurea and triphenyl phosphite in 130 g of benzene at 60°. The solution was warmed at reflux (65-70° with Dry Ice cooled condenser) for 1.25 hr, giving a dark brown solution having a small ^{31}P nmr peak at −126.2 ppm for unreacted phosphite and a large product peak at −18.4 ppm (~1:5 areas). The reaction mixture was stripped to 130° (3 mm). The residue was diluted with 200 ml of acetonitrile and 10 g of H_2O, and this solution was warmed at reflux for 3 hr. Solid that separated during warming was recrystallized from acetic acid-water to give **10a** as a white solid: mp 186-187° dec; ^{31}P nmr −21.6 ppm; ^1H nmr δ 10.0 (s, 2, OH), 7.3 (m, 10, C_6H_5), 5.4 (d of d, 1, J = 9, 5 Hz, NH), 4.1 (m, 1, CH), 1.3 (d of d, 3, J = 16 and 7 Hz, CH_3); acidity 2.00 equiv/mol, pK_1 = 2.20, pK_2 = 8.62.

Anal. Calcd for $C_{15}H_{17}N_2O_4P$: C, 56.25; H, 5.35; N, 8.75; P, 9.67. Found: C, 56.43; H, 5.36; N, 8.84; P, 9.60.

[α-(3,3-Dimethylureido)-4-nitrobenzyl]phosphonic Acid (10b). A mixture of 30.2 g (0.2 mol) of 4-nitrobenzaldehyde, 17.6 g (0.2 mol) of 1,1-dimethylurea, and 62.0 g (0.2 mol) of triphenyl phosphite in 100 ml of benzene was warmed at 86-87° for 1.5 hr to give a clear yellow solution: ^{31}P nmr −13.4 (d, J = 23 Hz) and −127.9 ppm (area ratio ~5:1). The reaction mixture was stirred as it cooled, and it was then filtered to give 54.1 g of off-white solid (9b), mp 155-170° after recrystallization from acetonitrile. A solution of this solid in acetone-water (10:1) was refluxed for 2 hr and then allowed to stand open to the atmosphere for 10 days. Acetonitrile was added to the residue, and the mixture was warmed to boiling and then filtered while hot to give a yellow solid. Recrystallization once from acetonitrile-ethanol and twice from 2-propanol gave white solid: mp 187-205° dec; ^{31}P nmr (CD_3SOCD_3) −16.4 ppm (d, J = 24 Hz); ^1H nmr δ 11.1 (s, 2, OH), 8.1 (d of d, 4, aryl), 6.5 (m, 1, NH), 5.3 (d of d, 1, J = 24, 8 Hz, CH), 2.9 (s, 6, CH_3).

Anal. Calcd for $C_{10}H_{14}N_3O_6P$: C, 39.60; H, 4.65; N, 13.86; P, 10.21. Found: C, 39.68; H, 4.75; N, 14.07; P, 10.38.

Diphenyl[α-(1,3-dimethylureido)benzyl]phosphine Oxide (11). After a solution of 0.5 mol of phenyl diphenylphosphinite, 0.55 mol of benzaldehyde, and 0.25 mol of 1,3-dimethylurea in 150 ml of chlorobenzene had been warmed at 130° for 1 hr, a ^{31}P nmr spectrum of the solution had peaks at −108.3 and −31.5 ppm (~1:1). An additional 0.25 mol of 1,3-dimethylurea was added, and warming at 130° was continued for 2 hr, giving a solution having a ^{31}P nmr signal only at −32.8 ppm. Concentration of the solution to 130° (5 mm) and then dilution of the residue with acetone gave 143 g (75% yield) of **11**. Recrystallization from chlorobenzene gave a white solid: mp 217-220°; ^{31}P nmr −32.6 ppm; ^1H nmr δ 7.0-8.1 (m, 15, aryl), 6.7 (d, 1, J = 9 Hz, PCH), 5.1 (q, 1, J = 5 Hz, $NHCH_3$), 3.0 (s, 3, $CHNCH_3$), 2.6 (d, 3, J = 5 Hz, $NHCH_3$); mass spectrum *m/e* 378 (molecular ion).

Anal. Calcd for $C_{22}H_{23}N_2O_2P$: C, 69.83; H, 6.13; N, 7.40; P, 8.18. Found: C, 70.04; H, 6.18; N, 7.28; P, 7.80.

Registry No. *meso*-**1a**, 43077-35-6; *dl*-**1a**, 43077-36-7; *meso*-**1b**, 43077-37-8; *dl*-**1b**, 43077-38-9; *meso*-**1c**, 43077-39-0; *dl*-**1c**, 43077-40-3; **1d**, 43077-41-4; **2**, 43077-42-5; **3a**, 43077-43-6; **4a**, 43077-44-7; **4b**, 43077-45-8; **5a**, 43077-46-9; **5b**, 43077-47-0; **6**, 43077-48-1; **7a**, 43077-49-2; **7b**, 43077-50-5; **7c**, 43077-51-6; **8**, 43077-52-7; **9b**, 43077-53-8; **10a**, 43077-54-9; **10b**, 43077-55-0; **11**, 43077-56-1; urea, 57-13-6; triphenyl phosphite, 101-02-0; acetaldehyde, 75-07-0; benzaldehyde, 100-52-7; tris(2-chloroethyl) phosphite, 140-08-9; thiourea, 62-56-6; *n*-butyraldehyde, 123-72-8; propionaldehyde, 123-38-6; 2-ethylhexaldehyde, 123-05-7; isobutyraldehyde, 78-84-2; ethyl diphenylphosphinite, 719-80-2; ethyl hydantoate, 6293-20-5; 4-chlorophenylurea, 140-38-5; vanillin, 121-33-5; triethyl phosphite, 122-52-1; phenylurea, 64-10-8; 1,1-diphenylurea, 603-54-3; phenyl diphenylphosphinite, 13360-92-4; 1,1-dimethylurea, 598-94-7; 4-nitrobenzaldehyde, 555-16-8; 1,3-dimethylurea, 96-31-1.

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Studies on the Monoalkylation of Hydroquinone[1]

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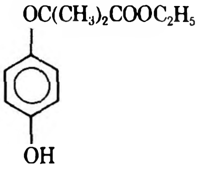
Conditions have been worked out for monoalkylation of hydroquinone to give the following compounds in the yields indicated: ethyl α-(*p*-hydroxyphenoxy)isobutyrate (56%), *tert*-butyl α-(*p*-hydroxyphenoxy)acetate (80%), hydroquinone monobenzyl ether (72%), and hydroquinone monomethyl ether (62%). Generalizations have been made which may help in the monoalkylation of other polyhydric phenols.

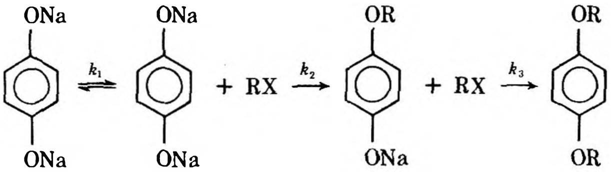
The monoalkylation of hydroquinone (2) represents a problem for which no generally satisfactory procedure has as yet been developed. Monoalkylation has been accomplished by using a large excess of hydroquinone[3-5] but this method is not efficient if the yield is calculated on **2**. In general, alkylation of **2** *via* the monosodium salt and 1 equiv of alkylating agent gives poor yields of monoalkylated product.[6,7] Alternately, one can make a monoprotected hydroquinone, itself a difficult process, alkylate, and remove the protecting group.[8] With the above in mind we report our efforts to prepare ethyl α-(*p*-hydroxyphenoxy)isobutyrate (1), a compound desired for other research. We report also on some general features which may make monoalkylation in other cases more readily accomplished than by existing methods.


2


1

The principle which guided our efforts was the use of a dianion as originally conceived by the late Hauser[9] and developed by him and others.[10,11] Thus we prepared the disodium salt of hydroquinone (2s) and studied its alkylation with a few alkylating agents under differing conditions. The results are summarized in Table I and are discussed in terms of the reactions illustrated in Scheme I.

Scheme I


solid dissolved
2s **2d** **3** **4**

The experiments in Table I all began with the solid disodium salt of hydroquinone (**2s**). This salt was only partly soluble at room temperature in dimethyl sulfoxide (DMSO) and dimethylformamide (DMF), but was soluble in the partly aqueous solvents. Examination of the results listed in Table I reveals that good yields of monoalkylation product are obtainable, although no one set of conditions is ideal for all alkylating agents. For example, monoalkylation with ethyl α-bromoisobutyrate (5) to give ethyl α-(*p*-hydroxyphenoxy)isobutyrate (1) proceeded well in dimethyl sulfoxide (DMSO, expt 1) and in dimethylformamide (DMF, expt 3). However, similar attempts at alkylation in partly aqueous media (expt 4 and 5) failed, as did attempts with *tert*-butyl α-bromopropionate (6) (expt 14 and 15). On the other hand, alkylation with *tert*-butyl bromoacetate (7) (expt 10 and 11), benzyl chloride (8) (expt 8), and methyl iodide (9) (expt 12) gave reasonably good yields of the respective monoalkylation products in partly aqueous media. However, when alkylation with benzyl chloride was attempted in DMF and DMSO, low yields of monoalkylation products, accompanied by larger amounts of dialkylation products, were obtained (expt 6 and 7).

The results in the solvents studied may be explained by assuming that (1) all alkylations occur only with soluble anions and alkylating agent, RX; (2) the rates of reaction, k_2, are greater with benzyl chloride, methyl iodide, and *tert*-butyl bromoacetate (7) than with ethyl α-bromoisobutyrate (5); and (3) the rate of reaction of dianion from **2d** (k_2) is greater than the rate of reaction of monoanion (k_3) in all cases.[12] The yield of **1** is good (expt 1 and 3) because k_3 is smaller than k_1. With the more reactive alkylating agents, **7**, **8**, and **9**, the yield of monoalkylated product, **3**, in nonaqueous media, DMF and DMSO, is poor because k_3 is greater than k_1. Hence the monoalkylated product reacts with reagent before more **2s** dissolves.

The results in the partly aqueous media are different with the various alkylating agents because the disalt is completely soluble. With the reactive alkylating agents **7**, **8**, and **9** (only 1 equiv of alkylating agent is used), the bis anion from **2d** is more reactive than the phenoxide **3**, so that good yields of monoethers of hydroquinone can be obtained. However, the less reactive alkylating agents, ethyl α-bromoisobutyrate (5) and *tert*-butyl α-bromopropionate, either are unreactive to **2d** in this medium or react with the medium. In either event, no monoalkylated product is obtained.

In conclusion, it appears that good yields of monoalkylation product of hydroquinone may be obtained under two sets of conditions: (1) when the disodium salt is not highly soluble in a nonaqueous solvent but the rate of reaction of the alkylating agent is slower than the rate of solution of the disodium salt in the solvent medium; and (2) when the disodium salt is soluble in a partly aqueous medium and the alkylating agent is sufficiently reactive to alkylate the dianion. How well this finding will relate to other polyhydric phenols remains to be seen.

Experimental Section[13]

***tert*-Butyl Bromoacetate.** To an ice-cold mixture of 38 g (0.51 mol) of *tert*-butyl alcohol and 40 g (0.51 mol) of pyridine was added 100 g (0.50 mol) of bromoacetyl bromide (Aldrich). After stirring overnight at room temperature, the mixture was poured into water and extracted thrice with ether. Combined ether extracts were worked up in the usual way except that Na_2SO_4 and K_2CO_3 were used to dry the extracts. This process yielded 61 g (63%) of *tert*-butyl bromoacetate, bp 78-79° (25 mm) [lit.[14] bp 78-79° (25 mm)].

2-Bromopropionyl Chloride. To a slurry of 52.1 g (0.25 mol) of phosphorus pentachloride in 200 ml of dry methylene chloride was

Table I
Alkylation of the Disodium Salt of Hydroquinone

Expt	Alkylating agent	Solvent	Temp, °C	Time, hr	Yield, %[a] Mono	Yield, %[a] Bis
1	$BrC(CH_3)_2CO_2C_2H_5$	DMSO	25	4	56	
2	$BrC(CH_3)_2CO_2C_2H_5$	DMSO	80	2	37	
3	$BrC(CH_3)_2CO_2C_2H_5$	DMF	25	4	50	20
4	$BrC(CH_3)_2CO_2C_2H_5$	50% Dioxane–H_2O	25	4		
5	$BrC(CH_3)_2CO_2C_2H_5$	75% NMP–H_2O	25	4		
6	$C_6H_5CH_2Cl$	DMF	25	4	13.2	77.5
7	$C_6H_5CH_2Cl$	DMSO	25	4	42	52.4
8	$C_6H_5CH_2Cl$	50% Dioxane–H_2O	25	1	72	
9	$BrCH_2CO_2C_4H_9$-*t*	DMF	80	2	6.4	54.1
10	$BrCH_2CO_2C_4H_9$-*t*	50% Dioxane–H_2O	25	1	80	
11	$BrCH_2CO_2C_4H_9$-*t*	75% NMP–H_2O	25	1	65	
12	CH_3I	50% Dioxane–H_2O	25	1	62	36
13	$BrCH(CH_3)CO_2C_4H_9$-*t*	DMF	80	2		81.5
14	$BrCH(CH_3)CO_2C_4H_9$-*t*	50% Dioxane–H_2O	25	4		
15	$BrCH(CH_3)CO_2C_4H_9$-*t*	75% NMP–H_2O	25	4		

[a] All yields represent isolated material and are based on alkylating agent. The yield based on hydroquinone is the sum of (mono + bis)/2.

added 38.3 g (0.25 mol) of 2-bromopropionic acid. After becoming homogeneous the mixture was refluxed for 30 min and solvent was removed by distillation at atmospheric pressure. The residue was distilled and the distillate, bp 60–70° (15 mm), was redistilled through a 10-cm Vigreux column to yield 42 g of 2-bromopropionyl chloride, bp 64–66° (100 mm) (contaminated with *ca.* 5% $POCl_3$). This material was of suitable purity to be used in the next step.

tert-**Butyl** α-**Bromopropionate.** To a mixture of 15 g (0.22 mol) of *tert*-butyl alcohol and 20 g (0.25 mol) of pyridine was added 26.1 g (0.15 mol) of α-bromopropionyl chloride. After stirring for 2 hr at reflux, the cooled mixture was added to an equal volume of water and extracted (3 × 150 ml) with ether. The combined ether extracts were worked up as usual to yield 10.0 g (32%) of *tert*-butyl α-bromopropionate, bp 88–90° (60 mm).

General Alkylation Procedure. To a solution of 5.5 g (50 mmol) of hydroquinone in 50 ml of DMSO was added 4.4 g (100 mmol) of sodium hydride (57% NaH in mineral oil suspension, washed with pentane). The resulting mixture was stirred at 80° for 2 hr and then cooled to room temperature. To the rapidly stirred slurry was added rapidly with caution 7.3 ml (5 mmol) of α-bromoisobutyrate in 3 ml of DMSO. After 4 hr the mixture was acidified (excess avoided when *tert*-butyl esters were involved) with 3 *N* HCl. The reaction products were extracted with ether and washed to remove DMSO. The washings were reextracted with ether and the combined ether extracts were washed with saturated $MgSO_4$. The ether was distilled and the residue was distilled to yield 6.3 g (56%) of **1**, bp 200° (3 mm), mp 85–86° (lit.[15] mp 84–86°).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.7; H, 7.1. Found (vacuum-sublimed sample): C, 64.7; H, 7.1.

Aqueous Alkylations. The following procedure is representative of alkylations carried out in aqueous media. A solution of 1.7 g (40 mmol) of sodium hydroxide and 2.2 g (20 mmol) of hydroquinone in 75 ml of degassed 1:1 dioxane–water was stirred in a nitrogen atmosphere. To this solution was added a solution of 3.9 g (20 mmol) of *tert*-butyl bromoacetate in 5 ml of dioxane. The mixture was stirred for 1 hr, at which time no odor of *tert*-butyl bromoacetate could be detected. After acidification of the mixture with 15 ml of 3 *N* HCl and extraction of 2:1 ether–benzene, the organic extracts were worked up in the usual way to yield 3.6 g (80%) of *tert*-butyl 2-(*p*-hydroxyphenoxy)acetate: mp 93°; ir (KBr) 2.94 (3401) (OH) and 5.78 μ (1730 cm^{-1}) (C=O); nmr ($CDCl_3$) δ 6.74 (s, 4, ArH), 4.45 (s, 2, $ArOCH_2CO_2R$), and 1.48 [s, 9, $COOC(CH_3)_3$]; mass spectrum *m/e* 224.

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.3; H, 7.2. Found: C, 64.2; H, 7.2.

Other compounds prepared by one or both of these methods include hydroquinone bisbenzyl ether, mp 127–128° (lit.[15] mp 128–130°); hydroquinone monobenzyl ether, mp 119–121° (lit.[15] mp 123–125°); hydroquinone dimethyl ether, mp 54–55.5° (lit.[16] mp 55–56°); hydroquinone monomethyl ether, mp 51–53° (lit.[16] mp 53°); hydroquinone bis[1-(carbo-*tert*-butoxy)]ethyl ether, mp 111–113°, ir (KBr) 5.73 μ (1745 cm^{-1}) (C=O), nmr ($CDCl_3$) δ 6.80 (s, 4, ArH), 4.55 [q, 2, $ArOCH(CH_3)$-], 1.55 [d, 6, $ArOCH(CH_3)$-], and 1.41 ppm [s, 18, $CO_2C(CH_3)_3$], mass spectrum *m/e* 366.

Anal. Calcd for $C_{20}H_{30}O_6$: C, 65.6; H, 8.3. Found: C, 65.7; H, 8.1.

Hydroquinone bis(carbo-*tert*-butoxymethyl) ether had mp 71–72°; ir (KBr) 5.74 μ (1742 cm^{-1}) (C=O); nmr (CCl_4) δ 6.72 (s, 4, ArH), 4.35 (s, 4, $ArOCH_2CO_2R$), and 1.44 [s, 18, $CO_2C(CH_3)_3$]; mass spectrum *m/e* 338.

Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.9; H, 7.7 Found: C, 63.7; H, 7.6.

Registry No. 1, 42806-90-6; **2,** 123-31-9; **2s,** 7664-46-2; *tert*-butyl bromoacetate, 5292-43-3; *tert*-butyl alcohol, 75-65-0; bromoacetyl bromide, 598-21-0; 2-bromopropionyl chloride, 7148-74-5; methylene chloride, 75-09-2; 2-bromopropionic acid, 598-72-1; *tert*-butyl α-bromopropionate, 39149-80-9; *tert*-butyl 2-(*p*-hydroxyphenoxy)acetate, 42806-92-8; hydroquinone bis[1-(carbo-*tert*-butoxy)]ethyl ether, 42806-93-9; hydroquinone bis(carbo-*tert*-butoxymethyl) ether, 42806-94-0.

References and Notes

(1) This work was supported by Grant 12445 of the National Science Foundation.

(2) This work was taken from the Ph.D. dissertation presented by James A. Cella to The Ohio State University, 1973.

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Reaction of Phenyl Salicylates with Perbenzoic Acid. Formation of *o*-Alkoxyphenols and Catechol[1]

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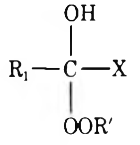
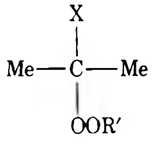
The reaction of phenyl salicylate with perbenzoic acid in 60 vol. % ethanol at pH >9 was found to afford *o*-ethoxyphenol and catechol together with other hydrolysis and alcoholysis products of the ester. The analogous reaction in aqueous methanol gave o-methoxyphenol; other phenyl salicylates substituted at the salicyl ring produced also o-alkoxyphenols, but the attempted reaction of other phenyl or methyl benzoates was unsuccessful. This novel alkoxylation seems to proceed *via* an aryl cation intermediate produced from phenyl salicylate and peracid.

The Baeyer–Villiger (B–V) reaction of ketones and aldehydes has been extensively studied,[2,3] but, so far as we know, there is no report on the similar reaction of esters. It is generally recognized that the migration of R_1 in the intermediate **1a**, an adduct of R′OOH to R_1COX, is accelerated by the adjacent oxygen atom.[4a] The similar acceleration of α oxygen atom was also observed for the rearrangement of 2-substituted 2-propyl *p*-nitroperbenzoates; *e.g.*, the relative rate for the rearrangement of **2b** *vs.* 2a with R′ = p-$O_2NC_6H_4CO$ is 1000.[4b]

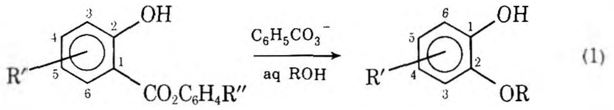


1a, X = R_2
b, X = OR_2



2a, X = Me
b, X = OMe

In view of the availability of two accelerating α oxygen atoms (1b), the B–V type reaction of esters seems to be possible. The present paper reports a novel reaction of some aromatic esters with perbenzoic acid (PBA), *i.e.*, the conversion of phenyl salicylates to o-alkoxyphenols (eq 1) which seems to be produced *via* aryl cations.



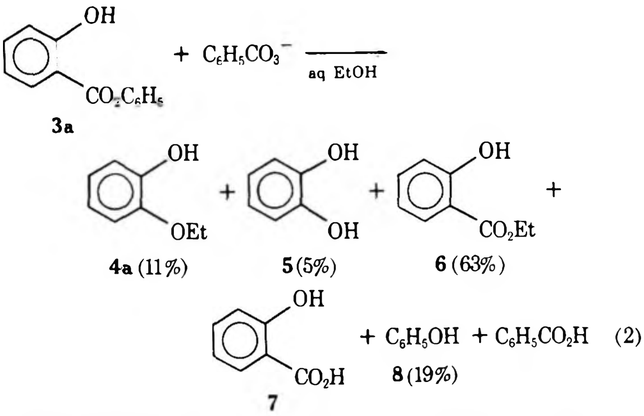
3a, R′ = R″ = H
b, R′ = 5-Me; R″ = H
c, R′ = H; R″ = *p*-Me

4a, R′ = H; R = Et
b, R′ = H; R = Me
c, R′ = 4-Me; R = Me

Results and Discussion

The reaction of phenyl salicylate (**3a**, 0.05 *M*) with perbenzoic acid (PBA, 0.05 *M*) was carried out in the presence of sodium carbonate (0.10 *M*, pH ~11) in 60 vol. % ethanol containing EDTA (5×10^{-4} *M*) to suppress spontaneous decomposition of PBA. This reaction affords *o*-ethoxyphenol (**4a**) and catechol (**5**) together with hydrolysis (**7** and **8**) and transesterification products (**6** and **8**) from the ester (eq 2).

The dependence of these products on the reaction time (Figure 1) shows that the decrease of ester **3a** is compatible with the increase of products, suggesting neither intervention of any stable intermediate nor interconversion between the products. The consumption of PBA is roughly comparable to that of **3a**, but, because of the further oxidation of produced phenols, the stoichiometry of PBA *vs.* **3a** is not clear and the yield of **4a** does not increase with excess PBA. The reaction at pH ~9 afforded a similar yield of **4a**, but the reaction did not occur at pH ~7.



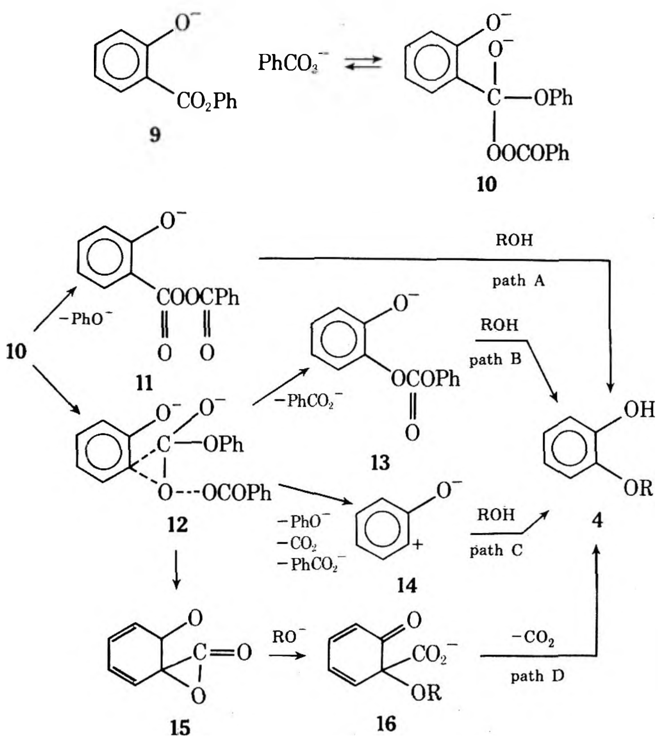
The reaction of **3a** with PBA in 60% methanol buffered by sodium bicarbonate also gave a similar yield of *o*-methoxyphenol (**4b**, *ca.* 9%). The same reaction of phenyl 2-hydroxy-5-methylbenzoate (**3b**) produces 2-methoxy-4-methylphenol (**4c**, 5%), but 2-methoxy-5-methylphenol was not obtained. The reaction of *p*-tolyl salicylate (**3c**) gave *o*-ethoxyphenol (**4a**) and *o*-methoxyphenol (**4b**) in aqueous ethanol and methanol, respectively. *o*-Alkoxyphenols were not obtained from the reaction of PBA with phenol, catechol, salicylic acid, and methyl or ethyl salicylate under the same conditions. These results indicate that the reaction of phenyl salicylate with PBA converts the carboalkoxyl group of the salicylate into the alkoxyl group from solvent alcohol.

The formation of *o*-alkoxyphenol from **3a** was not appreciable for the reaction with hydrogen peroxide or *tert*-butyl hydroperoxide in place of PBA. Attempted alkoxylation reaction under various conditions (pH, initial concentration, temperature, and time) were all unsuccessful for the reaction of phenyl *o*-methoxy-, *p*-hydroxy-, *p*-methoxy-, and *p*-chlorobenzoates, methyl *o*- and *p*-hydroxybenzoate, and *o*- and *p*-methoxybenzoates, transesterification being a main reaction. Thus, the alkoxylation reaction such as eq 1 is characteristic for phenyl salicylates.

Formation Mechanism of *o*-Alkoxyphenol. The reaction of phenyl salicylate with PBA to afford **4a** and **5** is interesting because no B–V type reaction of esters is known. Although the reaction proceeds at a comparable conversion rate at pH >9, it does not occur at pH <7, which shows that PBA anion is a reactive species, since the pK_a of PBA is 8.5 in 40% ethanol.[3c,5] The failure of formation of *o*- or *p*-alkoxyanisole from phenyl *o*- or *p*-methoxybenzoate indicates that the dissociation of the *o*-hydroxyl proton of **3a** is also necessary.[6] On the basis of these results several paths are conceivable for the formation of o-alkoxyphenol (paths A–D in Scheme I, etc.).

Firstly, the possibility of o-alkoxyphenol formation *via* path A may be denied from the following examination. *o*-

Scheme I



Hydroxybenzoyl peroxide (protonated **11**) synthesized from salicyloyl chloride and PBA was considerably stable in 20% chloroform-80% ethanol, its half-life being *ca.* 3 hr at 25°, while the formation of **4a** by the reaction of **3a** with PBA was almost complete within 1 hr (Figure 1). Moreover, *o*-ethoxyphenol was not obtained from the decomposition of **11** in the same solvent at 25 or 80°. These results deny the intervention of **11**. The formation of **11** from **10** would be prevented, probably because the departure of perbenzoate ion from **10** is more effective than that of phenolate ion because of the higher acidity of PBA ($\Delta pK_a = 2$).[7]

Secondly, the B-V type rearrangement might give carbonate **13** *via* the transition state **12** (path B). The alcoholysis of aryl carbonates as well as hydrolysis, however, is generally known as acyl-O fission to give phenols,[8,9] and o-oxy anion in the carbonates effectively catalyzes the hydrolysis to give catechols.[9] Moreover, the B-V reaction of salicylaldehyde gives a high yield of catechol *via* the same carbonate **13**[3b] but not **4**. Hence, the formation of **4** *via* carbonate **13** cannot be substantiated.

Thirdly, path C assumes the intermediacy of an aryl cation from the B-V type transition state **12**. If this is the case, cation **14** should be trapped by solvent alcohol to give alkoxyphenol **4**. This mechanism seems to be most probable as discussed in the following. The cationic character of the migration group is important for the B-V reaction[3] and other rearrangements of peroxides.[2-4] The ionic decomposition of *tert*-butyl *p*-nitroperbenzoate in methanol gave *tert*-butyl methyl ether and isobutylene, which are formed from *tert*-butyl cation.[4b] The anchimeric assistance of α oxygen atom is large owing to its electron-donating resonance in the B-V rearrangement.[4a] Since carbonyl adduct **10** has two α oxygen atoms, the electron-donating power to stabilize the transition state **12** should be large.[10] Moreover, the aryl cation is stabilized by a strongly electron-donating *o*-HO or *o*-O⁻ group as exemplified for the case of the NH_2 group.[11]

Fourthly, another path to **4** involves a spirodienone intermediate **15** (path D).[12a] With this α-lactone mechanism it is difficult to explain why the alkoxylation is specific for phenyl salicylates and unsuccessful for the case of phenyl *p*-hydroxybenzoate or methyl salicylate. Further, we cannot see why **15** should be formed instead of the well-established B-V type conversion to the more stable carbonate **13**. Moreover, it is not clear that its conversion to **4** is very facile at 25°.[12b]

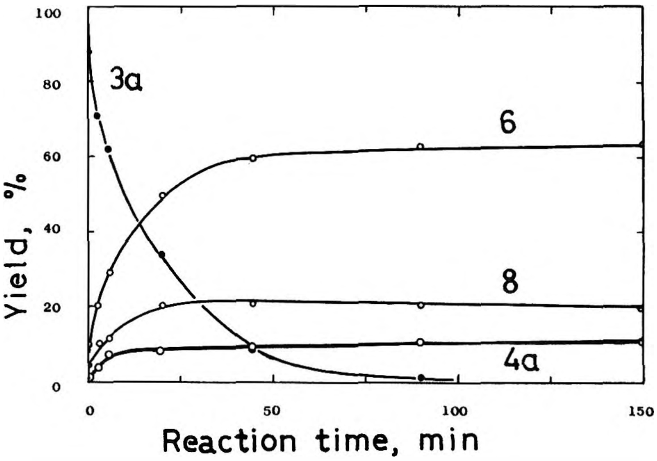


Figure 1. The reaction of phenyl salicylate (**3a**) with PBA in 60% ethanol at 25°. Initial concentrations: [**3a**] = [PBA] = 0.05 *M*, [Na_2CO_3] = 0.1 *M*, and [EDTA] = 5 × 10^{-4} *M*.

Finally, a nucleophilic substitution (S_N2) by RO^- on the aromatic ring of **10** is less probable on the basis of the observed similar yields of **4** from the reaction at pH 9 and 11, and of the absence of any electron-attracting group on the ring. Another path involving radical reaction to give **4** would be a coupling of phenoxy and alkoxy radicals. However, a radical attack on alcohols gives α-hydroxyalkyl radicals but not alkoxy radical;[13] further, there has been no indication of *o*-alkoxyphenol formation from a radical reaction of phenol and alcohol.

Hence, although a decisive choice of path C or D is still impossible, path C seems to be most appropriate. Trapping of **14** by acetonitrile leading to o-(*N*-acetylamino)-phenol was unsuccessful in these aqueous alcohols, and the reaction does not occur in pure acetonitrile.

This novel alkoxylation is limited to phenyl salicylates and failed for the case of other phenyl and methyl benzoates. Two factors seem to contribute to the success only with the case of phenyl salicylates: (i) stabilization of phenyl cation by the *o*-O⁻ group;[14a] (ii) stabilization of the C=O adduct **10**, *i.e.*, the increase of [**10**] by the electron-attracting phenoxy group.[14b] No formation of **4** by the reaction with hydrogen peroxide or *tert*-butyl hydroperoxide suggests that the O-O heterolysis induced by PhCO is important for the formation of aryl cation. The sole formation of **4c** from **3b** indicates that the produced aryl cation is not of a bridged structure such as benzene epoxide.

Mechanism for the Formation of Catechol. The conceivable paths for the catechol formation are paths A-D together with PBA oxidation of phenol. The formation of catechol and hydroquinone by peracid oxidation of phenol is well known.[15] The PBA oxidation of phenyl salicylate gave catechol and hydroquinone in a molar ratio of 30:1, while the PBA oxidation of phenol under the same conditions resulted in a ratio of 2:1. This large difference indicates that the main path affording catechol in this reaction is not the PBA oxidation of phenol.

Although unsymmetrical benzoyl peroxides are known to give phenols by a carboxy inversion process,[16,17] the intermediacy of **11** is not probable as mentioned in the previous section. Hence catechol is formed by hydrolysis of carbonate **13** (path B) or the trapping of **14** (path C) or **16** (path D) by water. Although the choice might be possible by the presence or absence of catechol for the reaction in absolute ethanol, the reaction failed because of the solubility of reactants in the solvent and hence the choice remains unanswered.

Experimental Section

Materials. PBA was synthesized by the reaction of benzoyl peroxide with alkaline hydrogen peroxide[18] and crystallized from *n*-hexane. Phenyl salicylate is of commercial origin and its purity (>98%) was checked by glc. Phenyl hydroxybenzoates were obtained by the preparation using phosphoryl chloride;[19] phenyl methoxybenzoates were prepared by the Schotten–Baumann method.[20] Substituents and melting points of phenyl-substituted benzoates are as follows: *p*-MeO, 58–59°; o-MeO, 59–60°; *p*-HO, 173–175°; 2-HO-5-Me, 86–88°. o-Hydroxybenzoyl peroxide was obtained by the usual method;[21,22] pyridine was dropped into a mixture of salicyloyl chloride and PBA at −30 to −40°. Its purity was *ca.* 30% on the basis of iodometric titration and further purification was unsuccessful: ir 3230 (OH), 1790 and 1765 (diacyl peroxide C=O), 700 and 760 (monosubstituted benzene), and 745 cm^{-1} (ortho-disubstituted benzene).

Authentic o-ethoxyphenol (**4a**) and *o*-methoxyphenol (**4b**) were synthesized from the B–V reaction of o-ethoxy- and o-methoxybenzaldehyde with peracetic acid in the presence of acetate buffer in 30% ethanol for 3 hr at 40°. Authentic 2-methoxy-4-methylphenol (**4c**) was synthesized from 2-hydroxy-4-methylacetophenone obtained by the Fries rearrangement of *m*-cresyl acetate,[23] followed by methylation with dimethyl sulfate, B–V reaction, and hydrolysis. 2-Methoxy-5-methylphenol was obtained similarly from *p*-cresyl acetate.

Typical Reaction and Product Analysis. Phenyl salicylate (**3a**, 1 mmol), PBA (1 mmol), and Na_2CO_3 (2 mmol) were allowed to react in 60% ethanol (20 ml) in the presence of EDTA (0.01 mmol) for 2.5 hr at 25°. The reaction mixture was acidified by acetic acid after the addition of *p*-cresol and *p*-methoxytoluene as internal standards for glc analysis. Catechol was converted to *o*-dimethoxybenzene by dimethyl sulfate and extracted. Identification and determination of products were carried out mainly by glc analysis using a Yanagimoto gas chromatograph, Model 550F: a 1.2-m column of 15% Apiezon grease on Celite 545 and/or a 1.2-m column of PEG on Chamelite CS.

o-Ethoxyphenol was extracted with chloroform from the diluted reaction mixture buffered at pH 5, chromatographed on silica gel using chloroform eluent, and confirmed by identification with ir, uv, and tlc analysis in comparison with the authentic sample: uv λ_{max} (0.1 *N* NaOH) 239 and 290 nm; λ_{max} (H_2O) 214 and 274 nm; ir 3500 (OH), 740 cm^{-1} (ortho-disubstituted benzene).

Registry No. 3a, 118-55-8; PBA, 93-59-4; phenyl *p*-methoxybenzoate, 4181-97-9; phenyl o-methoxybenzoate, 10268-71-0; phenyl *p*-hydroxybenzoate, 17696-62-7; phenyl 2-hydroxy-5-methylbenzoate, 10268-64-1; o-hydroxybenzoyl peroxide, 42806-89-3.

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(5) If PBA is a reactive species, the rate should decrease with increasing pH.

(6) The pK_a value of **3a** is 8.80 in water: B. Capon and B. C. Ghosh, *J. Chem. Soc. B*, 472 (1966).

(7) This is similar to the fact that in spite of the strong nucleophilicity of HOO^- esters are not perhydrolyzed by HOO^- because of its stronger departing ability compared to HO^-: K. B. Wiberg, *J. Amer. Chem. Soc.*, **77**, 2519 (1955).

(8) (a) G. D. Cooper and B. Williams, *J. Org. Chem.*, **27**, 3717 (1962); (b) G. D. Cooper and H. T. Johnson, *ibid.*, **30**, 3989 (1965).

(9) T. H. Hife, J. E. C. Hutchins, and D. M. McMahon, *J. Amer. Chem. Soc.*, **94**, 1316, 2837 (1972).

(10) The reaction of salicylaldehyde with PBA in aqueous ethanol gave catechol and its formate but not *o*-ethoxyphenol. This shows that two α oxygen atoms in **10** are necessary for the formation of the aryl cation **14**.

(11) E. M. Evleth and P. M. Horowitz, *J. Amer. Chem. Soc.*, **93**, 5636 (1971).

(12) (a) A referee's suggestion. (b) A α-lactone intermediate was suggested in the alcoholysis of α-halocarboxylate ion, which gave α-alkoxycarboxylic acid: J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1956, p 118. A dienonecarboxylic acid intermediate similar to **16** was suggested for the acid-catalyzed decarboxylation of salicylic acid: A. V. Willi, *Trans. Faraday Soc.*, **55**, 433 (1959); *Z. Phys. Chem.*, **30**, 285 (1961). Hence, the reaction sequence **15** → **16** → **4** may presumably be facile. However, a similar α-lactone intermediate from the induced decomposition of acetyl benzoyl peroxide was converted to substituted benzoic acid but not to solvolytic decarboxylation: C. Walling and Z. Cekovic, *J. Amer. Chem. Soc.*, **89**, 6681 (1967).

(13) For example, see C. Walling, "Free Radicals in Solutions," Wiley, New York, N. Y., 1957, pp 412 and 479.

(14) (a) The order of o-MeO > *p*-MeO for the B–V reaction was suggested as an indication for the stronger electron-donating power of the ortho substitutent.[3a] (b) The carbonyl addition of peroxide anion is less sensitive to steric retardation.[3b] Since EtO^- is probably more sensitive to steric effect than HO^- and hence than PBA anion, the following reason for the failure of the reaction with methyl salicylate cannot be neglected. That is, while the carbonyl addition of EtO^- and PBA anion to phenyl salicylate is competitive, methyl salicylate is consumed by a preferential attack of EtO^- on the carbonyl, since the steric retardation by its methoxy group is smaller than that by the phenoxy group of phenyl salicylate.

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A Reinvestigation of the Direction of Acid-Catalyzed Ring Opening of Substituted Spirocyclopropylcyclohexadienones[1]

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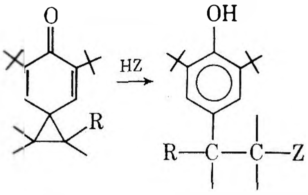
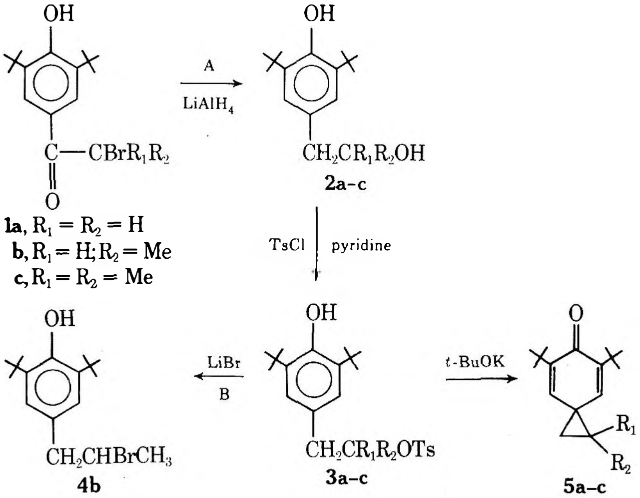
The reactions of 1-methyl-4,6-di-*tert*-butylspiro[2.5]octa-3,6-dien-5-one (**5b**) and 1,1-dimethyl-4,6-di-*tert*-butylspiro[2.5]octa-3,6-dien-5-one (**5c**) with various acidic reagents have been reinvestigated. In agreement with previous work, but in disagreement with that which would be concluded by using structural assignments from the literature, the cyclopropyl ring is shown to open from the more substituted side. The reason for the confusion is traced to the occurrence of aryl rearrangements, undetected by the previous investigators, during both the $LiAlH_4$ reduction of related 2-substituted 2-bromo-4′-hydroxy-3′,5′-di-*tert*-butylacetophenones (**1b** and **1c**) and the reaction of 2-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)-1-propyl tosylate (**7b**) with LiBr in acetone.

For several years, investigations have proceeded in our laboratory and that of Ershov on the reactions of 4-substituted hindered phenols. We have previously shown that some of the structural assignments made by the Russian workers were in error.[3] Using the corrected structures, a reinterpretation of the work done by Belostotskaya, Volod'kin, and Ershov[4] on the ring-opening reactions of various spirocyclopropylcyclohexadienones under acidic conditions suggests that the cyclopropyl ring opens from the less substituted side (eq 1). Because this was contrary to our expectations, we decided to reinvestigate this work. The proposed reaction products, from both laboratories, are summarized in Charts I-IV.



(1)

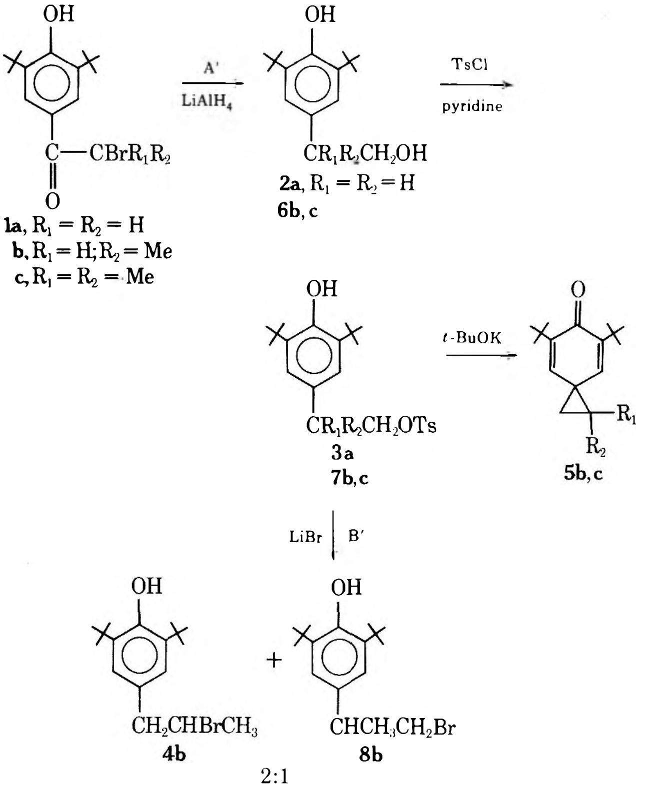
Chart I[a]



[a] The assignments shown are those of Ershov and coworkers.

Ershov, Volod'kin, and Portnykh first reported the $LiAlH_4$ reduction of 2-bromo-(3′,5′-di-*tert*-butyl-4′-hydroxy)acetophenone (**1a**) (Chart I).[5] Subsequently, the reduction products of 2-bromo-(3′,5′-di-*tert*-butyl-4′-hydroxy)propiophenone (**1b**) and 2-bromo-2-methyl-(3′,5′-di-*tert*-butyl-4′-hydroxy)propiophenone (**1c**) were described (Chart I).[6] Our first work reported the reduction of **1a** with $LiAlD_4$.[7] From the fact that this product had the structure $ArCH_2CD_2OH$, we concluded, in contrast to the earlier work,[5] that the reduction proceeds with aryl ring migration. We subsequently showed that the products from the $LiAlH_4$ reduction of **1b** and **1c** were **6b** and **6c**, respectively (Chart II),[3] rather than **2b** and **2c** (Chart I).[6]

Chart II[a]

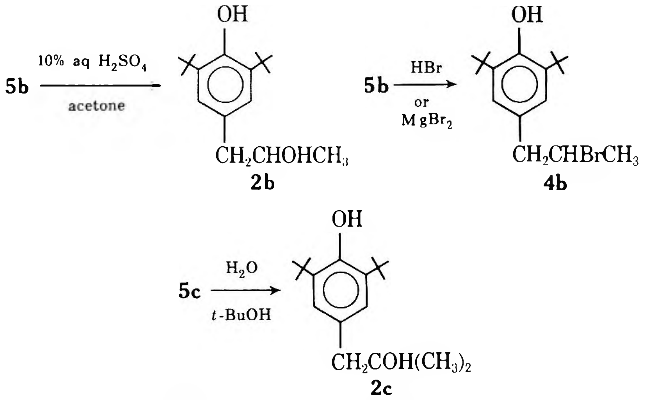


[a] Our results.

The Russian workers had used their structures, **2b** and **2c**, to assign structures to the products of the reactions shown in Chart III. Because the actual structures are **6b** and **6c**, respectively, a reinterpretation of these ring-opening reactions leads to the conclusion that the cyclopropyl ring opens from the less substituted side. This direction of ring opening is contrary to our expectations that the cleavage would be controlled by the stability of the incipient cationic center.[8]

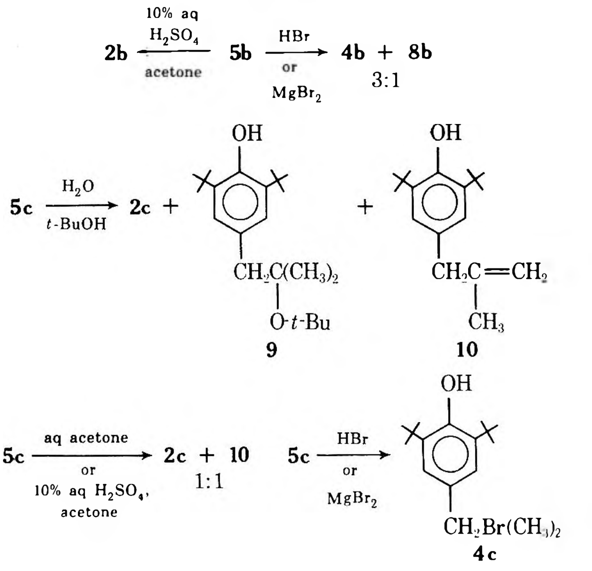
Chart IV summarizes our results. To our surprise we found that the products shown in the reactions of Chart III are in fact correct. As we had expected, the cyclopropyl ring does open mainly from the more substituted side,

Chart III[a]



[a] The assignments shown are those of Ershov and coworkers.

Chart IV[a]



[a] Our results.

rather than from the less substituted side as the reinterpreted results of the Russian workers would indicate.

The preparation of 2-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)-1-propanol (**6b**) has been described previously.[3] The preparation of its tosylate (**7b**) was accomplished in a manner similar to an earlier synthesis by Volod'kin, Belostotskaya, and Ershov.[9] The nmr spectrum was consistent with structure **7b**. Comparison to the nmr spectrum of alcohol **6b** is indicative, *viz.*, $CH_3CHArCH_2OH$, δ 1.28, 2.85, and 3.66, respectively, and $CH_3CHArCH_2OTs$, δ 1.25, 2.98, and 4.01, respectively. The structure $ArCH_2CHCH_3OTs$ (**3b**), proposed by the Russian workers, should exhibit methylene absorption near δ 2.76, as was found in $ArCH_2CD_2OH$.[6] However, the observed absorption at δ 4.01 is too far downfield to support this claim. We conclude that the Russian workers had tosylate **7b** rather than **3b**. If the reaction of this tosylate (**7b**) with LiBr proceeds by way of a simple displacement, as previously assumed,[4] then bromide **8b** would be formed. Since this bromide was claimed[4] to be the same as that formed from spiran **5b**, it would follow that the cyclopropyl ring opens from the less substituted side.

The critical reaction to investigate was now step B′ of Chart II. We repeated the previous procedure[4] with LiBr in acetone on tosylate **7b** and obtained a mixture whose nmr spectrum indicated the presence of approximately 67% 1-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)-2-bromopropane (**4b**) and 33% 1-bromo-2-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)propane (**8b**). The structure of **4b** follows on comparison with the nmr spectrum of 1-phenyl-2-bromopropane, *viz.*, $ArCH_2CHBrCH_3$, δ 3.07, 4.25, and 1.64, respectively, and $PhCH_2CHBrCH_3$, δ 3.11, 4.26, and 1.63, respectively. In order to confirm the structure of the minor product, **8b**, we attempted a direct bromination of alcohol **6b** with triphenylphosphine dibromide.[10] The bromination was successful and allowed us to identify the minor product as **8b**. However, efforts at removing small amounts of triphenylphosphine oxide during purification were unsuccessful and led to isomerization to **4b**. The product that the Russian group isolated in the LiBr-acetone reaction was apparently only the major product, **4b**. It is clear that the principal reaction of step B′ occurs with aryl ring migration. The sequence of reactions shown in Chart I therefore contains two aryl rearrangement steps (compare steps A and B with A′ and B′, respectively, of Chart II) that previously[4,6] went undetected.

The preparation of spiran **5b** was achieved by a minor variation of an earlier synthesis.[9] In our hands, reaction of **5b** with either HBr or $MgBr_2$ produced similar mixtures of products containing *ca.* 75% **4b** and 25% **8b**. Owing to the fortuitous cancellation of two errors in structural assignments, the Russian workers did in fact postulate the correct structure for the major product of the ring-opening reactions of **5b** with HBr and $MgBr_2$, and the ring does open predominantly from the more substituted side.

The reaction of spiran **5b** with 10% H_2SO_4 in acetone yielded the reported[4] secondary alcohol **2b** as the major product. Therefore, the ring opens from the more substituted side. The confusion here is that this secondary alcohol was previously[4] incorrectly identified as being the same alcohol as obtained from step A of Chart I. If this is correct, and since it is now known that the correct structure of the product from step A is **6b** (see step A′ of Chart II), one would conclude that the ring opens from the less substituted side. To confirm the structure of the alcohol product, **2b**, from **5b**, we repeated the synthesis of **2b**[11] and compared the nmr spectrum to that of 1-phenyl-2-propanol. Apparently, the previous conclusion of the identity of the alcohols from **5b** and step A was based solely on similarity of melting points.[12a,b] To investigate the possibility that **6b** forms first and subsequently rearranges to **2b**, we subjected **6b** to the reaction conditions. A quantitative recovery of **6b** was obtained.

The preparation of spiran **5c** was achieved in a manner similar to that used by the Russian workers.[9] Reaction of **5c** with aqueous *tert*-butyl alcohol was previously reported to yield only the tertiary alcohol **2c**.[4] In our hands this reaction was not reproducible and yielded a mixture containing alcohol **2c**, olefin **10**, and possibly ether **9**, in varying amounts. The structure of alcohol **2c** was confirmed by an independent synthesis, and its nmr spectrum, $ArCH_2COH(CH_3)_2$, δ 2.68 and 1.21, respectively, is quite different from that of isomer **6c**, $ArC(CH_3)_2CH_2OH$, δ 1.32 and 3.57, respectively. The product from the ring opening of **5c**, alcohol **2c**, was previously incorrectly identified[4] as being the same alcohol as obtained from step A of Chart I (compare step A′, Chart II).[4] This conclusion was apparently based on similarity of melting points.[12b,c] The presence of olefin **10** in the reaction mixture was indicated by comparison of the nmr spectrum, $ArCH_2CCH_3{=}CH_2$, δ 3.23, 1.70, and 4.71, respectively, to that of $PhCH_2CCH_3{=}CH_2$, δ 3.25, 1.62, and 4.75, respectively. The presence of ether **9** was indicated by a singlet at δ 2.63 (CH_2), additional absorption at δ 1.23 [$OC(CH_3)_3$], and additional absorption in the aromatic region. Further efforts to confirm its structure were not undertaken.

We also studied the ring-opening reactions of **5c** with aqueous acetone and 10% H_2SO_4 in acetone. In each case, the product consisted of a mixture containing approximately equal amounts of **2c** and **10**. In all three cases of ring opening in aqueous solvents, control experiments were performed which established the stability of alcohol **6c** under the reaction conditions.

The Russian workers did not indicate whether they studied the reactions of spiran **5c** with HBr or $MgBr_2$. We performed these experiments and in both cases found the product mixture to consist almost entirely of the tertiary bromide **4c**. The structure of the reaction product was established by comparison of its nmr spectrum with that of an independently synthesized sample.

It is clear from these results that spirodienone **5c** also undergoes cyclopropyl ring opening at the more substituted carbon atom.

Experimental Section[13]

2-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-1-propyl Tosylate (7b). Compound **7b** was prepared according to the previous procedure:[9] mp 98.5–100.0° (lit.[8] mp 84–86°); nmr δ 7.79, 7.65, 7.34, 7.20 (4 H, AA′BB′, ArH of tosyl group), 6.90 (2 H, s, ArH), 5.00 (1 H, s, ArOH), 4.01 (2 H, AB portion of ABX, CH_2O), 2.98 (1 H, sextet, J = 7 Hz, CH), 2.39 (3 H, s, $ArCH_3$), 1.39 (18 H, s, *t*-Bu), 1.25 (3 H, d, J = 6.5 Hz, CH_3).

1-Methyl-4,6-di-*tert*-butylspiro[2.5]octa-3,6-dien-5-one (5b). To a solution of **7b** (8.4 g, 0.020 mol) in 30 ml of THF was added KO-*t*-Bu (2.70 g, 0.024 mol) followed by an additional 20 ml of THF. The solution was stirred for 2 hr, added to ether, washed with water, and dried, and the solvent was removed under vacuum. The crude product was recrystallized from hexane to yield 2.9 g (59%) of white solid: mp 79.5–81.5° (lit.[9] mp 75–77°); nmr δ 6.39 (1 H, d, J = 2.5 Hz, vinyl H), 6.03 (1 H, d, J = 2.5 Hz, vinyl H), 1.2–1.8 (6 H, m, cyclopropyl and CH_3), 1.25 (18 H, s, *t*-Bu).

Reaction of Tosylate 7b with LiBr. The previous procedure[4] was followed. Reaction periods of 3 hr produced mixtures estimated by nmr to contain 11–17% starting material, 61–62% **4b**, and 21–27% **8b**. After 21 hr no starting material remained, and the reaction product consisted of a mixture of *ca.* 67% **4b** and 33% **8b**.

1-Bromo-2-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)propane (8b). Br_2 (3.8 g, 0.024 mol) in 10 ml of benzene was added to a solution of Ph_3P (4.7 g, 0.018 mol) in 20 ml of benzene in an ice-water bath, followed by dropwise addition of **6b**[3] (2.6 g, 0.010 mol) in 1.5 ml of pyridine and 10 ml of benzene at 25°. The solution was stirred for 1 hr and added to water, and the organic material was extracted into ether. The ether solution was washed with 5% $NaHCO_3$ and water, dried, and evaporated to a yellow oil which contained an appreciable quantity of Ph_3PO. Most of the Ph_3PO was removed by repeated solution in hexane to yield 2.9 g of oil: nmr δ 7.5 (Ph_3PO, <5%), 7.0 (2 H, s, ArH), 5.17 (1 H, s, ArOH), 2.7–3.9 (3 H, m, CH and CH_2), 1.42 (21 H, singlet and shoulder, *t*-Bu and CH_3); mass spectrum *m/e* (rel intensity) 328 (33), 326 (33), 313 (71), 311 (71), 233 (100).

Efforts at further purification of **8b** for microanalysis were unsuccessful; *e.g.*, chromatography on silica gel removed the Ph_3PO but also caused complete rearrangement of **8b** to **4b**.

Reactions of 5b. A. With HBr. HBr was slowly bubbled through a solution of **5b** (0.223 g, 0.90 mmol) in 25 ml of anhydrous ether for 20 min under N_2 at 0°. The solution was diluted with ether, washed with 5% $NaHCO_3$ and water, and dried, and the solvent was evaporated under vacuum to yield 0.231 g (78%) of oil. The product distribution by nmr was *ca.* 75% **4b** and 25% **8b**: nmr of **4b** δ 6.99 (s, ArH), 5.10 (s, ArOH), 4.25 (sextet, J = 6.5 Hz, CHBr), 3.07 (AB portion of ABX, CH_2), 1.64 (d, J = 6.5 Hz, CH_3), 1.42 (s, *t*-Bu); nmr of **8b**, the same as that reported in the preceding experiment. Spin-decoupling experiments using a Bruker HFX spectrometer were consistent with the above assignments.

B. With $MgBr_2$. Anhydrous $MgBr_2$ (0.267 g, 1.45 mmol) was added to a solution of **5b** (0.220 g, 0.89 mmol) in 10 ml of anhydrous ether, and the mixture was stirred for 3.75 hr at 25°. The ether solution was washed with water and dried, and the solvent was evaporated under vacuum to yield 0.21 g of light yellow oil. The nmr spectrum showed 27% starting material and bromides **4b** and **8b** in the ratio 75:25, respectively.

C. With 10% H_2SO_4. A solution of **5b** (0.589 g, 2.4 mmol) and 1.5 ml of 10% aqueous H_2SO_4 in 7.5 ml of acetone was stirred for 2.5 hr at 25° and diluted with 50 ml of ether and 25 ml of water. The ether layer was dried and evaporated under vacuum to yield 0.55 g of viscous oil. Nmr analysis indicated the presence of *ca.* 93% **2b**. See the following experiment for the nmr spectrum.

1-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-2-propanol (2b). The previous procedure[11] was followed: mp 58–61.5° (lit.[11] mp 56–58°); nmr δ 7.00 (2 H, s, ArH), 5.10 (1 H, s, ArOH), 3.90 (1 H, sextet, J = 6 Hz, CH), 2.65 (2 H, AB portion of ABX, CH_2), 1.70 (1 H, br s, OH), 1.42 (18 H, s, *t*-Bu), 1.20 (3 H, d, J = 6 Hz, CH_3); mass spectrum *m/e* (rel intensity) 264 (17.4), 249 (14.9), 219 (100).

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.31; H, 10.80.

For comparison, the nmr spectrum of 1-phenyl-2-propanol shows δ 7.2 (5 H, s, ArH), 3.96 (1 H, sextet, J = 6 Hz, CH), 2.66 (2 H, AB portion of ABX, CH_2), 2.28 (1 H, br s, OH), 1.16 (3 H, d, J = 6 Hz, CH_3).

2-Methyl-2-(3′,5′-di-*tert*-butyl-4′-hydroxphenyl)-1-propyl Tosylate (7c). Compound **7c** was prepared according to the previous procedure:[9] mp 82.0– 83.0° (lit.[9] mp 100–102°); nmr δ 7.77, 7.63, 7.34, 7.20 (4 H, AA′BB′, ArH of tosyl group), 7.08 (2 H, s, ArH), 5.10 (1 H, s, ArOH), 3.92 (2 H, s, CH_2O), 2.40 (3 H, s, $ArCH_3$), 1.39 (18 H, s, *t*-Bu), 1.30 (6 H, s, CH_3).

1,1-Dimethyl-4,6-di-*tert*-butylspiro[2.5]octa-3,6-dien-5-one (5c). The same procedure as that used for **5b** was followed: mp 92.8–96.0 (lit.[9] mp 92–94°); nmr δ 6.48 (2 H, s, vinyl H), 1.65 (2 H, s, CH_2), 1.39 (6 H, s, CH_3), 1.26 (18 H, s, *t*-Bu).

Methyl 3,5-Di-*tert*-butyl-4-hydroxyphenylacetate (11). A solution of 3,5-di-*tert*-butyl-4-hydroxyphenylacetic acid[14] (23.2 g, 0.088 mol) and 6 ml of concentrated H_2SO_4 in 580 ml of CH_3OH was heated under reflux for 4 hr and diluted with 3 l. of H_2O, and the organic material was extracted into $CHCl_3$. The solution was dried and evaporated under vacuum. Recrystallization from hexane yielded a pale yellow solid (50%): mp 83.6–84.5°; nmr δ 7.10 (2 H, s, ArH), 5.15 (1 H, s, ArOH), 3.69 (3 H, s, CH_3), 3.52 (2 H, s, CH_2), 1.42 (18 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 278 (32.4), 263 (100), 219 (16.2).

Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.56; H, 9.55.

1-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-2-methyl-2-propanol (2c). A solution of **11** (16.3 g, 0.058 mol) in 250 ml of ether was added to 0.77 mol of CH_3MgBr in 750 ml of ether over a period of 30 min without external heating. The solution was stirred at 25° for 2 hr, cooled to 0°, and quenched with water followed by 3.7% HCl. The ether layer was washed with water, dried, and evaporated, and the residue was recrystallized from hexane: mp 95.4–96.0° (lit.[4] mp 150–152°); nmr δ 7.01 (2 H, s, ArH), 5.11 (1 H, s, ArOH), 2.68 (2 H, s, CH_2), 1.50 (1 H, br s, ROH), 1.42 (18 H, s, *t*-Bu), 1.21 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 278 (12), 263 (4.1), 219 (49), 205 (100).

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.81; H, 10.98. Found: C, 77.65; H, 10.86.

1-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-2-bromo-2-methylpropane (4c). A mixture of **2c** (1.4 g, 5.0 mmol) in 25 ml of $CHCl_3$ and concentrated HBr (48%, 40 g) was heated under reflux for 8 hr and then diluted with water. The organic layer was washed with water, dried, and evaporated under vacuum to yield 1.6 g (93%) of brown oil which appeared to be pure by its nmr spectrum: nmr δ 7.08 (2 H, s, ArH), 5.13 (1 H, s, ArOH), 3.12 (2 H, s, CH_2), 1.72 (6 H, s, CH_3), 1.42 (18 H, s, *t*-Bu).

Efforts at further purification of **4c** for microanalysis were unsuccessful.

Reactions of 5c. A. With HBr. Procedures similar to those used for **5b** were followed. The crude product appeared to be pure by its nmr spectrum, which was virtually identical with that of **4c** prepared above. This bromide is not stable and appreciably decomposed on storage at 4° for 3 days.

B. With $MgBr_2$. The crude product exhibited an nmr spectrum virtually identical with that of **4c**.

C. With 10% H_2SO_4. Analysis of the crude product by nmr spectroscopy revealed the presence of *ca.* 50% **2c** and 50% of olefin **10**: nmr of **10** δ 6.99 (2 H, s, ArH), 5.02 (1 H, s, ArOH), 4.6–4.9 (2 H, m, vinyl H), 3.23 (2 H, br s, CH_2), 1.70 (3 H, br s, CH_3), 1.42 (18 H, s, *t*-Bu).

D. With Aqueous Acetone. A solution of **5c** (0.268 g, 1.0 mmol) in 5 ml of acetone and 1 ml of H_2O was stirred at room temperature for 3 hr, diluted with water, and extracted with ether. The ether extract was washed with water, dried, and evaporated under vacuum to yield 0.18 g of white solid, which nmr spectroscopy indicated to consist of *ca.* 42% **5c**, 29% **2c**, and 29% **10**.

Acknowledgment. We thank Miss Jill H. Paul and Mr. Jack Landis for their kind assistance.

Registry No. 2b, 18734-98-0; **2c**, 18735-02-9; **4b**, 20023-76-1; **4c**, 42806-98-4; **5b**, 17207-15-7; **5c**, 17207-20-4; **6b**, 19510-15-7; **7b**, 42807-02-3; **7c**, 26157-90-4; **8b**, 42807-04-5; **10**, 42807-05-6; **11**, 6386-41-0; 3,5-di-*tert*-butyl-4-hydroxyphenylacetic acid, 1611-03-6.

References and Notes

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(2) (a) American Chemical Society Petroleum Research Fund Graduate Fellow, 1969–1970; (b) National Science Foundation Undergraduate Research Participant, 1970–1971.

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(12) (a) See ref 3 and 5. We have come to a dead end on this point. Reference 12 within ref 3 was claimed to contain the necessary melting point data. This reference does not appear to exist, and we have not been able to locate this data in the literature. (b) Our melting points for alcohols **2b** and **6b** differ by 35°. (c) Our melting points for alcohols **2c** and **6c** differ by 55°.

(13) Nmr spectra were determined in $CDCl_3$ solution using a Varian A-60 spectrometer. Melting points are corrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Mass spectra were determined using a Varian CH5 spectrometer at 70 eV with direct sample inlet and linear mass scan.

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The Course of the Dehydration of 5-Hydroxytetrahydro-*exo*-dicyclopentadiene with Acid

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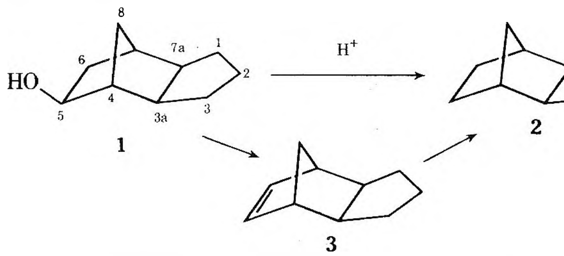
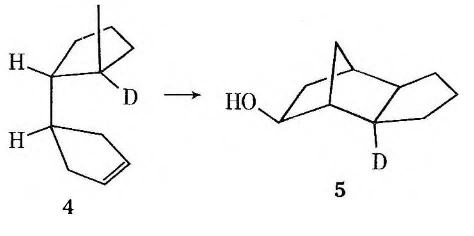
A study of the dehydration of 3a-deuterio-5-hydroxytetrahydro-*exo*-dicyclopentadiene with acid suggests that the formation of 5,6-dihydro-*exo*-dicyclopentadiene proceeds through 2,3-dihydro-*exo*-dicyclopentadiene or the equilibrating ions formed from the latter by protonation followed by a 1,3-hydride shift, a 1,2-hydride shift, and proton loss.

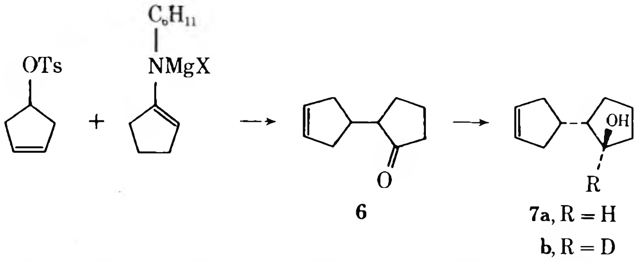
Some years ago it was conclusively shown by Schleyer and Donaldson[2] and simultaneously by Wilder and Youngblood[3] that the dehydration product of 5-*exo*-hydroxytetrahydro-*exo*-dicyclopentadiene[4] (**1**) with 85% phosphoric acid was not the previously suggested[5] 2,3-dihydro-*exo*-dicyclopentadiene (**3**) but 5,6-dihydro-*exo*-dicyclopentadiene (**2**).



We sought to gain some understanding of the course of this remarkable and deep-seated rearrangement by a study of the dehydration of samples of **1** suitably substituted by deuterium, and chose the corresponding 3a-deuterio compound **5** as likely to be illuminating. This substance should be readily available by the π-route solvolysis[6] of a *trans*-2-(3′-cyclopentenyl)cyclopentanol sulfonate (**4**) bearing deuterium at the 1 position.

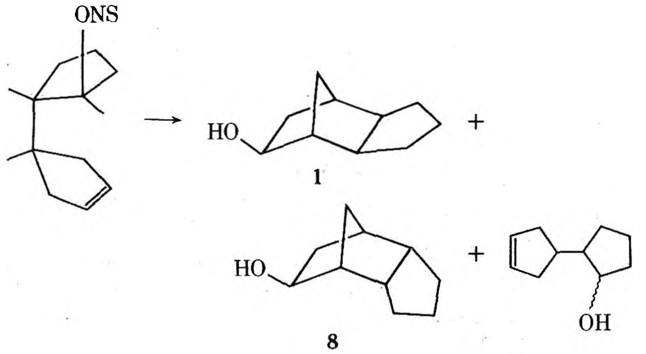


Several approaches to the formation of 2-(3′-cyclopentenyl)cyclopentanone (**6**), from which **4** could easily be made, were explored. The most efficient proved to be the alkylation by 3-cyclopentenyl tosylate of the magnesium salt of the Schiff base formed from cyclohexylamine and cyclopentanone, the procedure of Stork;[7] neither 2-carbethoxycyclopentanone nor the pyrolidine enamine of cyclopentanone could be alkylated successfully with 3-cyclopentenyl tosylate.



Reduction of ketone **6** with lithium aluminum hydride in refluxing ether gave a 1:1 mixture of the two epimeric alcohols, and this ratio was not altered by refluxing the epimeric mixture with aluminum isopropoxide in isopropyl alcohol, a procedure we had hoped would maximize the trans isomer. It was found, however, that by conducting the reaction at low temperatures the trans isomer could be made to predominate, and in tetrahydrofuran at −70° the reduction of **6** with lithium aluminum hydride yields an epimeric mixture with a trans/cis ratio of 5.7:1. In contrast, hydrogenation of **6** over platinum yields a mixture of saturated epimeric alcohols in which the cis isomer predominates (2.2:1).[8]

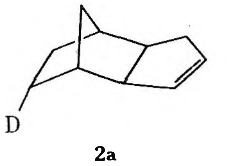
Treatment of mixtures of epimeric alcohols so produced with *p*-nitrobenzenesulfonyl chloride in pyridine at low temperatures gave an unstable, crystalline, sharply melting *p*-nitrobenzenesulfonate, and solvolysis of this substance at 50° in 97% formic acid containing a small amount of sodium formate followed by treatment with lithium aluminum hydride gave **1** in 29% yield along with both cis and trans isomers of 2-(3′-cyclopentenyl)cyclopentanol, and traces (1–5% estimated) of 5,6-dihydro-*exo*-dicyclopentadiene (**2**) and 5-hydroxytetrahydro-*endo*-dicyclopentadiene (**8**), the endo isomer of **1**. The *cis*- and *trans*-2-(3′-cyclopentenyl)cyclopentanols reflect the extent of nonassisted solvolysis[9] and the high ratio of exo isomer to endo isomer **8** is in accord with the observations of Schleyer and Donaldson.[10,11]



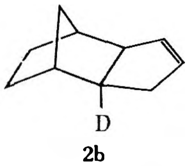
Repetition of this sequence on ketone **6** but using lithium aluminum deuteride for its reduction gave successively a mixture of epimeric alcohols in which **7b** predominated, the *p*-nitrobenzenesulfonate **4**, and finally **5**. A sample of **5**, prepared from **4** containing 98.2% of one deuterium atom per molecule by analysis,[12] also contained 98.2% of one deuterium.

The dehydration of **1** as originally carried out by Bruson gives only moderate amounts of **2**; we found after much experimentation that a much more satisfactory yield is obtained by passing vaporized **1** over a column of glass helices coated with 85% phosphoric acid heated to 180°. Under these conditions three major products, separable by preparative glpc, are formed in ratio of 20:4:1. The major component was **2**, the minor tetrahydro-*endo*-dicyclopentadiene. The remaining component was not identified, but was shown not to be either tetrahydro-*exo*-dicyclopentadiene or adamantane. Yields of purified **2** ranged between 20 and 45%. Under less vigorous conditions appreciable amounts of **3** are formed.

When another sample of monodeuterated alcohol **5** (98.7% of one deuterium, characteristic C–D absorption at 2150 cm^{-1}) was dehydrated in the same way, the olefin **2** obtained had 91.3% of one deuterium per molecule and exhibited infrared absorption at 2178 cm^{-1} with a shoulder at 2152 cm^{-1}.[13] Although the 60-MHz nmr spectra of the product and of undeuterated **2** are poorly resolved, it is possible to infer from a comparison of the two plus some mechanistic assumptions that the product contains 38% of **2a** and 52% of **2b**.



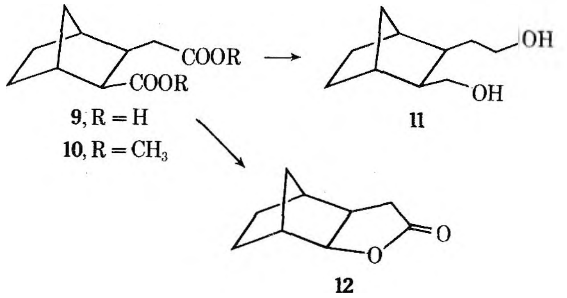
2a



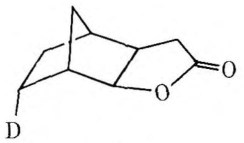
2b

Thus the spectrum of undeuterated **2** exhibits signals centered at δ 5.35 (2 H, olefinic protons), 3.30–1.8 (5.87 H, allylic and methine protons), and 1.8–0.7 (6.23 H, methylene protons), total 14.10 H, whereas **2** produced from **5** (monodeuterated) showed signals in the same ranges whose relative integrations were 2:5.35:5.85, total 13.2 H, respectively. The reduction in absorption in the region δ 1.8–0.7 indicates that 0.38 (6.23 − 5.85) of one deuterium atom occurs in the methylene region and that 0.52 (5.87 − 5.35) of one deuterium occurs in the methine region. Furthermore, within the methylene envelope, the integrated absorption from δ 1.8 to 1.35 is substantially unchanged (2.05 H *vs.* 2.13 H), and it is in this region that Nickon[13] has shown the exo protons of norbornane to absorb (δ 1.4). The reduction in methylene protons thus occurs in the region associated either with the endo 5 (or 6) protons or the bridge methylene protons on carbon 8. A rational set of Wagner–Meerwein rearrangements and hydride shifts will not give rise to deuterium substitution at C_6 or C_8 of **2** and we therefore conclude that this deuterium is endo at C_5.

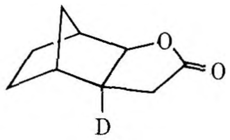
The conclusion that dehydration of **5** gives rise to a mixture of **2a** and **2b** is supported by degradative studies on the dehydration product. On oxidation with permanganate, olefin **2** yields the diacid **9**, readily convertible into the corresponding dimethyl ester **10**, diol **11**, and, following oxidative decarboxylation with lead tetraacetate, into the lactone **12**. This series of reactions, when applied to the dehydration product of **5**, gave diacid **9** containing 86.8% of one deuterium[14] and diester **10** showing C–D stretching absorption at 2183–2188 cm^{-1} with an apparent molar extinction coefficient of 7.3.[15] The absence of an appreciable absorption at 2200 cm^{-1}, the observed[16] C–D absorption of 1-deuterionorbornane, strongly suggests that there is no deuterium at the bridgehead positions. The corresponding diol **11** contained 87.4% of one deuterium and absorbed at 2174 cm^{-1} with an apparent molar extinction coefficient of 8.0. Since there is no significant increase in C–D absorption in going from the diester **10** to the diol **11**, deuterium cannot be located α to either of the carbonyl grounds of **10** and hence not at either 1 or 3a of **2**, since Jones[17] has shown that deuterium substituted α to an ester carbonyl function does not absorb in the region 2100–2200 cm^{-1}. That deuterium cannot be at 3a of **2** is also clear from the nmr spectrum of lactone **12** from the deuterated series, which showed absorption corresponding to one proton as a broadened doublet centered at δ 4.1 and thus must have hydrogen at this position. This spectrum, when compared with that of undeuterated lactone **12**, allows the further conclusion that 43%[14] of one deuterium is present in the group of atoms responsible for absorption between δ 3.82 and 1.70 (the two protons α to the carbonyl and the methine protons) and 32% of one deuterium atom is present in the group responsible for absorption between δ 1.70 and 0.6 (the methylene protons). By elimination, the deuterium in the former group can be assigned to the position β to the carbonyl, since the infrared and nmr evidence adduced earlier has shown that deuterium cannot be α to the carbonyl or at the bridgeheads.



Thus lactone **12** derived from deuterated **2** appears to be a mixture of **12a** and **12b**.



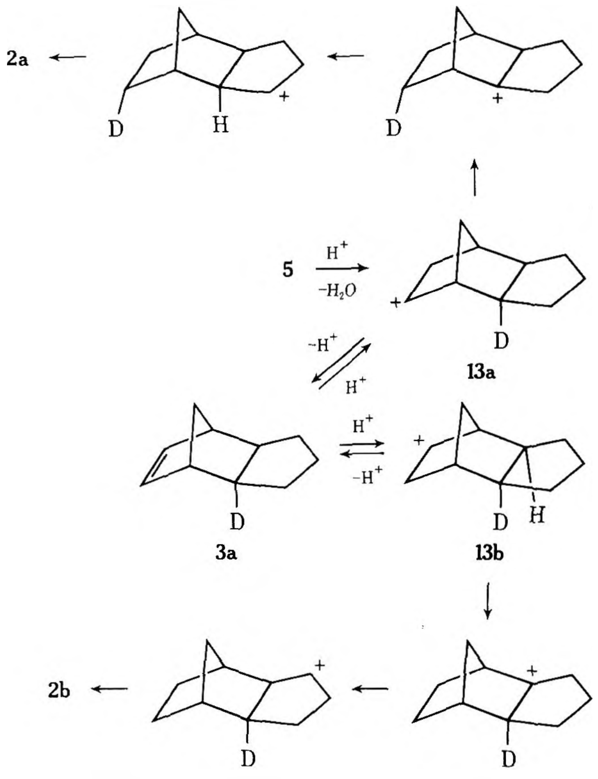
12a



12b

By nmr integration, the ratio of **12a** to **12b** is 1:1.34 and that of **2a** to **2b** is 1:1.37; in view of the uncertainties associated with these nmr integrations, the agreement is perhaps fortuitous.

These data can be accommodated by a reaction course involving a 1,3-hydride shift from position 3a to 5 in the carbonium ions derived from **1**, followed by a 1,2-hydride shift, the final product arising by proton loss.



To the extent that the observed ratio of **2b** to **3a** (1.37) can be relied on, it is consistent with a small positive isotope effect. This value is much smaller than the maximum effect.[18a,b] It may indicate the extent of this hydride transfer in the transition state, although any formation of olefin **2** directly from ion **13a** without equilibration to ion **13b** or conversion to olefin **3a** would lower the ratio of **2b** and **2a** and thus produce an apparent reduction in isotope effect.

A measure of the extent of conversion of **13** directly to olefin **2** without the intermediacy of olefin **3** or equilibration of ions **13a** and **13b** could in principle be obtained by using optically active alcohol **1**. Alcohol **2** derived directly from **1** though ion **13** should retain activity, whereas **2** derived from olefin **3** or subsequent to the equilibration of **13a** and **13b** would, of course, be racemic.

Experimental Section

2-(3′-Cyclopentenyl)cyclopentamone (6). A solution of ethylmagnesium bromide prepared from 27.0 g (0.26 mol) of ethyl bromide and 6.6 g (0.275 mol) of magnesium turnings in 140 ml of dry tetrahydrofuran was added dropwise to 41.4 g (0.25 mol) of the cyclohexylimine of cyclopentanone[19] over a period of 1.5 hr. The reaction mixture was refluxed for 1 hr, cooled to room temperature, and added dropwise over a period of 5 hr to a solution of 62.3 g (0.26 mol) of Δ^3-cyclopentenyl tosylate[20] in 300 ml of dry tetrahydrofuran. The reaction mixture was then refluxed for 18 hr, at which time the pH of the heterogeneous solution was 8-9. The cooled solution was treated with 0.5 equiv of 10% sulfuric acid, refluxed for an additional 3 hr, cooled to room temperature, and extracted with 2 l. of ether. The ethereal solution was washed with 10% hydrogen chloride, 5% sodium bicarbonate, and brine, and dried over anhydrous sodium sulfate. The ethereal extracts, on concentration, afforded a deep-red, viscous liquid, which was distilled under reduced pressure to give 10 g (27%) of a light-yellow liquid, bp 54° (0.5 mm). The pot residue was polymeric.

The uv spectrum of this distillate indicated the presence of cyclopentylidenecyclopentanone. Analysis by glpc (20 ft × 0.375 in. 25% UCON Polar or Anakrom, column temperature 165°, flow rate 100 cc/min) showed two major components with retention times of 32 and 53 min. The two components were collected and examined by infrared analysis. The first component had absorptions characteristic of a cyclopentanone, of a double bond, and of unsaturation in a strainless five-membered ring (1740, 3044, and 1625 cm^{-1}, respectively), while the second component had characteristic absorption frequencies at 1710 and 1640 cm^{-1} which were assinged to the α,β-unsaturated cyclopentylidenecyclopentanone system.

The first component yielded a semicarbazone, mp 180-181° dec.

Anal. Calcd for $C_{11}H_{17}N_3O$: C, 63.77; H, 8.21. Found: C, 63.50; H, 8.25.

2-(3′-Cyclopentenyl)cyclopentanol (7a). A solution of 200 mg (1.33 mmol) of 2-(3′-cyclopentenyl)cyclopentanone in 20 ml of anhydrous ether was added to a threefold excess of lithium aluminum hydride in 20 ml of anhydrous ether at such a rate as to maintain gentle refluxing. Following the addition, the heterogeneous reaction mixture was refluxed for an additional 6 hr. The cold reaction mixture was taken up in additional ether and carefully washed with 5% sodium hydroxide and water. The solution was dried over magnesium sulfate, filtered, and concentrated to give 182 mg of a light-yellow liquid (90%). A thin film infrared analysis indicated the presence of an unsaturated alcohol and the absence of any ketone. This material was shown by glpc (10 ft × 0.125 in. 20% UCON Polar, column temperature 165°, flow rate 26 cc/min) to consist of two major components in equal amounts (retention times 24 and 27.5 min), presumed to be the cis and trans isomers. A 1.46-g sample of a similar mixture was dissolved in 6 ml of isopropyl alcohol containing 13 mg of starting ketone **6** and 0.93 g of freshly distilled aluminum isopropoxide. Refluxing for a period of 1 week failed to change the isomeric ratio as indicated by glpc. The components were identified as cis (retention time 24 min) and trans (27.5 min) by the following observation. A 200-mg neat sample of ketone **6** was shaken with 100 mg of platinum oxide under 2.7 atm of hydrogen for 17 hr. The filtered reaction mixture gave 190 mg of a light-yellow oil, which was shown by infrared analysis to contain ketonic as well as alcoholic material. Three components were present with retention times of 17, 20.5, and 23.5 min (glpc conditions as already described). The first component had the same retention time as the dihydro derivative of ketone **6**. The ratio of the latter two components to one another was 2.2:1. Since these reduction conditions in other instances[8] have given rise to a greater amount of cis product, we assign the cis configuration to the component with the retention time of 20.5 min.

An ethanolic solution of 100 mg of the cis and trans alcohols resulting from the lithium aluminum hydride reduction of ketone **6** was quantitatively reduced over platinum oxide in 5 min at 760 mm. The solution was filtered and concentrated to give 95 mg of a saturated alcoholic mixture as indicated by infrared analysis. Glpc analysis under identical conditions as those previously described showed two components to be present in equal amounts with retention times of 20.5 (cis) and 23.5 min (trans).

Table I indicates the stereospecificity obtained by varying the lithium aluminum hydride reduction conditions.

2-(3′-Cyclopentenyl)cyclopentyl *p*-Nitrobenzenesulfonate. A 17.7-g (0.115 mol) solution of 2-(3′-cyclopentenyl)cyclopentanol, whose trans to cis ratio was 4:1, in 40 ml of anhydrous pyridine was cooled to −24° and treated with three 8.5-g (0.115 mol) portions of recrystallized *p*-nitrobenzenesulfonyl chloride over a period of 1 hr. The reaction was maintained at −24° for 48 hr, taken up in ether, and washed successively with cold 10% hydrogen chloride, 5% sodium bicarbonate, and water. The ethereal extract was dried over magnesium sulfate at low temperatures, filtered, and concentrated *in vacuo* to give 37.5 g of a red oil. The oil was triturated with petroleum ether (bp 30-60°) and a small amount of anhydrous ether to give a murky, heterogeneous solution. From this solution 30 g of a light-yellow powder, mp 58.5-60°, was isolated after cooling to −70°. Further recrystallizations failed to alter the melting point of a small sample. An infrared spectrum showed $\lambda_{\max}$ ($CHCl_3$) 3050, 1375-1350, 1180, and 680 cm^{-1}. An analysis for this compound was not obtained owing to its facile decomposition at room temperature. Many attempts to prepare the above mentioned solid *p*-nitrobenzenesulfonate fail when higher reaction temperatures were employed. Furthermore, a crystalline tosylate could not be obtained by this procedure.

5-Hydroxytetrahydro-*exo*-dicyclopentadiene (1). A. A solution of 50 g (0.27 mol) of 5-formoxydihydro-*exo*-dicyclopentadiene[21] in 250 ml of absolute ethyl alcohol was shaken with 100 mg of platinum dioxide under 2.7 atm of hydrogen for 12 hr. The solution was treated with Norit, filtered through a cake of Celite, diluted with enough ethyl alcohol to bring the total volume to 400 ml, and added to 200 ml of water containing 60 g of sodium hydroxide. This heterogeneous mixture was refluxed for 2 hr, salted with a large volume of saturated sodium chloride, and extracted with ether. The ethereal extracts were washed with saturated sodium chloride and dried over magnesium sulfate. The light-yellow liquid, 39.0 g, obtained from the dried ethereal extracts, was distilled at 71° (0.3 mm) to give 32 g of a colorless, viscous liquid. Two recrystallizations from nitromethane gave 25 g (61%) of a colorless solid, mp 53-55° (reported[22] mp 53-54°). Its phenylurethane melted at 105-106° (reported[22] mp 107-108°).

B. A 1.1-g sample of an oily mixture containing 80% by weight of 2-(3′-cyclopentenyl)cyclopentyl *p*-nitrobenzenesulfonate and 20% of the corresponding alcohol was dissolved in 145 ml of 0.04 *M* sodium formate in 97% formic acid, which had been preheated to 50 ± 2°. The reaction mixture was stirred for 20 hr at this temperature, cooled, and extracted with technical pentane. The pentane extracts were washed with 10% sodium carbonate and water. The sodium sulfate dried extracts yielded 0.681 g of a sweet-smelling yellow oil containing formates and alcohols, $\lambda_{\max}$ (neat) 1735 and 3350 cm^{-1}, respectively, which was reduced with 0.250 g of lithium aluminum hydride in 25 ml of anhydrous ether to give 0.394 g of neutral material. Glpc analysis showed this reaction mixture to contain alcohol 1 (retention time 30 min) as 41% (0.163 g) of the total mixture (10 ft × 0.125 in. UCON Polar on Anakrom, column temperature 165°, flow rate 26 cc/min). The retention time of authentic alcohol 1 was 30 min under these conditions. Trace amounts of 5,6-dihydro-*exo*-dicyclopentadiene (2) and 5-hydroxytetrahydro-*endo*-dicyclopentadiene (8) were detected by comparison with the retention times of authentic samples of each.[2,3,23] In that the sulfonate used in this solvolysis was prepared from a 0.549-g mixture of *cis*- and *trans*-2-(Δ^3-cyclopentenyl)cyclopentanol containing 60% trans by weight, and that complete esterification of the trans alcohol seemed to be a reasonable assumption, the theoretical yield of alcohol 1 was 0.329 g. The observed yield of alcohol 1 was 29% overall or 49% based on trans alcohol.

A 0.380-g sample of the reduced solvolysis reaction mixture in benzene was chromatographed on 38 g of commercial Fischer alumina, monitoring the eluted material by glpc. When such analysis showed 85% of alcohol 1 to be present in a respective fraction, the column was washed with 9:1 ether-methanol, which gave 0.100 g of a light-yellow oil. Its phenylurethane melted at 105-106°, undepressed on mixture with the phenylurethane of authentic alcohol 1, mp 106-107.5°. The infrared spectra of the two urethanes were identical. However, it was impossible to crystallize the ether-methanol eluted material.

5,6-Dihydro-*exo*-dicyclopentadiene (2). A slow stream of nitrogen was passed into a 10-ml pear-shaped two-neck flask charged with 5.0 g of 5-hydroxytetrahydro-*exo*-dicyclopentadiene (1). The flask was in turn connected to a hot (180 ± 5°) 8 × 0.5 in. horizontal column packed with glass helices, which had previously been coated with 85% phosphoric acid. The column in turn was connected to two traps maintained at 0°.

The charged flask was heated by means of an infrared lamp such that the sample was vaporized over a period of 3 hr. Nitrogen was swept through the system for an additional 2 hr, the trapped material was taken into ether, and the ethereal solution was washed with 5% sodium bicarbonate and water. The magnesium sulfate dried solution afforded 4 g of a colorless liquid, which was chromatographed on 80 g of No. I Woelm alumina to give 3.9 g of petroleum ether eluted material (86% of theoretical), n^{21}_{D} 1.5020 (reported[24] n^{25}_{D} 1.4990). This sample, which was analyzed by glpc on a 150-ft UCON Polar Golay column at 90°, consisted of three major components in the ratio of 20:4:1 (retention times 27, 30, and 33 min). The reaction mixture was separated by preparative glpc (20 ft × 0.375 in. 20% Apiezon L, column temperature 130°, injector temperature 180°, flow rate 100 cc/min, retention times 37, 40.4, and 48 min). The retention time of authentic 5,6-dihydro-*exo*-dicyclopentadiene under these conditions was 37 min. The infrared spectrum of authentic material was identical with that of the material collected.

Table I
Effect of Temperature on the Isomeric Ratio of Cis and Trans Alcohols from Reduction of Ketone 6

Medium	Temp, °C	Trans:cis
$LiAlH_4$–Et_2O	Reflux	50:50
$LiAlH_4$–THF	25	78:22
$LiAl(t\text{-}BuO)_3H_4$–THF	25	65:35
$LiAlH_4$–THF	0	80:20
$LiAlH_4$–THF	−70	85:15

Anal. Calcd for $C_{10}H_{14}$: C, 89.55; H, 10.45. Found: C, 89.27; H, 10.33.

For several runs the overall yield of purified olefin was 20-45%.

The material corresponding to the retention time of 48 min was identified as tetrahydro-*endo*-dicyclopentadiene by comparison with authentic material (retention time 48.5 min) prepared by total hydrogenation of commercial dicyclopentadiene over platinum oxide. The infrared spectra of the two samples were essentially identical. The authentic material melted at 79-81°, while the material collected from the reaction mixture melted at 80-82°, and an admixture melted at 77-80°.

The remaining component was shown not to have a retention time that corresponded with that of authentic samples of tetrahydro-*exo*-dicylopentadiene or adamantane. Because of the poor separation of this component and olefin 2, a sample was not obtained in a sufficiently pure state to permit its positive identification. Although the retention time of 40.4 min corresponds most closely with that of 5,6-dihydro-*endo*-dicyclopentadiene, the nmr spectrum suggests the absence of a bridged system inasmuch as there is only a small contribution to the spectrum at δ 2.

5-*endo*-Hydroxydihydro-*exo*-dicyclopentadiene. A solution containing 4.04 g (0.028 mol) of 5-ketodihydro-*exo*-dicyclopentadiene[22] in 100 ml of anhydrous ether was added with external cooling to 0.685 g (0.018 mol) of lithium aluminum hydride in 23 ml of anhydrous ether at such a rate as to maintain the reaction temperature at 0 ± 3°. Following the addition the stirred solution was allowed to come to room temperature and stand for a period of 12 hr. An infrared spectrum of the recovered reduced material (4.10 g) indicated the presence of an alcohol and the absence of starting ketone. A 200-mg sample was further purified by a short-path distillation, bp 75° (1 mm), yielding 190 mg of a colorless liquid. The nmr spectrum (deuteriochloroform with deuterium oxide) showed absorptions at δ 5.58 (2 H), 4.2 (0.85 H), 3.8 (0.15H), and 3.0-0.7 (10 H). A 100-mg (0.66 mmol) sample of the alcoholic distillate was mixed with 80 mg (0.68 mmol) of distillated phenyl isocyanate and heated to 85° for 1 hr. The semisolid reaction mixture was cooled and triturated with petroleum ether to give 130 mg of a colorless solid, mp 85-105°. Two recrystallizations from ethyl alcohol gave 100 mg (60%) of a phenylurethane, mp 118-119.5°.

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.84; H, 7.06. Found: C, 75.65; H, 7.20.

The nmr spectrum of the endo urethane showed absorptions at δ 7.6-6.6 (6 H), 5.52 (2 H), and 3.4-0.7 (10 H).

A 1.5-g (6 mmol) sample of the endo urethane was refluxed with 400 mg of lithium aluminum hydride in 20 ml of dry tetrahydrofuran for 18 hr. The dried neutral ethereal extracts afforded 890 mg (99% crude) of a light yellow oil, $\lambda_{\max}$ (neat) 3400 (s), 3050, and 1700 cm^{-1} (w).

3-Hydroxy-2-norbornaneacetic Acid Lactone (12). A solution containing 0.300 g (1.5 mmol) of 3-carboxy-2-norbornaneacetic acid (9),[2] 0.24 g (3.0 mmol) of dry pyridine, and 0.800 g (1.8 mmol) of lead tetraacetate in 10 ml of dry benzene was gently refluxed for 1.5 hr, cooled, filtered, and washed successively with 5% sodium carbonate, 10% hydrogen chloride, and water. The sodium sulfate dried extracts afforded 0.131 g (57%) of a slightly yellow oil, $\lambda_{\max}$ (neat) 1765-1760 cm^{-1} with a small shoulder at 1740 cm^{-1}. Glpc analysis on a 150-ft UCON Polar Golay column at 170° indicated that the reaction mixture was at least 95% pure (retention time 2 hr). An analytical sample was prepared by preparative glpc (5 ft × 0.25 in. 20% UCON Polar, column temperature 170°, flow rate 60 cc/min, retention time 15 min).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.49; H, 8.31.

The nmr spectrum showed a poorly resolved quartet centered at δ 4.43 (1 H), and complex absorptions at δ 2.60–0.7 (11.14 H).

2-(3′-Cyclopentenyl)-1-deuteriocyclopentyl *p*-Nitrobenzenesulfonate (4). A 47-g sample of 2-(3′cyclopentenyl)-1-deuteriocyclopentyl *p*-nitrobenzenesulfonate, mp 59–60°, was prepared from 40 g of 2-(3′-cyclopentenyl)cyclopentanone by using those procedures already outlined in the hydrogen series. Thus, the ketone in 2 l. of tetrahydrofuran was reduced with 3.5 g of lithium aluminum deuteride and the resulting 41 g of isomeric alcohols was converted into the sulfonate at −24°.

The 3,5-dinitrobenzoate of the corresponding alcohol was prepared, mp 86°, and analyzed for deuterium by combustion techniques.[25]

Anal. Calcd for $C_{17}H_{17}N_2O_6D$: D, 5.55 atom %. Found: D, 5.45 atom %.

3a-Deuterio-5-hydroxytetrahydro-*exo*-dicyclopentadiene (5). A. A mixture of 1.5 l. of 97% formic acid and 19 g (0.28 mol) of sodium formate was preheated to 50 ± 2° and treated with 47 g (0.14 mol) of 2-(3′-cyclopentenyl)-1-deuteriocyclopentyl *p*-nitrobenzenesulfonate. The resultant black reaction mixture was stirred at 50 ± 2° for 9 hr, diluted with water, and extracted with petroleum ether. The extracts were washed with 10% sodium carbonate and water. The magnesium sulfate dried solution afforded 22.3 g of a red oil, which was refluxed for 4 hr with 4.8 g of lithium aluminum hydride in 300 ml of anhydrous ether. The reduction mixture gave 20 g of a red oil, which was distilled to give 6.5 g of material, bp 48–68° (0.5 mm). This was shown by glpc analysis to contain approximately 83% of **5** relative to the isomeric alcohols present. This 6.5 g of distillate was triturated with nitroethane to give 2 g of alcohol **5**, mp 50–53°. The mother liquors afforded 4.2 g of a colorless liquid which was chromatographed in benzene on 300 g of Fischer alumina. The column was washed with 7 pints of benzene, giving only trace amounts of eluted material, and was then eluted with 9:1 benzene ether. The course of the chromatography was followed by glpc. When the ratio of alcohol **5** to isomeric alcohols was shown to be 5:1; the column was washed with 9:1 ether–methanol to give 2.8 g of a colorless oil. This oil afforded 1 g of alcohol **5**, mp 51–53°, from nitroethane. This represents a yield of 7.4% based on ketone **6**.

An 80-mg sample was recrystallized from 100 mg of nitroethane and sublimed at 30–33° (0.1 mm) to give 55 mg of alcohol **5**, mp 54.2–55° (reversibly), λ_{max} (CCl_4) 2150 cm^{-1}.

Anal. Calcd for $C_{10}H_{15}OD$: D, 6.25 atom %. Found: D, 6.14 atom %.

B. A 30-g sample of 2-(3′-cyclopentenyl)-1-deuteriocyclopentyl *p*-nitrobenzenesulfonate was added to 750 ml of dry glacial acetic acid preheated to 50 ± 2°. The solid containing reaction mixture after 8 hr was worked up in the manner above. An 800-mg sample of alcohol **5**, mp 50–54°, was obtained.

Dehydration of 3a-Deuterio-5-hydroxytetrahydro-*exo*-dicyclopentadiene (5). The samples of alcohol **5** obtained in the formolysis and acetolysis reactions described in the preceding section were combined and recrystallized from nitroethane to give 3.1 g of a colorless solid, mp 52–55°. A 100-mg sample was recrystallized and sublimed at 35° (0.1 mm), mp 53–54°.

Anal. Calcd for $C_{10}H_{15}OD$: D, 6.25 atom %. Found: D, 6.17 atom %.

The remaining 3.0-g sample was dehydrated by passing it through a column of glass helices at 180° coated with 85% phorphoric acid, as described in the preparation of olefin **2**. The infrared spectrum of a sample of the 723 mg (27%) of preparative glpc purified deuterated olefin **2** showed C–D absorption at 2178 cm^{-1} with a shoulder at 2150 cm^{-1} (carbon tetrachloride). The neat nmr spectrum integrated to 13.19 protons with absorptions at δ 5.55 (2 H, reference), 3.3–1.8 (5.35 H), 1.8–1.35 (2.05 H), and 1.35–0.7 (3.8 H).

Anal. Calcd for $C_{10}H_{13}D$: D, 7.14 atom %. Found: D, 6.52 atom %.

5-*endo*-Deuteriodihydro-*exo*-dicyclopentadiene. To 0.336 g (0.008 mol) of lithium aluminum deuteride in 15 ml of dry tetrahydrofuran was added 1.58 g of crude 5-*exo*-dihydro-*exo*-dicyclopentadienyl *p*-toluenesulfonate in 10 ml of dry tetrahydrofuran. The reaction mixture was refluxed for 17 hr and worked up to give 836 mg of a colorless oil. This was chromatographed on 20 g of No. I Woelm alumina, affording 390 mg of petroleum ether eluted material. Further purification by glpc (15 ft × 0.25 in. SF-96, column temperature 90°, flow rate 52 cc/min) gave 250 mg of deuterio olefin, retention time 25 min. This 250-mg sample was distilled at 40° (21 mm) to give 200 mg of a colorless olefin, λ_{max} (CCl_4) 2184 cm^{-1} with a shoulder at 2160 cm^{-1} (reported[22] endo "C–D" stretch 2185 cm^{-1}, shoulder at 2160 cm^{-1}). The nmr showed absorptions at δ 5.6 (2 H), 3.0–1.84 (5.45 H), and 1.84–0.7 (4.78 H).

5-*exo*-Deuteriodihydro-*exo*-dicyclopentadiene. A solution of 1.83 g of 5-*endo*-dihydro-*exo*-dicyclopentadienyl *p*-toluenesulfonate in 50 ml of dry tetrahydrofuran was refluxed with 0.390 g of lithium aluminum deuteride for 48 hr. The isolated 937 mg of yellow oil was chromatographed on 25 g of No. I Woelm alumina to give 150 mg of petroleum ether eluted olefin. Glpc analysis (15 ft × 0.25 in. SF-96, column temperature 100°, flow rate 50 cc/min) indicated that 72% of the mixture was olefin, retention time 12 min. Without further purification the crude olefin ws submitted to an infrared analysis. The spectrum (carbon tetrachloride) showed C–D stretch at 2174 cm^{-1} (reported[13] exo C–D stretch 2170 cm^{-1} for *endo*-deuterionorbornane).

Oxidation of Deuterated Olefin 2 Prepared from Alcohol 5. A 560-mg (4.17 mmol) sample of deuterated 5,6-dihydro-*exo*-dicyclopentadiene (**2**) prepared from alcohol **5** in 15 ml of A.R. Acetone was stirred with 1.85 g (11.7 mmol) of potassium permanganate and 0.100 g (5.57 mmol) of water for 18 hr. After recrystallization from water, 400 mg of deuterated 1,3-diacid **9** was isolated, mp 163–163.5° (reported[2] mp 165°).

Anal. Calcd for $C_{10}H_{13}O_4D$: D, 7.14 atom %. Found: D, 6.20 atom % with 1% residue.

Esterification of Deuterated Diacid 9. An 80-mg (0.4 mmol) sample of deuterated diacid **9** in 10 ml of anhydrous ether was treated with enough ethereal diazomethane, generated from Diazald, to give a permanent (15 min) yellow solution. This solution was concentrated *in vacuo* to give 91 mg of a colorless liquid which was chromatographed on 10 g of Fischer alumina. A 71-mg (78%) sample of a colorless benzene-eluted liquid was isolated, homogeneous to glpc analysis (15 ft × 0.25 in. 20% UCON Polar at 190°, flow rate 100 cc/min, retention time 57 min). A 52.7-mg sample in 0.265 ml of carbon tetrachloride showed C–D absorption at 2188–2184 cm^{-1} with an apparent molecular extinction coefficient of 7.3.

A 71-mg sample of this deuterated dimethyl ester was refluxed with 100 mg of lithium aluminum hydride in 20 ml of anhydrous ether for 12 hr to give 75 mg of an extremely viscous oil, which was chromatographed on 1 g of Fischer alumina. The 40 mg of purified viscous diol showed C–D absorption at 2174 cm^{-1} with an apparent molecular extinction coefficient of 8.

Anal. Calcd for $C_{12}H_{17}O_4D$: D, 5.55 atom %. Found: D, 4.85 atom %.

Deuterated Lactone 12. A 300-mg sample of deuterated diacid **9** was converted into 126 mg of crude deuterated lactone **12** according to the procedure described for the formation of lactone **12.** This 126 mg of yellow liquid was chromatographed on 2.5 g of Fischer alumina to give 66.2 mg of deuterated lactone **12** containing silicone grease.

A sample of this mixture containing 46.6 mg of the lactone and a 73.1-mg sample of naphthalene was dissolved in carbon tetrachloride. The nmr spectrum showed absorptions for the lactone at δ 4.32–3.82 (0.95 H), 3.82–1.7 (4.57 H), and 1.70–0.6 (5.80 H). The presence of silicone grease was evident from its characteristic absorption at δ 0.1. This mixture was chromatographed to give a sample of lactone, which showed C–D absorption at 2187 cm^{-1}.

Anal. Calcd for $C_9H_{11}O_2D$: D, 8.33 atom %. Found: **D**, 6.90 atom %.

Infrared spectra were recorded on a Perkin-Elmer 421 spectrophotometer. Aerograph Models A-700, 600, and A-90-P were used for glpc analyses. All nmr spectra were recorded on a Varian A-60 nuclear magnetic resonance spectrometer. Boiling and melting points are uncorrected.

Registry No. 1, 10271-44-0; **2**, 3129-29-1; **2a**, 42913-47-3; **2b**, 42913-48-4; **4**, 42913-49-5; **5**, 42913-50-8; **6**, 42908-41-8; **6** semicarbazone, 42908-42-9; *cis*-**7a**, 43027-55-0; *trans*-**7a**, 43000-59-5; **9**, 43000-60-8; **9**-*d*, 42912-45-8; **10**-*d*, 42912-46-9; **12**, 33045-15-7; **12a**, 42913-35-9; **12b**, 42913-36-0; ethyl bromide, 74-96-4; cyclohexylimine cyclopentanone, 42908-34-9; 2-(3′-cyclopentyl)cyclopentyl *p*-nitrobenzenesulfonate, 42908-35-0; 5-formyloxydihydro-*exo*-dicyclopentadiene, 42913-37-1; 5-*endo*-hydroxydihydro-*exo*-dicyclopentadiene, 42913-38-2; 5-ketodihydro-*exo*-dicyclopentadiene, 42913-39-3; 5-*endo*-hydroxydihydro-*exo*-dicyclopentadiene phenylurethane, 42913-40-6; 5-*exo*-dihydro-*exo*-dicyclopentadiene *p*-toluenesulfonate, 42913-41-7; 5-*exo*-deuteriodihydro-*exo*-dicyclopentadiene, 42913-42-8; 5-*endo*-dihydro-*exo*-dicyclopentadienyl *p*-toluenesulfonate, 42913-43-9; *trans*-2-(3′-cyclopentenyl)-1-deuteriocyclopentyl 3,5-dinitrobenzoate, 42913-44-0.

References and Notes

(1) Hooker, Fellow, 1964–1965; Union Carbide Fellow, 1963–1964.

(2) P. v. R. Schleyer and M. M. Donaldson, *J. Amer. Chem. Soc.*, **78**, 5702 (1956).

(3) P. Wilder, Jr., and G. T. Youngblood, *J. Amer. Chem. Soc.*, **78**, 5706 (1956).

(4) For convenience, we name this and related substances as derivatives of dicyclopentadiene but use the *Chemical Abstracts* numbering.

(5) H. A. Bruson and T. W. Riener, *J. Amer. Chem. Soc.*, **70**, 2809 (1948).

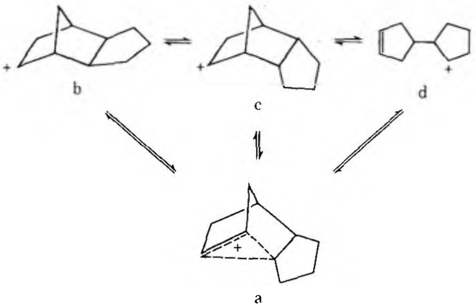
(6) (a) W. S. Johnson, D. M. Bailey, R. Owyang, R. A. Bell, B. Jaques, and J. K. Crandall, *J. Amer. Chem. Soc.*, **86**, 1959 (1964); (b) P. D. Bartlett, S. Bank, R. J. Crawford, and G. H. Schmid, *ibid.*, **87**, 1288 (1965); (c) R. G. Lawton, *ibid.*, **83**, 2399 (1961); (d) G. LeNy, *C. R. Acad. Sci.*, **251**, 1526 (1960); (e) H. L. Goering and M. F. Sloan, *J. Amer. Chem. Soc.*, **83**, 1397, 1992 (1961); (f) S. Winstein and P. Carter, *ibid.*, **83**, 4485 (1961).

(7) G. Stork and S. R. David, *J. Amer. Chem. Soc.*, **85**, 2178 (1963).

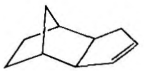
(8) W. Hückel and H. Kindler, *Ber.*, **80**, 202 (1947), have shown that hydrogenation of 2-methylcyclopentanone over platinum gives predominantly *cis*-2-methylcyclopentanol, and it was by analogy to this finding that we have assigned configuration to our reduction products. Similar reduction of our epimeric mixture of unsaturated alcohols (see Experimental Section) allowed glpc comparisons of the mixtures of saturated epimeric alcohols prepared in these two ways.

(9) P. D. Bartlett, S. Bank, R. J. Crawford, and G. H. Schmid, *J. Amer. Chem. Soc.*, **87**, 2188 (1965), found a ratio of cyclized to uncyclized products of 2.6:1 in the acetolysis of 1-(3′-cyclopentyl)-2-propyl *p*-nitrobenzenesulfonate and further found that, in going from the primary 2-(3′-cyclopentenyl)ethyl *p*-nitrobenzenesulfonate to the secondary 1-(3′-cyclopentenyl)-2-propyl *p*-nitrobenzenesulfonate, the unassisted solvolysis to give uncyclized products is enhanced considerably, whereas assisted solvolysis to give cyclized material is little changed.

(10) The bridged ion a formed in this solvolysis is in equilibrium with the three classical ions b, c, and d, and Schleyer [P. v. R. Schleyer and M. M. Donaldson, *J. Amer. Chem. Soc.*, **82**, 4645 (1960)] has shown that the products formed from this system in the presence of sulfuric acid are derived almost exclusively from structure b.



(11) We anticipated the predominant formation of the exo isomer **1** in solvolysis in formic acid, since Schleyer (ref 10) has shown that in this solvent equilibrium between e and f appears to be reached and this equilibrium favors the exo isomer e 99:1.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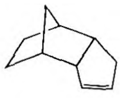
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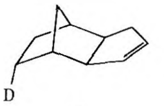
(12) All deuterium analyses were carried out by Mr. Joseph Nemeth by the falling-drop method.

(13) Compounds g and h, prepared by LiAlD$_4$ reduction (with inversion of the corresponding exo and endo tosylates, respectively (see Experimental Section), show C–D stretching absorption at 2184 cm^{-1} with a shoulder at 2160 and 2174 cm^{-1}, respectively. These data agree well with the values reported by Nickon and Hammons [*J. Amer. Chem. Soc.*, **86**, 3322 (1964)] for i and j, *i.e.*, 2185 cm^{-1}, shoulder at 2160 and 2170 cm^{-1}, respectively.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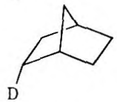
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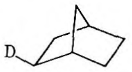
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(14) In this or subsequent compounds derived from it, the lower deuterium content is considered to be a reflection of contamination of the samples by silicone grease, shown to be present by its characteristic absorption at δ 0.1 in the nmr. On the scale of these experiments, processing to remove this contaminant seemed impractical.

(15) Calculated according to N. Jones and C. Sandorfy, "Technique of Organic Chemistry," Vol. IX, A. Weissberger, Ed., Interscience, New York, N. Y., 1956, p 271.

(16) A. Nickon and J. H. Hammons, *J. Amer. Chem. Soc.*, **86**, 3322 (1964).

(17) R. N. Jones and B. Nolin, *Can. J. Chem.*, **34**, 1382 (1956).

(18) (a) L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960, p 22. (b) After this work was completed, Lee's study of the acetolysis and formolysis of 2-(Δ^3-cyclopentenyl)-2-^{14}C-ethyl *p*-nitrobenzenesulfonate appeared [*J. Amer. Chem. Soc.*, **88**, 2834 (1966)]. His results suggest that some equilibration between **13a** and **13b** (as much as 12% in the analogous norbornyl case studied by Lee) may take place during the formation of **5** by the π route solvolysis of **4**. Any such equilibration would lead to a further apparent reduction in isotope effect but would not affect our main conclusions.

(19) K. Jewers and J. McKenna, *J. Chem. Soc.*, 2209 (1958).

(20) S. Winstein, E. L. Allred, and J. Sonnenberg, *J. Amer. Chem. Soc.*, **81**, 5833 (1959).

(21) F. Bergmann and H. Japhe, *J. Amer. Chem. Soc.*, **69**, 1826 (1947).

(22) H. A. Bruson and T. W. Riener, *J. Amer. Chem. Soc.*, **67**, 727 (1945).

(23) S. J. Cristol, W. F. Seifert, and S. B. Soloway, *J. Amer. Chem. Soc.*, **82**, 2351 (1960).

(24) P. D. Bartlett and A. Schneider, *J. Amer. Chem. Soc.*, **68**, 6 (1946).

(25) This analysis was carried out for us through the courtesy of Drs. David Stewart and T. Reagan, Eastman Kodak Laboratories, Rochester, N. Y.

Bridged Polycyclic Compounds. LXXVII. Coupling Reactions of 7-Chlorobenzonorbornadienes with Phenylmagnesium Bromide. Evidence for Carbocationic Intermediates[1,2]

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The syn (**1**-Cl) and anti (**2**-Cl) epimers of 7-chlorobenzonorbornadiene have been treated with a variety of organometallic reagents. Neither chloride reacted with phenyllithium or with a variety of organometallic species prepared by the addition of varying amounts of cuprous bromide to phenyllithium. The syn isomer reacted slowly with phenylmagnesium bromide in THF to give *syn*-7-phenylbenzonorbornadiene (**1**-Ph), while the anti chloride was inert. Additions of cuprous bromide to the Grignard reagent before addition of chloride promoted reaction. Anti chloride was slowly converted to *anti*-7-phenylbenzonorbornadiene (**2**-Ph), while syn chloride was more rapidly converted to a mixture of *syn*-7-phenylbenzonorbornadiene (**1**-Ph) and the *endo*-phenylbenzotricycloheptene (**3**-Ph). Those stereospecific coupling reactions are discussed in terms of ion-pair mechanisms.

The coupling reactions of alkyl halides with organometallic compounds (eq 1) are synthetically useful processes for the preparation of hydrocarbons. For this reason and because of similarities to the second part of the postulated path for the Wurtz–Fittig reaction, the mechanisms of such reactions received considerable early attention.[3-5]

$$\text{R-metal} + \text{R}'\text{X} \longrightarrow \text{R-R}' + \text{metal-X} \qquad (1)$$

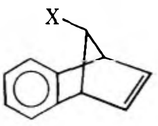
In studies on the reaction of Grignard reagents with allylic halides,[6] Young and his coworkers reported that crotyl chloride (1-chloro-2-butene) and α-methylallyl chloride (3-chloro-1-butene) reacted with phenylmagnesium bromide to give identical mixtures of butenylbenzenes. They proposed that the electrophilic magnesium atom coordinated with the halogen atom of the allylic halide, promoting heterolytic cleavage, to give a mesomeric butenyl cation which became free enough to lose its identity as either a crotyl or an α-methylallyl group before coordination with the phenyl anionoid species. Similar results were reported with phenyllithium and with butyllithium in ether[7] and with phenylsodium in pentane,[8] and analogous rationalizations were offered.

More recently Prevost and coworkers[9] studied coupling of α-methylallyl chloride and *cis*- and *trans*-crotyl chlorides with *n*-butylmagnesium bromide in ether and with *n*-butyllithium and *n*-butylsodium in pentane. Their more precise analytical methods showed that differences existed between product mixtures formed from the three isomers, and that with the organolithium and -sodium compounds, complete retention of geometric isomerism obtained (almost complete with the organomagnesium compound), but that each chloride gave a product mixture rich in the product of coupling at the primary position. They concluded that the mixtures were the result of combinations of cationic processes, direct displacement processes (S_N2), and abnormal allylic displacements (S_N2′) or cyclic processes. Wawzonek[10] also studied the reaction of the crotyl chlorides with phenyllithium, phenylsodium, and phenylmagnesium bromide, and noted that the lithium reagent gave some phenylmethylcyclopropanes. All three organometallic reagents gave mixtures of the three butenylbenzenes.

Detailed studies have been reported recently by Magid and his students[11] on the reaction of phenyllithium in ether with a variety of allylic halides. The allylic halides were made isomeric by methyl substitution or by deuterium placement; in one case an optically active substance was used. Their data made it clear that, for some cases at least, a cationic process in which the two ends of the allylic system lose their identity before coordination with the phenyl nucleophile cannot be the sole process.[12] Although these authors do not exclude cationic processes from consideration, they seem to favor competition between cyclic processes involving S_N2-like and S_N2′-like transition states to rationalize their mixture compositions. The effect of structural variations in allylic chloride upon product composition, such that α,α-dimethylallyl chloride and the γ,γ isomer both give almost entirely coupling at the primary carbon atom, and α,γ-dimethylallyl chloride labeled with deuterium or ^{14}C gives complete scrambling, seems to us to argue for the existence of cationic mechanisms in the process mix.

Adding to the confusion is the suggestion[13] that coupling of Grignard reagents with allyl bromide involves free-radical intermediates. Similar suggestions[14] involving radical or radical ion intermediates have been made by Eastham, by Ward and Lawler, by Lepley, by Russell, and by others, and it appears particularly clear, from both electron-spin resonance and chemically induced dynamic nuclear polarization experiments, that radical intermediates can intervene in these reactions, particularly with organolithium compounds.

In view of these recent developments, which raise serious doubts regarding the existence of a reaction path involving carbocations in such coupling reactions, we decided to turn our attention to this problem again. We obviously needed a system where radical, direct displacement, and cationic paths would give different products, and where cyclic paths perhaps could also be noted and/or excluded. One such system is the 7-chlorobenzonorbornadiene system, where syn (**1**-Cl) and anti (**2**-Cl) isomers are available,[15] and they or their bromine analogs have been subjected to a variety of ionic and radical reactions.



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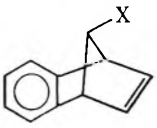

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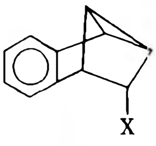

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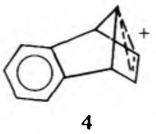

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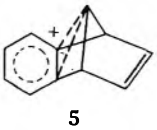

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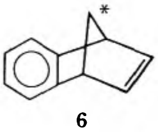


6

1-Cl upon acetolysis yields **1**-OAc, and **2**-Cl yields only **2**-OAc, both reactions occurring with complete retention.[15b] Similarly **1**-Cl and **2**-Cl undergo methanolysis with retention,[16] and **1**-Br[17] and **2**-Br[18] also suffer hydrolysis with retention.

The methanolysis of **1**-Cl in the presence of sodium methoxide is diverted to give substantial amounts of *endo*-2-methoxy-4-benzotricyclo[4.1.0.0^{3,7}]heptene (**3**-OCH_3) as well as **1**-OCH_3.[16,19] These data have been bases for the conclusion that the nonclassical carbonium ions **4** and **5** intervene in solvolytic reactions of **1** and **2**, respectively. Furthermore, the rate enhancement due to double-bond participation in **1** is much greater than that of the aromatic π system in **2**. Thus **1**-Cl acetolyzes about 10^3 times as fast as **2**-Cl in acetic acid,[15b] and by a factor of about 10^5 when return from solvent-separated ion pairs is excluded.[20] Similarly, **1**-Br solvolyzes in 80% ethanol 4×10^4 times as fast as **2**-Br.[17]

While carbocation reactions of **1** and **2** show large rate and product differences, neither of these effects is true for radical reactions. Thus **1**-Br and **2**-Br in reduction with tri-*n*-butyltin deuteride (initiated with azoisobutyronitrile) give identical mixtures of **1**-*d* and **2**-*d*.[21] When an equimolar mixture of **1**-Br and **2**-Br was treated with approximately one half the amount of tri-*n*-butyltin hydride required for complete reaction, the remaining starting material was, within the limits of pmr analysis, half **1**-Br and half **2**-Br. Thus tributyltin radical shows no kinetic preference for either of these bromides.[21b] These data make it clear that the radical **6** is identical with either **1** or **2** and is classical (although not necessarily planar).

The stereochemical results described above are those of a radical chain process and may not follow for geminate pair recombination. However, for a high degree of stereoselectivity, steric interference with recombination of the radicals must be low. For example, the thermal decomposition of (*S*)-1,1′-diphenyl-1-methylazomethane proceeds with a maximum of 17% retention of configuration with only a nitrogen molecule intervening between the members of the radical pair.[22] It thus seems unlikely that complete retention of configuration in the organometallic couplings could be due to cage radical combination. Rather it seems reasonable to assume that, if a cationic intermediate is involved, each epimer would react with complete retention of configuration (or perhaps **1**-Cl might give **3**-Ph), while a free-radical intermediate would lead to mixing.

Substituents at C-7 in norbornanes or unsaturated analogs are generally inert toward SN2 displacements, and this is true for **2**-Br as well.[15a,23] While derivatives of **1** have not been studied, one would guess that these also would be unreactive. In any case, such reactions would proceed with inversion, **1** giving **2** and vice versa.

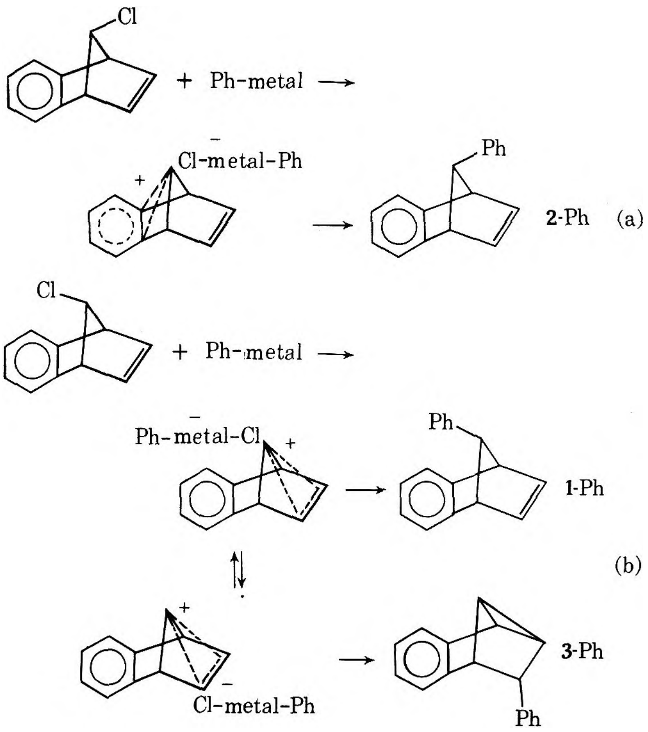
When **1**-Cl was treated with phenylmagnesium bromide in tetrahydrofuran (THF) for 5 days at reflux, all of the chloride reacted and 27% of **1**-Ph was obtained. No lines in the pmr spectrum attributable to **2**-Ph were observed, nor was **3**-Ph present. The formation of **1**-Ph from **1**-Cl was therefore stereospecific.[24]

When **2**-Cl was treated with phenylmagnesium bromide in ethyl ether or in THF under more severe conditions than those which succeeded with **1**-Cl, it was recovered unchanged. As reactions of organometallic compounds are often irreproducible, a competition reaction was run between **1**-Cl and **2**-Cl with an excess of phenylmagnesium bromide. All of the **1**-Cl was consumed, and, besides the dimeric product, only **1**-Ph and **2**-Cl were recovered. Clearly then, **1**-Cl was substantially more reactive than **2**-Cl.

Although these results were interesting and fit the carbocation theory, we were somewhat confused by the failure of **2**-Cl to react, as it had been reported[25] that **2**-Ph was produced by reaction of **2**-Cl with phenylmagnesium bromide in ether fairly rapidly, albeit in poor yield. As Battiste's paper dealt with copper(I)-catalyzed reactions of peroxides with **1**-H, we guessed that their success might be attributable to copper catalysis of the Grignard coupling.[26] We were therefore pleased to find that addition of cuprous bromide to the Grignard reagent before addition of **2**-Cl led to a slow coupling reaction. After 9 days of reflux in ether, 13% of **2**-Ph (no **1**-Ph) was obtained and 85% of **2**-Cl was recovered. Even more interesting was the fact that analogous treatment of **1**-Cl (for 4 days) gave 36% of **1**-Ph and 29% of **3**-Ph (no **1**-Cl was recovered and no **2**-Ph or exo epimer of **3**-Ph was formed).

The relative reactivities of **1**-Cl and **2**-Cl and the products obtained seem to us to be consistent only with the idea that the alkyl halides are transformed to the cations **4** or **5** during the reaction course. As our data offer no evidence regarding the complex question of the nature of the Grignard reagent or of the copper-promoted reagent, we can say very little about the nature of the ion paired with **4** or **5**. What can be confidently stated is proposed in Scheme I, where the organometallic compound is simply described as Ph-metal.

Scheme I



With the anti chloride (a) the gegenion need only rotate to be in a position to donate the nucleophilic phenyl group to the cationic center, and a similar scheme is proposed for the Grignard reagent reacting as in b. However, with the copper-promoted reagent, one must assume that the lifetime of the ion pair is large, that is, that coordination of the cation with the phenyl anionoid species is slow enough to allow competitive migration of the anion to a position from which phenyl can be donated to the opposite face of the cation to give **3**-Ph. The postulated longer lifetime is reasonable, as the enhanced reactivity over the simple Grignard reagent speaks for a more stable ion pair. The fact that *no* mixing of **1** and **2** species occurs even in the copper-promoted reactions speaks against the idea of radical intermediates, as it seems impossible to make any reasonable argument involving geminate recombination, considering the stereochemistry noted. Obviously S_N2 mechanisms are also excluded.

Although these Grignard reactions proceeded, neither 1-Cl nor 2-Cl reacted with phenyllithium, with CuBr-promoted phenyllithium, with lithium diphenylcuprate,[27] or with phenylcopper[28] prepared from phenyllithium with excess cuprous bromide, that is, with phenyllithium recipes containing either excess phenyllithium or excess copper species. In each case substantially all of the starting chloride was recovered. Apparently these reagents are not electrophilic enough to promote ionization of the halide. Pentafluorophenylcopper is reported to couple with iodobenzene, methyl iodide, 1-bromoadamantane, and benzyl bromide,[29a] and with 7-chloronorbornadiene,[29b] and the authors suggest that cationic intermediates are involved in the latter three cases. It would thus appear that the electron-attracting fluorine substituents increase the electrophilicity of the copper atom enough to produce ionic intermediates. It would clearly be of interest to study the reaction of 1 and 2 with pentafluorophenylcopper.

Experimental Section

Coupling of *syn*-7-Chlorobenzonorbornadiene (1-Cl) with Phenylmagnesium Bromide. In 5 ml of THF, 198 mg (8 mmol) of Mg shavings was stirred in a sealed flask under N_2. Bromobenzene (0.84 ml, 8 mmol) was added *via* a syringe. The mixture was heated until all the magnesium had reacted. To the cooled flask 707 mg (4.00 mmol) of 1-Cl[30] in 15 ml of THF was added *via* syringe. The mixture was heated at reflux for 5 days. Water was then added, and the mixture was extracted with ether. The ethereal layer was washed twice with saturated sodium chloride solution. The ether layer was then dried ($MgSO_4$). Evaporation of the solvent left 816 mg of a dark oil whose pmr spectrum indicated that none of the starting chloride was present. Chromatography on an alumina column gave, upon elution with hexane, 223 mg (27%) of a solid identified as *syn*-7-phenylbenzonorbornadiene (1-Ph), whose pmr spectrum indicated that no 2-Ph was present. Recrystallization from hexane gave white needles (150 mg, 18%, mp 98.5–99°) with a pmr spectrum ($CDCl_3$) characteristic of the syn 7-substituted derivative, δ 6.75–7.35 (m, 11 H), 4.13 (q, J = 2 Hz, 2 H), 4.01 (m, 1 H).

Anal. Calcd for $C_{17}H_{14}$: C, 93.54; H, 6.46. Found: C, 93.34; H, 6.60.

Further elution of the column with benzene and finally with ether gave 303 mg (54%) of a dark oil whose pmr spectrum indicated a mixture of the 7,7′ dimers of benzonorbornadiene[15a] which were not readily separable by further column chromatography.

A similar experiment with 2-Cl[15a] for 60 hr gave 95% recovery of 2-Cl and after 30 days gave, upon chromatography, only 2-Cl (plus some biphenyl from the Grignard preparation).

Competition Reaction of *syn*- (1-Cl) and *anti*-7-Chlorobenzonorbornadiene (2-Cl) with Phenylmagnesium Bromide. The reaction was run as described above with ether as solvent and the following reagents: 195 mg (8 mmol) of magnesium, 0.84 ml (8 mmol) of bromobenzene, 353 mg (2 mmol) of 2-Cl, and 353 mg (2 mmol) of 1-Cl. After 5 days the reaction mixture was worked up as usual, yielding a yellow oil which when chromatographed on an alumina column yielded 240 mg of the mixture of dimers noted in the reaction with 1-Cl (0.85 mmol, 42% based on 1-Cl and 2-Cl) and 476 mg of a mixture of 1-Ph, 2-Cl, and biphenyl. This mixture was then chromatographed on an activated silica gel column which separated the biphenyl from the remaining two products. Pmr analysis of the remaining mixture (329 mg) indicated a 1:4.5 molar ratio of 1-Ph to 2-Cl (0.4 mmol of 1-Ph, 10%; 1.8 mmol of 2-Cl, 45%).

Cuprous Bromide Catalyzed Reaction of 2-Cl with Phenylmagnesium Bromide. Cuprous bromide (300 mg, 2 mmol) was added in 2 ml of ether to the Grignard reagent prepared from 194 mg (8 mmol) of Mg and 0.84 ml (8 mmol) of bromobenzene in 2 ml of ether. The solution immediately turned dark red, then black. The mixture was then heated at reflux for 20 min, and 707 mg (4 mmol) of 2-Cl in 20 ml of ether was then added. After 9 days the solution as worked up in a manner similar to that for the noncatalyzed reaction, yielding 714 mg of a yellow liquid whose pmr spectrum indicated a ratio of 2-Cl:2-Ph of 5.7:1 (3.4 mmol of 2-Cl, 85%, and 0.52 mmol of 2-Ph, 13%).

Chromatography on alumina gave 412 mg (2.3 mmol, 58%) of 2-Cl upon elution with hexane. Further elution with benzene and finally with ether gave 195 mg (0.48 mmol, 12%) of a solid with a pmr spectrum similar to that reported[25] for *anti*-7-phenylbenzonorbornadiene (2-Ph). The 2-Ph was recrystallized out of hexane, yielding a white solid (mp 87–88°) with the following pmr spectrum ($CDCl_3$): δ 7.04–7.33 (m, 9 H), 6.58 (t, J = 2 Hz, 2 H), 4.15 (q, 2 H), 3.96 (broad s, 1 H). Pmr absorption attributable to 1-Ph was found in neither the crude product nor the eluted products.

Cuprous Bromide Catalyzed Reaction of 1-Cl with Phenylmagnesium Bromide. The reaction was run as with the anti epimer using 353 mg (2 mmol) of 1-Cl, 0.42 ml (4 mmol) of bromobenzene, 97 mg (4 mmol) of Mg, and 150 mg (1 mmol) of CuBr. After 4 days of reflux in ether the mixture was worked up and yielded 430 mg of a yellow oil whose pmr spectrum indicated a mixture identified as biphenyl (1.0 mmol), 1-Ph (0.72 mmol, 36%), and 3-Ph (0.57 mmol, 29%). Chromatography on an alumina column gave 120 mg (27%) of *endo*-2-phenyl-4-benzotricyclo[4.1.0.$0^{3,7}$]heptene (3-Ph), mp 87.5–88°, upon elution with hexane. Recrystallization from hexane gave an analytical sample characterized by the following pmr spectrum ($CDCl_3$):[31] δ 6.5–7.4 (m, aromatic, 9 H), 4.10 (1 H, d of d, H-3, J = 8.3 Hz), 3.75 (1 H, d of t, H-2, J = 8.3, 2.5 Hz), 3.22 (1 H, d of t, H-1, J = 5.5, 3 Hz), 2.62 (1 H, t, H-6, J = 5 Hz), and 2.26 (1 H, m, H-7, J = 5.5, 3, 2.5 Hz).

Anal. Calcd for $C_{17}H_{14}$: C, 93.54; H, 6.46. Found: C, 93.30; H, 6.22.

Further elution of the column with 1% benzene in hexane gave 100 mg (25%) of 1-Ph.

Photorearrangement of 1-Ph. A 100-mg portion of 1-Ph was dissolved in 0.5 ml of ether and placed in a Pyrex nmr tube with 0.06 ml (60 mg) of distilled acetophenone. Irradiation (20 hr) with a Hanovia 450-W Model L mercury arc lamp, followed by evaporation of the solvent, gave 145 mg of a yellow oil whose pmr spectrum, after correction for acetophenone, was identical with that of the other sample of 3-Ph. This material was not separated or purified, but we judge that this would be a useful preparation of 3-Ph, if 1-Ph is available.

Attempted Coupling of *anti*-7-Chlorobenzonorbornadiene (2-Cl) with Phenyllithium. To a solution of 177 mg (1 mmol) of *anti*-7-chlorobenzonorbornadiene (2-Cl) in 5 ml of anhydrous ether (under nitrogen) was added 1.0 ml of 1.9 *M* phenyllithium (Alfa) *via* syringe. The mixture was heated at reflux for 3 days. Water was then added and the solution was washed with two 20-ml portions of water. The ether layer was concentrated, yielding a yellow liquid. The crude product was purified on a column of alumina, yielding 164 mg (93%) of the starting chloride. A similar experiment was performed in distilled THF with a reaction time of 22 days and gave only the starting chloride. A third experiment was also performed with freshly prepared phenyllithium and a reaction time of 7 days in ether resulted in 85% recovery of the starting chloride.

Attempted Coupling of *syn*-7-Chlorobenzonorbornadiene (1-Cl) with Phenyllithium. In freshly distilled THF, 528 mg (3 mmol) of 1-Cl and 4.5 ml (2 *M*, 9 mmol) of freshly prepared phenyllithium were refluxed for 7 days. Work-up similar to that used for the reactions of 2-Cl yielded 835 mg of a yellow oil whose pmr spectrum indicated a ratio of 1:13:11 for 1-Br:1-Cl:Ph_2 and recovery of 2.56 mmol (85%) of 1-Cl and 0.20 mmol (6.7%) of 1-Br. The formation of 1-Br is apparently due to capture of 4 by lithium bromide.[32]

Attempted Cuprous Bromide Catalyzed Coupling of *anti*-7-Chlorobenzonorbornadiene (2-Cl) with Phenyllithium. To 4 ml (2 *M*, 8 mmol) of freshly prepared phenyllithium was added 300 mg (2 mmol) of CuBr under nitrogen. After 20 min, 707 mg (4 mmol) of 2-Cl was added in ether, making a total volume of 20 ml. The solution was heated at reflux for 7 days, after which time the solution had turned yellow. Work-up similar to that for the uncatalyzed phenyllithium reactions yielded 1.15 g of a dark oil whose pmr spectrum indicated recovery of 3.9 mmol (98%) of the starting chloride (2-Cl), as well as biphenyl.

Attempted Coupling of Lithium Diphenylcuprate with *anti*-7-Chlorobenzonorbornadiene (2-Cl). Lithium diphenylcuprate was prepared[27] by adding 12 ml (2 *M*, 24 mmol) of freshly prepared phenyllithium to 1.72 g (12 mmol) of CuBr which was in ether solution under nitrogen at 0°. The ice bath was removed and to this solution 707 mg (4 mmol) of 2-Cl was added in 20 ml of ether. The mixture was heated slowly and as the ether evaporated 25 ml of distilled THF was added. This mixture was heated at reflux for 3 days. Aqueous ammonium chloride was added with additional ether, and the ether layer was washed three times with a saturated NaCl solution and one time with water. The aqueous layer had a deep blue color which faded to a clear solution by the final washing. The ether layer was then dried over $MgSO_4$ and evaporated to yield 1.84 g of a yellow oil whose pmr spectrum indicated quantitative recovery of the starting chloride (2-Cl) in addition to 7 mmol of biphenyl.

Attempted Coupling of Lithium Diphenylcuprate with *syn*-7-Chlorobenzonorbornadiene (1-Cl). The reaction was run as with the anti epimer using 528 mg (3 mmol) of 1-Cl, 9 ml (2 *M*, 18 mmol) of phenyllithium, and 1.29 g (9 mmol) of CuBr. After 4 days at reflux in THF, work-up as described for the 2-Cl reaction yielded 1.97 g of a yellow oil whose pmr spectrum indicated biphenyl and recovery of 432 mg (2.46 mmol, 82%) of 1-Cl and 90 mg (0.41 mmol, 13%) of 1-Br. The products were identified by pmr absorption of the bridge protons with the 1-Cl absorption at δ 4.33–4.41 (t) and the 1-Br at δ 4.45–4.51.

Phenylcopper. As described by Costa,[28] 4 ml (2 *M*, 8 mmol) of freshly prepared phenyllithium was added to a solution of CuBr (1.15 g, 8 mmol) in 30 ml of ether under nitrogen at 0°. The white solution turned yellow-brown gradually and finally a white precipitate of phenylcopper formed.

Attempted Coupling of Phenylcopper with *anti*-7-Chlorobenzonorbornadiene (2-Cl). To a suspension of 8 mmol of phenylcopper at 0° in 30 ml of ether, 707 mg (4 mmol) of 2-Cl was added in 10 ml of ether. The ice bath was removed and the solution was stirred for 7 days. The solution had a green color and water was added. The ether layer was washed two times with a saturated NaCl solution and the combined aqueous layers were reextracted with ether. The combined ether layers were then washed with an ammonium chloride solution and dried over $MgSO_4$. Evaporation yielded 1.65 g of a light yellow oil whose pmr spectrum indicated a 1:1 ratio of biphenyl and 2-Cl (660 mg, 94%).

To a suspension of 6 mmol of phenylcopper at 0°, 5 ml of dry pyridine was added, giving a dark-colored solution. After approximately 5 min, 707 mg (4 mmol) of 2-Cl was added in 10 ml of pyridine. The solution was heated at 45° for 5 days and then approximately 50 ml of 1 *M* HCl was added with 50 ml of ether. The ether layer was washed two times with 1 *M* HCl, one time with a saturated NaCl solution, one time with an ammonium chloride solution, and finally with water. The ether layer was then dried over $MgSO_4$ and evaporated, yielding 753 mg of a yellow oil whose pmr spectrum indicated a 92% recovery of the starting chloride.

Attempted Coupling of Phenylcopper with *syn*-7-Chlorobenzonorbornadiene (1-Cl). Using the same procedure as with 2-Cl, 1-Cl (528 mg, 3 mmol) was heated for 5 days with 6 mmol of phenylcopper in approximately 15 ml of pyridine. Work-up yielded 730 mg of a yellow oil whose pmr spectrum indicated recovery of 2.15 mmol (72%) of the starting chloride (1-Cl). Biphenyl was the only other product in the mixture.

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Registry No. 1-Cl, 14518-75-3; 1-Ph, 42880-72-8; 2-Cl, 10239-89-1; 2-Ph, 10239-94-8; 3-Ph, 42880-74-0; phenyl bromide, 108-86-1; phenyllithium, 591-51-5; lithium diphenylcuprate, 23402-69-9; phenylcopper, 3220-49-3.

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Stepwise Cycloadditions of Pentadienyllithiums to 1,3-Dienes

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Solutions of pentadienyllithium and either furan or toluene in tetrahydrofuran produce cyclic dimers of pentadiene both in the presence and in the absence of added 1,3-pentadiene. A stepwise mechanism is proposed for the dimerization in which the furan and toluene act as proton donors to pentadienyllithium and to 1:1 adducts of pentadienyllithium and 1,3-pentadiene. Reactions of other pentadienyllithiums and 1,3-dienes under similar conditions provide a simple, low-yield route to crossed diene dimers.

Previously we[1] reported that tetrahydrofuran (THF) solutions of pentadienyllithium (**1**) and either furan or toluene produced cyclic pentadiene dimers with and without added 1,3-pentadiene. This paper describes the pentadiene dimerizations in detail and also the formation of similar 1:1 adducts from other pentadienyllithiums and 1,3-dienes.

Results

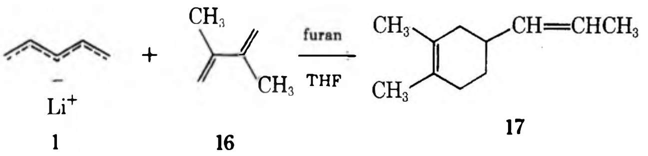
An initially equimolar THF solution of furan and pentadienyllithium (**1**), generated from 1,4-pentadiene and *n*-butyllithium, after 18 hr at 25° contained no **1** by pmr. Addition of excess D_2O to the solution followed by distillation produced furan-*2-d* in 37% yield, and two fractions less volatile than THF in 24 and 10% yields based on 1,4-pentadiene. Glpc analysis showed that the two fractions contained at least four and ten components, respectively. The lower boiling (24%) fraction was separated by preparative glpc into two components which were identified as 3-methyl-5-propenyl- and 3-methyl-4-propenylcyclohexene (**6** and **7**) by elemental analyses and comparison of their glpc retention times, mass spectra, and pmr spectra with those of the thermal dimers of 1,3-pentadiene.[2] Hydrogenation of the lower boiling distillation fraction at 1 atm over Pt produces a mixture of *cis-* and *trans*-1-methyl-3-propylcyclohexane (**8** and **9**) and *trans-* and *cis*-1-methyl-2-propylcyclohexane (**10** and **11**). The components of this saturated hydrocarbon mixture were identified by comparison of their glpc retention times, mass spectra, and pmr spectra with those of independently synthesized **8–11**. In addition to isomers **8–11** a small amount of *n*-decane was detected in the hydrogenated mixture by glpc. Isomers **9** and **10** could not be separated by the glpc conditions employed.

The higher boiling (10%) fraction obtained from reaction of **1** and furan contained two major components which were isolated by preparative glpc and identified as trimers of 1,3-pentadiene by elemental analyses, mass spectra, and pmr spectra. Hydrogenation of the higher boiling fraction over Pt at 1 atm produced a mixture with three major components which were identified as $C_{15}H_{30}$ isomers by mass spectrometry and as saturated hydrocarbons by pmr. Therefore the higher boiling fraction from reaction of **1** and furan consisted of pentadiene trimers containing one ring.

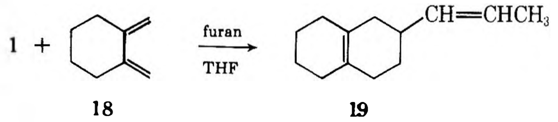
When a solution of **1** and toluene in THF was allowed to react for 48 hr at 70°, hydrolyzed, and analyzed by glpc, not only pentadiene dimers and trimers, but also isomeric phenylhexenes **12–15** were formed. Relative yields under varied conditions follow: **12** (41–68%), **13** (4–7%), **14** (13–28%), and **15** (13–28%). Compounds **12**, **14**, and **15** were isolated by preparative glpc and identified by their mass spectra (M^+ at m/e 160) and their pmr spectra shown in Table I. The two allylic methyl doublets in the pmr spectrum of **12** suggest that it is a mixture of cis and trans isomers. Compounds **14** and **15** could also be mixtures of cis and trans isomers. The structure of **13** is presumed to be isomeric to those of **12**, **14**, and **15** because of its similar glpc retention time.

The pentadiene dimers obtained from reaction of **1** and toluene were hydrogenated and then analyzed by glpc. Reactions of **1** and toluene with three different mixtures of *cis-* and *trans*-1,3-pentadiene also were studied. Externally added 1,3-pentadiene caused lower yields (based on **1**) of pentadiene dimers and resulted in somewhat different relative yields of **8–11** after hydrogenation. Results of typical experiments appear in ref 1.

When 2,3-dimethyl-1,3-butadiene (**16**) was added slowly to a mixture of **1** and furan in THF at 25°, a mixture of isomeric crossed dimers (**17**) of pentadiene and **16** was isolated by preparative glpc. The yield of **17** depended on reactant and furan concentrations and addition and reaction times as shown in Table II. Structural assignment of mixture **17** is based on mass, pmr, and ir spectra and elemental analysis.



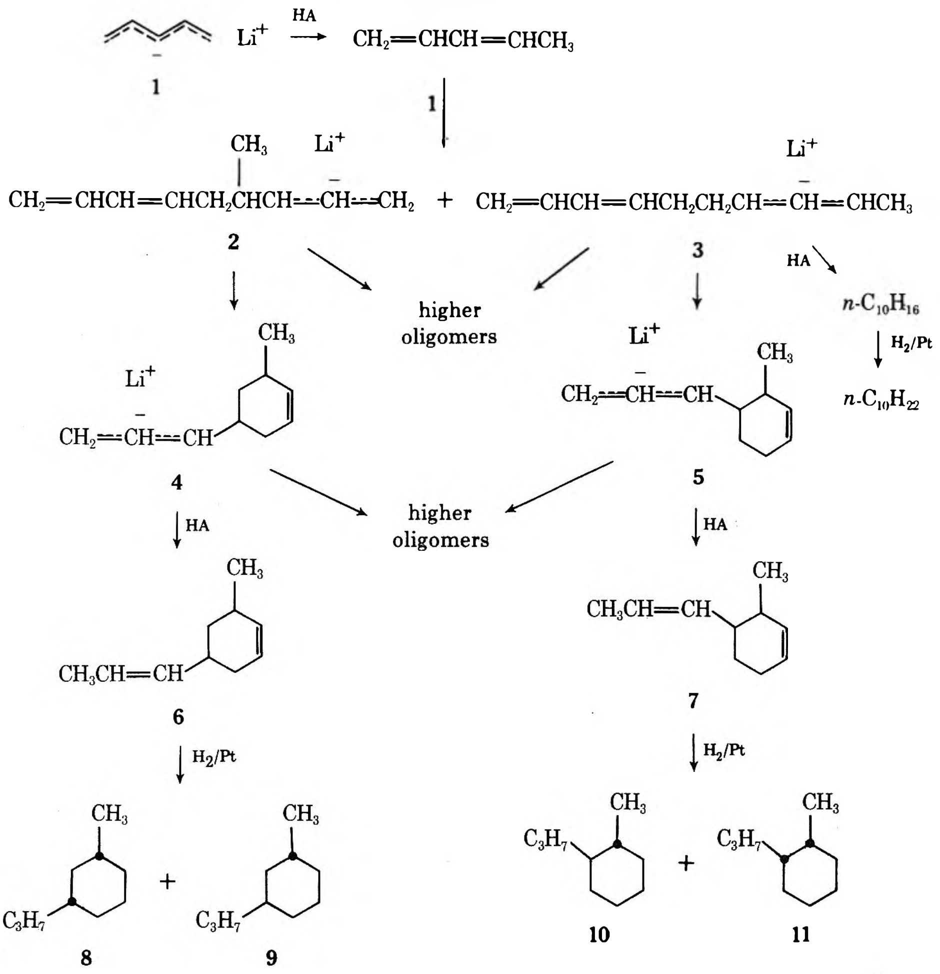
Similarly, addition of 1,2-dimethylenecyclohexane (**18**) to **1** and furan at 25° gave a 6% yield of crossed adduct **19** (presumably a mixture of isomers). The structural assignment of **19** is based on its pmr and mass spectra and elemental analysis.



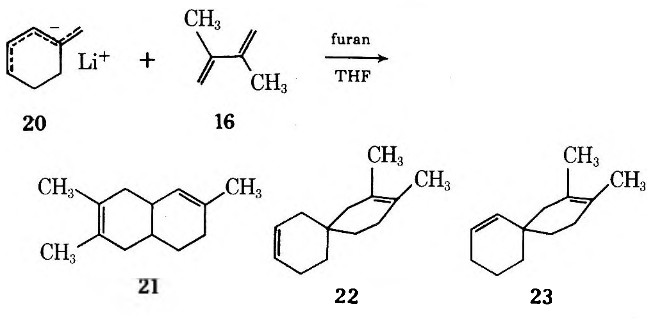
Both 1,3-butadiene and 1,3-cyclohexadiene gave small yields of possible 1:1 adducts with pentadiene when treated with **1** and furan in THF, but the products were not analyzed. 2,5-Dimethyl-2,4-hexadiene and **1** did not appear to react under conditions which produced adducts with other dienes. 4-Methyl-1,3-pentadiene formed only products of higher molecular weight under conditions which produced 1:1 adducts from **1** and **16**.

Additions of two substituted pentadienyllithiums to 1,3-dienes were explored. Solutions of **20** (generated from 4-methylenecyclohexene and *n*-butyllithium), **16**, and furan in THF at 25° produced mixtures of 1:1 adducts. Two fractions, formed in 1–3 and 8–9% yields under varied conditions, were separated by preparative glpc. The second fraction was shown to contain at least two components by analysis on a different glpc column. By glpc–mass spectrometry the first fraction and both components

Scheme I
Mechanism of Anionic Dimerization of 1,3-Pentadiene

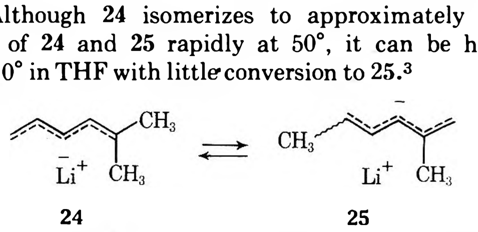


of the second fraction had molecular ions at m/e 176, which fits $C_{13}H_{20}$ isomers. Hydrogenations of the crude product mixture over Pt at 1 atm and 25° and over Raney nickel at 100 atm and 150° both gave three saturated compounds which were separated by preparative glpc and analyzed by mass spectrometry. One had M^+ at m/e 182 ($C_{13}H_{26}$), corresponding to an alkylated cyclohexane. The other two saturated compounds, formed in nearly equal amounts, both had M^+ at m/e 180 ($C_{13}H_{24}$), corresponding to two rings. Independent hydrogenation of the second (8-9%) fraction of the original reaction mixture gave the two m/e 180 compounds. From our proposed mechanism for pentadiene dimerization (Scheme I) and these mass spectral results, we tentatively assign structures **21**-**23** to the major components of the original reaction mixture. A pmr spectrum of the 8-9% fraction had a 1.5:18.5 ratio of olefinic to aliphatic protons, which might correspond to approximately a 1:1 mixture of **21** and either **22** or **23**.



Solutions of **20**, furan, and 1,3-butadiene in THF at 25° formed 1:1 hydrocarbon adducts in up to 13% yield. At least seven compounds were present in the product mixture, all of which had mass spectra with M^+ at m/e 148. Hydrogenation of the mixture over Pt at 1 atm produced a mixture containing at least six compounds, of which the four major ones had M^+ at m/e 154 ($C_{11}H_{22}$, one ring) and the two minor ones had M^+ at m/e 152 ($C_{11}H_{20}$, two rings). No further analysis of this mixture was attempted.

Treatment of 5-methyl-1,4-hexadiene with n-butyllithium in THF produces 1,1-dimethylpentadienyllithium (**24**).[3] Although **24** isomerizes to approximately at 1:1 mixture of **24** and **25** rapidly at 50°, it can be held for hours at 0° in THF with little conversion to **25**.[3]



A solution of **24**, furan, and 1,3-butadiene in THF at 0° for 12 hr ($\leq$12% of **24** could have isomerized) produced at least two 1:1 adducts, both in *ca.* 2% yield, and at least three 1:2 adducts of **24** and butadiene in 14% total yield. The adduct mixtures had mass spectra with M^+ at m/e 150 and 204, respectively, but no further attempts were made to characterize them.

Discussion

Four methods now are available for dimerization of 1,3-pentadiene. Photolysis[4] and Ni catalysis[5] produce mainly divinylcyclobutanes and 1,5-cyclooctadienes.

Table I
Pmr Spectra of Phenylhexenes[a]

	Chemical shift, δ					
	a	b	c	d	e	f
$C_6H_5CH_2{}^a\overset{CH_3{}^c}{CH^b}CH^d{=}CH^eCH_3{}^f$ (**12**)	2.6 (m)	2.6 (m)	0.9 (d, J = 6 Hz)	5.3 (m)		1.5 (two doublets)
$C_6H_5CH_2{}^aCH_2{}^bCH^c{=}CH^dCH_2{}^eCH_3{}^f$ (**14**)	2.6 (m)	1.8–2.5 (m)	5.4 (m)		1.8–2.5 (m)	0.9 (m)
$C_6H_5CH_2{}^aCH_2{}^bCH_2{}^cCH^d{=}CH^eCH_3{}^f$ (**15**)	2.6 (t)	1.6–2.0 (m)		5.4 (m)		1.6–2.0 (m)

[a] Spectra were obtained with dilute CCl_4 solutions. Integrated areas of signals support the assignments.

Table II
Products from Reaction of Pentadienyllithium (1) and 2,3-Dimethyl-1,3-butadiene (16) in THF at 25°

Concn			Addn time, hr	Reaction time, hr	Yield,[a] %	
1, *M*	**16**, *M*	furan, *M*			**17**	**6** + **7**
0.35	0.71		0.8	5	3.5	0
0.29	0.60	0.60	0.3	0.9	9.4	0
0.22	0.88	0.88	1.0	4.8	14.3	0
0.22	0.88	0.88	0.3	4	9	0
0.19	0.19	1.9	0.8	9	5.7	2.9
0.19	0.38	1.9	0.7	9	10.3	2.2
0.20	0.80	2.0	0.8	17	13	*b*

[a] Yields based on **1** were determined by comparison of glpc peak areas to an internal standard, dodecane. [b] No yield was determined.

Thermolysis produces 50–90% 3-methyl-4-propenylcyclohexenes (**7**),[2] while our anionic route produces more **6** than **7**.

The mechanism in Scheme I explains production of pentadiene dimers from pentadienyllithium and furan or toluene in THF. (Some isomeric denotations have been omitted for brevity). Our mechanism for additions of pentadienyllithiums to 1,3-dienes is based on the Ziegler[6] mechanism for initiation and propagation of anionic diene polymerization. Formations of other simple 1:1 adducts and small oligomers from strong nucleophiles and 1,3-dienes proceed by similar mechanisms. Allyllithiums have been prepared by addition of alkyllithiums to 1,3-dienes and examined by pmr spectroscopy.[7] 1-(*N,N*-Dialkylamino)-2-butenes have been prepared from alkyllithiums, dialkylamines, and 1,3-dienes.[8] Phenylhexenes similar to the ones we isolated from **1** and toluene have been prepared from toluene and isoprene with an organosodium initiator.[9] Polymerization of 1,3,6,8-nonatetraene with a coordination-type catalyst gives a polymer with repeating 5-propenyl-$\Delta^{1,2}$-cyclohexen-3-yl units[10] by a cyclization analogous to formation of our **6**.

In Scheme I the carbon acid HA participates in the reaction in two ways, donation of a proton to **1** to produce 1,3-pentadiene and donation of a proton to the anionic dimers **3**, **4**, and **5** to produce **6**, **7**, and decatrienes. In principle cycloaddition of **1** and 1,3-pentadiene could be concerted, but the presence of *n*-decane in the hydrogenated dimers indicates strongly that the cyclic dimers arise *via* closure of the decatrienyl anions **2** and **3**.

The difference in reaction temperatures required for furan and toluene to promote pentadiene dimerization shows that toluene is a weaker acid kinetically than furan. This conclusion also is supported by an experiment in which an equimolar mixture of **1** and toluene in THF still showed some **1** in its pmr spectrum after 10 days at 25°.

Production of all possible isomers **8–11** in the cyclodimerized mixture after hydrogenation and production of phenylhexene isomers **12–15** indicate that there is no strong preference for addition of either pentadienyllithium or benzyllithium to either the 1 or the 4 position of 1,3-pentadiene.[11]

The dependence of diene dimer yields on carbon acid concentration is best illustrated by comparison of the first and third lines of data in Table II. In the absence of furan less dimer and more higher oligomers are formed. The last three lines of Table II show that more efficient use of the pentadienyllithium in cycloaddition is attained when the diene is used in excess.

The yields of our 1,3-diene dimerizations are low. In brief experiments aimed at finding another carbon acid to improve the yields, we tried diphenylmethane in place of furan and obtained even less **17** from **1** and **16**. Inclusion of hexamethylphosphoramide in the reaction mixture did not help either. The utility of our method appears to be limited to single-step preparation of cyclohexenes not readily available by other routes. Formations of an octahydronaphthalene from **1** and **18** and a spiro[5.5]undecadiene from **20** and **16** are illustrations of its potential.

Experimental Section

General. All temperatures are uncorrected. Pmr spectra were run on Varian A-60A, A-56/60, or T-60 spectrometers. Mass spectra were run on a Varian-MAT CH-5 mass spectrometer. Glpc–mass spectra were run on a Varian-MAT CH-7 or GNOM-111 mass spectrometer and a Varian 2700 series chromatograph. Ir and uv spectra were run on Perkin-Elmer Models 521, 237B, and 202 spectrophotometers. Analytical glpc was run on a Hewlett-Packard Model 700 chromatograph with thermal conductivity detection, and preparative glpc was run on a Varian Model A-90-P chromatograph. Glpc yields were not corrected with thermal conductivity response factors, but these corrections should be slight for isomeric compounds. All reactions with organometallic compounds were run under nitrogen or argon in dry glassware. THF was distilled from sodium naphthalenide or CaH_2. Furan was distilled from CaH_2. Toluene was distilled and stored over sodium wire.

Glpc columns were as follows: A, 0.125 in. × 10 ft, 20% Apiezon L on 60/80 Chromosorb P; B, 0.25 in. × 10 ft, 20% Apiezon L on 60/80 Chromosorb W; C, 0.125 in. × 4 ft, 20% Apiezon L on 60/80 Chromosorb W; D, 0.25 in. × 6 ft, 30% of a solution of 26% $AgNO_3$ in ethylene glycol on 60/80 firebrick; E, 0.375 in. × 10 ft, 20% Carbowax 20M on 60/80 Chromosorb W; (F) 0.125 in. × 21 ft, 10% DEGS on 60/80 Chromosorb W; and (G) 0.25 in. × 6 ft, 20% Apiezon L on 60–80 Chromosorb W.

Dienes. 1,3-Butadiene (Matheson) and 5-methyl-1,4-hexadiene (Chemical Samples) were used without further purification. 1,4-Pentadiene[12] was >96% pure by glpc (C, 45°), bp 24–26.5° (lit.[12] bp 26–27.5°). 4-Methyl-1,3-pentadiene[13] was isolated 99% pure by preparative glpc (E, 85°). 2,3-Dimethyl-1,3-butadiene (**16**)[14] was pure by pmr. 1,2-Dimethylenecyclohexane (**18**)[15] was purified by preparative glpc (E, 105°). A commercial mixture of 1,3-pentadienes (Aldrich) was distilled from CaH_2 and contained by glpc (D, 23°) 26% *trans*- and 61% *cis*-1,3-pentadiene and 13% cyclopentene. *cis*-1,3-Pentadiene[16] contained 81% *cis*-1,3-pentadiene and 19% cyclopentene by glpc (D), and *trans*-1,3-pentadiene[16] contained 75% *trans*- and 13% *cis*-1,3-pentadiene and 12% cyclopentene by glpc (D). 4-Methylenecyclohexene was synthesized by a method similar to that of Gosselink.[17]

Reactions of Pentadienyllithiums with Dienes. General. Solutions of pentadienyllithiums **1**, **20**, and **24** were generated by treatment of appropriate 1,4-dienes with *n*-butyllithium in THF[18] and aged for 8–16 hr to destroy excess *n*-BuLi.[19] A solution of the 1,3-diene, furan or toluene, and glpc standard (if employed) in THF was added with stirring. After varying periods, the reaction was terminated by addition of water. Products were dissolved in ether, washed with water and saturated aqueous NaCl solution, dried, and either distilled or freed of ether and analyzed by glpc.

Reaction of 1 with Furan. To a solution of 0.147 mol of 1 (from 10.0 g 1,4-pentadiene) in THF was added 10.1 g (0.149 mol) of furan at 25°. Disappearance of 1 was followed by pmr of a small sample. After 18 hr, 1 could not be detected, and excess furan was distilled. A sample removed from the reaction flask showed the pmr spectrum of 2-lithiofuran: δ 7.8 (d, 1 H), 6.3 (d, 1 H), 6.1 (d of d, 1 H, J_{34} = 3.0, J_{45} = 1.5 Hz). The reaction mixture was quenched with excess D_2O and distilled to yield 3.7 g (37% by glpc, F, 50°) of furan-*2-d* in a mixture with hydrocarbons and THF. Pmr of the distillate (CCl_4) showed 1.0 atom D at the 2 position. After hydrolysis and extraction with ether, distillation of the products gave fractions of 2.40 [24%, bp 55–75° (28 Torr)] and 1.05 g [10%, bp 63–83° (0.1 Torr)]. An oily residue and solid (6.1 g, 61%) did not distil. The lower boiling fraction contained at least four compounds by glpc (A, 136°), and had the following spectral properties: uv (hexane) end absorption at 205 nm (ϵ 1400); mass spectrum (70 eV) *m/e* 136 (M^+); pmr ($CDCl_3$) δ 5.0–5.8 (m, 4 H), 0.8–2.8 (m, 12 H). A mixture of the major components of the lower boiling fraction (6 and 7) was purified by preparative glpc (B, 165°).

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.12; H, 11.68.

The higher boiling fraction contained at least ten compounds by glpc (B, 247°). The two major components were isolated by preparative glpc (B, 247°). They had similar spectral properties: mass spectrum (70 eV) *m/e* 204 (M^+); pmr (CCl_4) δ 4.8–6.2 (6 H), 0.9–3.0 (18 H).

Anal. (a mixture of two major components). Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.04; H, 11.74.

Hydrogenation of the higher boiling fraction by the method used for 6 and 7 produced a mixture containing three major components, separated by preparative glpc (B, 250°). The mass spectrum (18 eV) for each showed M^+ at *m/e* 210.

Hydrogenation of 6 and 7. A 0.5-g sample of the lower boiling fraction obtained from reaction of 1 with furan was hydrogenated in 10 ml of ethanol at 1 atm for 12 hr over Pt generated from chloroplatinic acid.[20] In the product mixture four components were resolved by glpc (A, 136°, relative areas 4:40:46:10). The three major components were isolated by preparative glpc (B, 165°) and shown to be **8**, a mixture of **9** and **10**, and **11**, respectively, by identity of their glpc retention times and mass and pmr spectra with those of authentic samples. The first (4%) component was shown to be *n*-decane by comparison of its glpc (A) retention time with that of an authentic sample. In an independent experiment **11** isomerized ($\leq$3%) to the more stable **10** under the above hydrogenation conditions.

***trans-* and *cis*-1-Methyl-2-propylcyclohexane (10 and 11).** The crude product from a Grignard reaction of 0.1 mol of 2-methylcyclohexanone (Aldrich) and *n*-propylmagnesium bromide was distilled from 10 drops of H_2SO_4 to give 4.36 g (bp 145–175°) of a mixture which contained 10% 2-methylcyclohexanone and at least three other components by glpc (B, 140°).

A 1.0-g sample of the mixture was hydrogenated (5 ml of hexane, 150 mg of Raney Ni, 100 atm, 150°, 6 hr) to two major products, present in a 34:66 ratio by glpc (A, 136°). Samples of these were collected by preparative glpc (B, 138°). The first (34%) compound was **10**: mass spectrum (70 eV) *m/e* 140 (M^+); pmr (CCl_4) complex pattern at δ 0.6–2.0 with singlets at δ 0.90 and 0.95. The second (66%) compound was **11**: mass spectrum (70 eV) *m/e* 140 (M^+); pmr (CCl_4) δ 0.83 (d, *J* = 6–7 Hz), 1.21 (s), 1.39 (s, shoulder at 1.43), 1.60 (broad s), 1.88 (m); the ratio of areas of the methyl signals (δ 0.8–0.9) to other signals was 6:14.

Assignment of isomeric structures **10** and **11** was verified by two methods. (1) Their pmr spectra are strikingly similar to those of *trans*- and *cis*-1,2-dimethylcyclohexane, which have been analyzed in detail.[21] (2) Equilibrations of pure samples of **10** and **11** over 5% Pd/C[22] at 241 ± 2° for 99 hr each gave a mixture of 75% **10** and 25% **11** (glpc, A, 136°), confirming that **10** is the more stable trans isomer.

***cis*- and *trans*-1-Methyl-3-propylcyclohexane (8 and 9).** From 3-methylcyclohexananone (Aldrich) by the method given above for **10** and **11** a 67:33 mixture (glpc, A, 136°) of **8** and **9** was prepared and separated (preparative glpc, B, 135°). The component of shorter retention time was **8**: mass spectrum (70 eV) *m/e* 140 (M^+); pmr (CCl_4) δ 0.88 (d, *J* = 2 Hz), 0.89 (t, *J* = 3.5 Hz), 1.18 (broad d, *J* = 2 Hz), 1.60 (s), 1.77 (s). The component of longer retention time was **9**: mass spectrum (70 eV) *m/e* 140 (M^+); pmr (CCl_4) δ 0.88 (m), 1.2 (m), 1.4 (m); relative areas of the δ 0.88 and lower field signals were 6:14. The structures of **8** and **9** were verified by (1) comparison with the pmr spectra of *cis*- and *trans*-1,3-dimethylcyclohexane[21] and (2) equilibration over 5% Pd/C[22] to a 79:21 mixture of **8**:**9**, confirming **8** as the more stable cis isomer.

Reaction of 1 and Toluene. A THF solution of 0.7 *M* 1 and 4 *M* toluene was stirred for 48 hr at 70°. Products were isolated by the general method and analyzed by glpc (C, 120°) to contain a 17% yield (based on 1) of pentadiene dimers and a 12% yield (based on 1) of a mixture of phenylhexenes (in order of increasing retention time) **12**:**13**:**14**:**15** in relative yields of 54:6:17:24. Samples of **12**, **14**, and **15** were isolated for mass and pmr spectra by preparative glpc (B, 210°).

Reactions of 1 and 1,3-pentadiene were carried out by the general method. In the absence of a proton donor (furan or toluene) no pentadiene dimers were found by glpc. In the presence of toluene at many reactant concentrations and reaction times, some of which are in ref 1, varied yields (after hydrogenation) of *n*-decane and **8–11** were determined by comparison of glpc (A) peak areas to those of mixed *cis*- and *trans*-decalin (internal standard). Small amounts of 4-methylnonane would not be detected by this glpc analysis.

Reactions of 1 and 2,3-dimethyl-1,3-butadiene (16) were carried out by the general method. A mixture of the cis and trans isomers of 1,2-dimethyl-4-(1-propenyl)cyclohexene (**17**) was isolated by preparative glpc (G, 190°): pmr (CCl_4) 4.7–5.6 (m), 2.4–2.6 (m), 1.8–2.3 (m), 1.66 (s), 1.56 (s), 1.1–1.4 (m); ratio of olefinic/aliphatic areas was 2:16; mass spectrum (70 eV) *m/e* 150 (M^+).

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 88.00; H, 11.97.

Reaction of 1 and 1,2-Dimethylenecyclohexane (18). A solution of 1 (17 mmol) and 11.4 g (170 mmol) of furan in 110 ml of THF was stirred at 25° while a solution of 1.4 g (13 mmol) of **18** in 100 ml of THF was added dropwise over 2 hr. The solution was stirred for an additional 2 hr and worked up by the general method. Distillation (after addition of 1 ml of hexadecane) gave 0.56 g [bp 40–50° (30 Torr)] of **18** and 1.30 g [bp 90–140° (7 Torr)] of a mixture containing 10% **19** (0.13 g, 0.68 mmol, 6%) and 90% hexadecane by glpc (B, 204°). Purification of **19** by preparative glpc (B, 200°), gave material with the following spectra: pmr ($CDCl_3$) δ 5.0–5.5 (m, 2 H), 1.0–2.3 (m, 18 H); mass spectrum (70 eV) *m/e* 176 (M^+).

Anal. Calcd for $C_{13}H_{20}$: C, 88.64; H, 11.36. Found: C, 88.35; H, 11.50.

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Registry No. 1, 42806-72-4; **6**, 1611-23-0; **7**, 1611-25-2; **8**, 42806-75-7; **9**, 34522-19-5; **10**, 42806-77-9; **11**, 4926-71-0; **12**, 42806-79-1; **14**, 35008-86-7; **15**, 23086-43-3; **16**, 513-81-5; *cis*-**17**, 42806-82-6; *trans*-**17**, 42806-83-7; **18**, 2819-48-9; **19**, 42806-85-9; furan, 110-00-9; 2-lithiofuran, 2786-02-9; 2-methylcyclohexanone, 583-60-8; 3-methylcyclohexanone, 591-24-2; toluene, 108-88-3; *cis*-1,3-pentadiene, 1574-41-0; *trans*-1,3-pentadiene, 2004-70-8.

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Halogenated Ketenes. XXV. Cycloadditions with Allenes[1]

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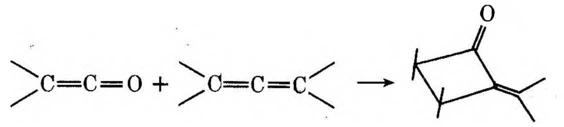
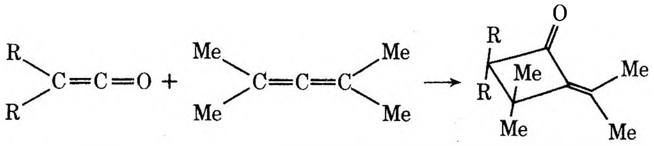
The cycloaddition of variously substituted ketenes with tetramethylallene, 1,2-cyclononadiene, and 1-methyl-1,2-cyclononadiene to give α,β-unsaturated cyclobutanones is described. Tetramethylallene and 1,2-cyclononadiene exhibit unusual reactivity in such cycloadditions. Several other allenes investigated were very unreactive.

Allenes undergo cycloaddition reactions with ketenes to yield α,β-unsaturated cyclobutanones. Tetramethylallene exhibited unexpected reactivity in cycloadditions with dimethyl- and diphenylketenes as reported by Hasek and coworkers in 1965.[2] Moore and coworkers have reported the cycloaddition of *tert*-butylcyanoketene and 1,2-cyclononadiene and revealed that, when the diene is partially resolved, both epimers show appreciable optical activity.[3] This type of stereospecificity has also been reported for the cycloaddition of dimethylketene with 1,3-dimethylallene and 1,2-cyclononadiene.[4,5] We now report on an investigation into the general nature of the cycloaddition of ketenes and allenes with particular emphasis on halogenated ketenes.



The reaction of ketenes with tetramethylallene is a 1,2-cycloaddition reaction and can be generally represented as follows.



The α,β-unsaturated cyclobutanones and the yields of the preparations are shown in Table I. The infrared spectra of the cycloadducts revealed the carbonyl absorptions at 1740–1760 cm^{-1} and the C=C absorptions at 1660 cm^{-1}.

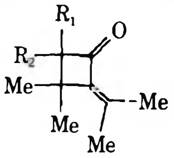
The cycloadditions of the halogenated ketenes and tetramethylallene were effected whereby the ketene was generated in the presence of the diene. This was accomplished by the triethylamine dehydrohalogenation of an appropriately substituted acid halide in refluxing hexane containing tetramethylallene. The order of addition of acid halide and amine was very critical. If the acid halide is added to a refluxing solution of hexane, tetramethylallene, and triethylamine, in some cases no cycloadduct can be isolated and in others a very small amount. This is the result of the amine reacting with the cycloadduct as it is formed. Conversely, the addition of triethylamine to the acid halide, hexane, and the diene results in a much improved yield in spite of the fact that this order of addition is desirable for the formation of α-halovinyl esters.[6] Unfortunately, some of the α-halovinyl ester is produced and is difficult to separate from the cycloadduct.

The cycloadducts of phenylmethyl- and phenylethylketenes with tetramethylallene were prepared by combining tion of the amine at −78° prior to the addition of the allene. Subsequent warming to room temperature produces a 25% yield of the cycloadduct.

The cycloadducts of phenylmethyl- and phenylethylketenes with tetramethylallene were prepared by combining equimolar amounts of the insolable ketene and the allene at room temperature.

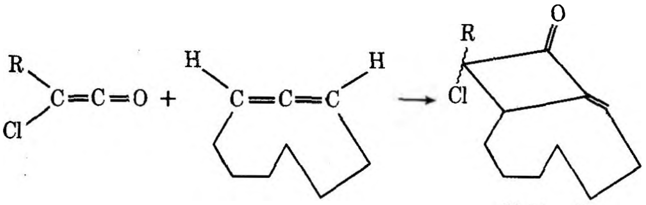
The nmr data for the tetramethylallene cycloadducts are recorded in Table II. The two methyl groups of the isopropylidene substituent are in different environments and thus are revealed as two singlets in the spectra (δ 1.7–1.9 and 1.95–2.1). The methyl protons closest to the carbonyl are expected to be further downfield. The two methyl groups attached to the 3 carbon of the cyclobutanone are above and below the plane of the ring and will be in identical environments only when the substituents on the ketene are identical (a symmetrical ketene). This is evident in the dichloroketene (IV) and bromochloroketene (V) cycloadducts in that IV shows only one singlet at δ 1.5 for the two methyl groups and V reveals two singlets at δ 1.5 and 1.6; yet it is interesting to note that, in the ethylchloroketene adduct (III), these methyl groups occur at identical chemical shifts. The spectrum of the methylbromoketene adduct (II) revealed five singlets with equivalent areas as expected. However, the methylchloroketene adduct (I) revealed only four singlets in a ratio of 2:1:1:1. Apparently, the methyl of the ketene functionality and the methyl trans to the chloro substituent overlap at δ 1.4.

Table I
Cycloadducts from Halogenated Ketenes and Tetramethylallenes



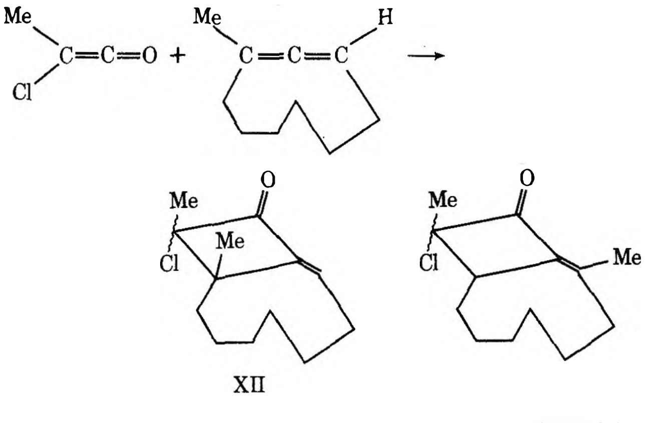
Compd	R₁	R₂	Yield, %
I	Me	Cl	72
II	Me	Br	65
III	Et	Cl	70
IV	Cl	Cl	55
V	Cl	Br	45
VI	Cl	H	25
VII	Me	H	20
VIII	Me	Ph	90
IX	Et	Ph	90

The *in situ* cycloaddition of 1,2-cyclononadiene with methylchloroketene and dichloroketene occurred smoothly and in good yield (72 and 75%, respectively). The infrared spectra revealed C=C absorptions at 1670 cm^{-1} and carbonyl absorptions at 1770 cm^{-1}. The carbonyl absorptions are higher than those observed for the tetramethylallene adducts, but this is probably to be expected because of the strain imposed by the rigid cyclic system.



X, R = Cl
XI, R = Me

Likewise the cycloaddition of methylchloroketene and 1-methyl-1,2-cyclononadiene occurred readily to yield the expected adduct in 70% yield. The nmr spectrum revealed that both isomers were produced with a predominance of that isomer resulting from cycloaddition with the least substituted double bond.

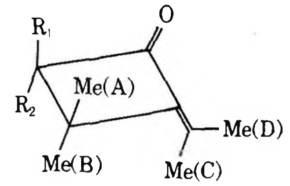


XII

Several of the other allenes which were investigated included phenylallene, 1,2-nonadiene, 1,1-dimethylallene, allene, and trichloromethylallene. In all of these cases, either no cycloadduct could be detected or a very small amount was produced.

Cyclopentadiene is one of the most reactive olefinic compounds in ketene cycloaddition reactions, and tetramethylallene appears to closely parallel this diene in reactivity. In an effort to compare the two dienes a competitive experiment was performed and it was found that a ratio of the two cycloadducts was 5:1 in favor of the cyclopentadiene.

Table II
Nmr Data of Tetramethylallene Cycloadducts[a]



Compd	A	B	C	D	R₁	R₂
I	1.4	1.5	1.8	2.0	Me, 1.4	Cl
II	1.4	1.5	1.9	2.1	Me, 1.7	Br
III	1.4	1.4	1.8	2.0	Et, 1.85 (q), 1.1 (t)	Cl
IV	1.5	1.5	1.9	2.0	Cl	Cl
V	1.5	1.6	1.9	2.1	Cl	Br
VI	1.45	1.3	1.8	2.0	Cl	H, 4.1
VII	1.4	1.2	1.7	1.95	Me, 1.0 (d)	H, 2.5 (q)
VIII	1.5	0.9	1.8	2.1	Me, 1.4	Ph, 7.2 (m)
IX	1.5	0.9	1.8	2.1	Et, 1.95 (q), 0.75 (t)	Ph, 7.2 (m)

[a] All δ values are singlets unless otherwise noted.

Tetramethylallene is obviously not typical of all the allenes regarding ketene cycloadditions. Of the allenes studied, only tetramethylallene and 1,2-cyclononadiene produced significant amounts of cycloadducts. The reactivity of the cyclononadiene is probably due to relieving the strain in the cyclic system. The tetramethylallene reactivity is apparently due to the presence of the four methyl groups which are electron releasing, thus increasing the electron density of the cumulative system. Generally, the more nucleophilic the diene, the more reactive is the diene in a ketene cycloaddition.

Experimental Section

Proton nmr spectra were recorded on Jeolco Minimar 60-MHz and Jeolco PS-100 nmr spectrometers employing tetramethylsilane as an internal standard and CCl_4 as the solvent. Vpc was performed on an F & M Scientific Model 700 gas chromatograph with a 10 ft × 0.25 in. column packed with 10% SE-30 on acid-washed Chromosorb W (80–100). Solvents and triethylamine were distilled from sodium and stored over Linde type 4-A molecular sieve. Tetramethylallene was obtained by the $AlCl_3$-catalyzed rearrangement of the tetramethylcyclobutadione dimer of dimethylketene followed by pyrolysis over a hot wire. The other allenes were prepared by the Skattebøl method.[7]

General Procedure for *in Situ* Ketene–Allene Cycloadditions. A 0.075-mol portion of triethylamine in 20 ml of dry pentane or hexane was added dropwise with stirring to a refluxing solution of 0.075 mol of acid halide and 0.10 mol of allene in 150 ml of dry pentane or hexane. After the addition was complete, the mixture was stirred for another 1 hr at reflux and then stirred at room temperature overnight. The mixture was filtered and the solvent was evaporated. Vacuum distillation of the filtrate provided the α,β-unsaturated cyclobutanone.

2-Chloro-4-isopropylidene-2,3,3-trimethylcyclobutanone (I). The cycloadduct of methylchloroketene and tetramethylallene was prepared in 72% yield at 70° (0.10 mm): mol wt (theory), 186.5; mass spectrum, parent peaks at m/e 186 (^{35}Cl) and 188 (^{37}Cl).

Anal. Calcd for $C_{10}H_{15}ClO$: Cl, 19.03. Found: Cl, 19.03.

2-Bromo-4-isopropylidene-2,3,3-trimethylcyclobutanone (II). Methylbromoketene and tetramethylallene cycloadded to produce a 65% yield, bp 93–95° (0.25 mm).

Anal. Calcd for $C_{10}H_{15}BrO$: Br, 34.63. Found: Br, 34.56.

2-Chloro-2-ethyl-4-isopropylidene-3,3-dimethylcyclobutanone (III). The cycloadduct of ethylchloroketene and tetramethylallene was prepared in 70% yield, bp 75° (0.1 mm).

Anal. Calcd for $C_{11}H_{17}ClO$: Cl, 17.70. Found: Cl, 17.47.

2,2-Dichloro-4-isopropylidene-3,3-dimethylcyclobutanone (IV). The cycloadduct of dichloroketene and tetramethylallene was prepared in 55% yield at 80° (0.10 mm): mol wt (theory), 207;

mass spectrum, parent peaks at *m/e* 206 (^{35}Cl, ^{35}Cl), 208 (^{35}Cl, ^{37}Cl), and 210 (^{37}Cl, ^{37}Cl).

Anal. Calcd for $C_9H_{12}Cl_2O$: C, 51.1; H, 5.79. Found: C, 51.52; H, 5.73.

2-Bromo-2-chloro-4-isopropylidene-3,3-dimethylcyclobutanone (V). Bromochloroketene and tetramethylallene yielded the cycloadduct at 85° (0.10 mm): mol wt (theory), 251.5; mass spectrum, parent peaks at *m/e* 250 (^{35}Cl, ^{79}Br), 252 (^{35}Cl, ^{81}Br; ^{37}Cl, ^{79}Br), and 254 (^{37}Cl, ^{81}Br).

4-Isopropylidene-2,3,3-trimethylcyclobutanone (VII). The cycloadduct of methylketene and tetramethylallene was prepared in a 20% yield at 40° (0.25 mm): mol wt (theory), 152; mass spectrum, parent peak at *m/e* 152.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.51. Found: C, 78.79; H, 10.54.

10,10-Dichlorobicyclo[7.2.0]undec-1-en-11-one (X). The cycloadduct of dichloroketene and 1,2-cyclononadiene was prepared in 75% yield at 108° (0.005 mm): nmr δ 1.5 (m, 8 H), 2.35 (m, 4 H), 3.3 (m, 1 H), and 6.7 (m, 1 H).

Anal. Calcd for $C_{11}H_{14}Cl_2O$: Cl, 30.47. Found: Cl, 30.64.

10-Chloro-10-methylbicyclo[7.2.0]undec-1-en-11-one (XI). The methylchloroketene and 1,2-cyclononadiene cycloadduct was prepared in 73% yield at 98–100° (0.005 mm): nmr δ 1.5 (m, 9 H), 2.0 (m, 4 H), 2.3 (m, 2 H), 2.85 (2 d, 1 H), and 6.4 (m, 1 H).

Anal. Calcd for $C_{12}H_{17}ClO$: Cl, 16.70. Found: Cl, 16.52.

Cycloaddition of Methylchloroketene and 1-Methyl-1,2-cyclononadiene (XII). The cycloaddition of this unsymmetrical allene with methylchloroketene produced both the isomers of the cycloadduct in a ratio of 2:1 with the least substituted cycloadduct predominating in a 70% yield: bp 105° (0.005 mm); ir 1770 (C=O) and 1670 cm^{-1} (C=O); nmr δ 1.5 (m, 12 H), 2.05 (m, 4 H), 2.3 (m, 2 H, allyl protons), 2.85 [(2 d for methinyl proton of one isomer) and 6.4 (t for vinyl proton of second isomer)] (1 H). The ratio of methinyl proton to vinyl proton is 2:1.

Anal. Calcd for $C_{13}H_{19}ClO$: Cl, 15.68. Found: Cl, 16.01.

2-Chloro-4-isopropylidene-3,3-dimethylcyclobutanone (VI). A 0.075-mol portion of chloroacetyl chloride was added with stirring to a solution of 0.075 mol of triethylamine in 100 ml of dry pentane at −78°. After the addition was complete, a pentane solution of 0.10 mol of tetramethylallene was added. The mixture was allowed to warm slowly to room temperature overnight. After filtration and solvent evaporation, the filtrate was vacuum distilled to yield the cycloadduct (25%): bp 75° (0.15 mm); mol wt (theory), 172.5; mass spectrum, parent peaks at *m/e* 172 (^{35}Cl) and 174 (^{37}Cl).

4-Isopropylidene-2,3,3-trimethyl-2-phenylcyclobutanone VIII). Equimolar amounts of phenylmethylketene and tetramethylallene were combined and stirred for 30 hr at 50°, bp 92 (0.05 mm).

2-Ethyl-4-isopropylidene-3,3-dimethyl-2-phenylcyclobutanone (IX). Equimolar quantities of phenylethylketene and tetramethylallene were combined and stirred for 30 hr at 50°, bp 105° (0.05 mm). .

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Registry No. I, 42915-13-9; II, 42915-14-0; III, 42915-15-1; IV, 42915-16-2; V, 42915-17-3; VI, 42915-18-4; VII, 42915-19-5; VIII, 42915-20-8; IX, 42915-21-9; X, 42915-22-0; XI, 42915-23-1; XIIA, 42915-24-2; XIIB, 42915-25-3; methylchloroketene, 13363-86-5; tetramethylallene, 1000-87-9, methylbromoketene, 29264-45-7; ethylchloroketene, 29264-44-6; dichloroketene, 4591-28-0; bromochloroketene, 42915-26-4; methylketene, 6004-44-0; 1,2-cyclononadiene, 1123-11-1; 1-methyl-1,2-cyclononadiene, 42915-27-5; chloroacetyl chloride, 79-04-9; phenylmethylketene, 3156-07-8; phenylethylketene, 20452-67-9.

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Addition of Sulfonyl Iodides to Allenes[1]

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Sulfonyl iodides add rapidly to allenes to give 1:1 adducts. The addition of sulfonyl iodides to 1,2-propadiene yields a mixture of products, including the two 1:1 adducts resulting from attack by the sulfonyl radical on both the central and terminal positions of the allenic unit. Complete kinetic control has probably not been achieved under the conditions of these additions. In contrast, the addition of sulfonyl iodides to phenylallene and 3-methyl-1,2-butadiene proceeds rapidly and in excellent yield to give only the products resulting from central attack by the sulfonyl radical, *i.e.*, $R_1R_2C{=}C(SO_2R)CH_2I$. The addition of *p*-toluenesulfonyl iodide to 2,3-pentadiene behaves in a similar fashion, giving a moderate yield of 1:1 adduct resulting from central attack. The structures of the adducts were proven by zinc–acid reduction to the unsaturated sulfones.

Although the chemistry of sulfonyl halides has been extensively investigated, most of the work has concentrated on the chemistry of the readily available sulfonyl chlorides. Much less work has been done with the relatively stable, but less readily available sulfonyl bromides, and relatively few of the highly reactive, very unstable sulfonyl iodides have been prepared.

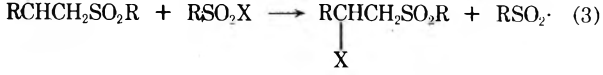
The sulfur–halogen bond of sulfonyl halides has been found to be particularly susceptible to homolytic cleavage; consequently, the free-radical reactions of sulfonyl halides comprise a large portion of their chemistry. Much of the work in this area of date has involved the free-radical addition of sulfonyl halides to olefins,[2–10] the following chain mechanism being generally accepted.

$$RSO_2X \xrightarrow{h\nu} RSO_2\cdot + X\cdot$$

or (1)

$$RSO_2X + In\cdot \longrightarrow RSO_2\cdot + InX$$

$$RSO_2\cdot + RCH{=}CH_2 \longrightarrow R\dot{C}HCH_2SO_2R \qquad (2)$$



$$R\dot{C}HCH_2SO_2R + RSO_2X \longrightarrow R\underset{\displaystyle \overset{|}{X}}{C}HCH_2SO_2R + RSO_2\cdot \qquad (3)$$

Step 1 is the chain-initiating step, which may be effected by either irradiation or the addition of an initiator (In·) such as a peroxide.

Perhaps the most extensive work with sulfonyl iodides has been carried out by Truce and Wolf,[11] who prepared a series of sulfonyl iodides and found that these would readily add to acetylenes to give the iodovinyl sulfones. Yields were generally very good, and the reaction conditions were mild.

Although the sulfonyl iodides are clearly a highly reactive, potentially useful class of compounds, relatively little is known of their chemistry. Brief investigations in these laboratories[12,13] had previously shown that *p*-toluenesulfonyl iodide could be added to three allenes to give 1:1 adducts.[14] Examination of the literature revealed that the position of initial attack of free radicals on allene has been a point of considerable controversy. Although there are relatively few examples of free-radical additions to allenes, recent studies have somewhat clarified the situation, and the general area of addition reactions of allenes has been recently reviewed.[15]

Since the π bonds of allenes are orthogonal, the initially formed radical resulting from central attack on allene resembles a primary radical rather than an allylic one, a rotation of 90° being required before full allylic stabilization is achieved.[16] Thus, it is reasonable that the isomeric vinylic radical intermediate $CH_2{=}\dot{C}{-}CH_2X$ is similar in energy to the nonplanar allylic radical intermediate $CH_2{=}C(X)\dot{C}H_2$, and Heiba[17] has indeed shown that the activation energies for forming $CH_2{=}\dot{C}{-}CH_2SPh$ and $CH_2{=}C(SPh)\dot{C}H_2$ from allene and PhS· differ only by 1.1 kcal/mol. However, $\cdot CF_3$, $\cdot CCl_3$, and $\cdot CH_3$ have been reported to add exclusively to the terminal position of allene,[15,17-20] while $(CH_3)_3Sn\cdot$, Br·, and PhS· give varying amounts of central attack.[15,17,21-23] The factors governing the orientation of addition are not well understood, but clearly polar factors cannot be a major factor owing to the difference in polarity between $\cdot CH_3$ and $\cdot CF_3$.

Considering the lack of a good theoretical explanation for the observed orientations of addition, it was desirable to examine carefully the light-initiated addition of a series of sulfonyl iodides to allenes. Besides the interest in the theoretical aspects of the orientation of addition and the expansion of knowledge of the behavior of sulfonyl iodides, the resulting 1:1 adducts contain several functional groups and might prove to be valuable synthetic intermediates.

Results

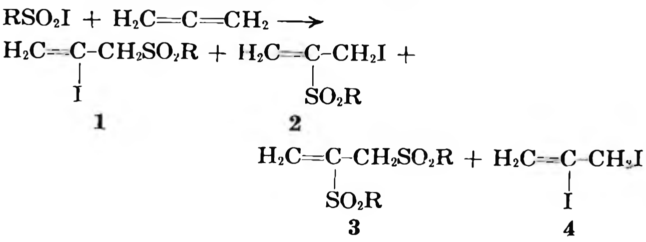
We have added five sulfonyl iodides to 1,2-propadiene. Nmr analysis (60 MHz) of the crude products indicated that a mixture of four products was produced in the addition of all five sulfonyl iodides to allene. In order to positively identify the reaction products, the crude reaction mixtures were separated by either elution chromatography or fractional crystallization. Table I illustrates the generality of the reaction and lists the isolated yields.

The 2,3-diiodopropene (**4**) was isolated and found to be a very unstable oil which liberated iodine vapors upon standing for a short time at room temperature. Considering the instability of this product, it is not surprising that occasionally this material was lost to decomposition during work-up.

A more serious problem, however, was presented by the relative instability of the allylic iodides **2a–e**. These allylic iodides were generally much less stable than the vinyl iodides **1a–e** and could be lost during lengthy column chromatography. Clearly the isolated yields are not reproducible and hence no conclusions concerning ratios of central *vs.* terminal attack can be drawn from the data in Table I. These data should therefore be considered as being representative of what might be accomplished from a synthetic viewpoint.

In order to determine the true product ratios, all five reactions were repeated under identical conditions (using benzene as a solvent) and the crude products obtained by removal of solvent at reduced pressure were analyzed immediately by nmr using a Varian XL-100 (100 MHz) instrument. The results of this analysis are shown in Table II.

Table I
Addition of Sulfonyl Iodides to Allene



$$RSO_2I + H_2C{=}C{=}CH_2 \longrightarrow \underset{\mathbf{1}}{H_2C{=}\underset{I}{C}{-}CH_2SO_2R} + \underset{\mathbf{2}}{H_2C{=}\underset{SO_2R}{C}{-}CH_2I} + \underset{\mathbf{3}}{H_2C{=}\underset{SO_2R}{C}{-}CH_2SO_2R} + \underset{\mathbf{4}}{H_2C{=}\underset{I}{C}{-}CH_2I}$$

1–4	R	Product isolated yield, %[d] 1	2	3	4
a	CH_3	32	20	0 (18)[c]	22
b	CH_3CH_2	25	12	28	31
c	$(CH_3)_2CH$	4	33	52	17
d	C_6H_5	46	0[b]	14	Trace
e	*p*-$CH_3C_6H_4$[a]	60	0[b]	16	0[b]

[a] Reaction run in ether. [b] Present by nmr, but not isolated from this reaction. [c] Isolated in a second trial by fractional crystallization. [d] Per cent yields of **3** and **4** are based on a theoretical yield of one half the number of moles of sulfonyl iodide used.

Table II
Nmr Analysis of the Addition of Sulfonyl Iodides to Allene

$$RSO_2I + H_2C{=}C{=}CH_2 \longrightarrow \mathbf{1} + \mathbf{2} + \mathbf{3} + \mathbf{4}$$

1–4	R	Material recovery, %	Product, mol % of product mixture 1	2	3	4
a	CH_3	94	35	34	17	15
b	CH_3CH_2	83	28	42	17	13
c	$(CH_3)_2CH$	37	11	66	15[b]	8
d	C_6H_5	99[a]	46	29	11	14
e	*p*-$CH_3C_6H_4$	100	47	28	13	12

[a] Average of two separate trials. [b] Incomplete resolution in the nmr reduces the accuracy of this figure.

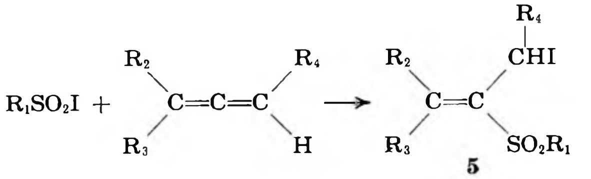
We have also added sulfonyl iodides to phenylallene, 3-methyl-1,2-butadiene, and 2,3-pentadiene, and have found that addition occurs rapidly and in generally high yield. The results of these additions are tabulated in Table III.

Note that yields were generally excellent. In all cases the only isomer observed was the internal olefin resulting from iodine abstraction by the terminal position and from central attack of the sulfonyl radical. No evidence of isomers resulting from terminal attack of the sulfonyl radical was observed in the nmr spectra of crude material. The products of the addition of sulfonyl iodides to phenylallene also seemed to be only one stereoisomer, which was tentatively assigned as β-(alkyl/arylsulfonyl)-*cis*-β-(iodomethyl)styrene, *i.e.*, a trans relationship between the aromatic ring and the sulfonyl group as expected. However, this would also probably be the most thermodynamically stable isomer in every case, and therefore a postisomerization cannot be ruled out.

Discussion

The possible mechanistic pathways involved in the addition of a sulfonyl iodide to 1,2-propadiene are outlined in Scheme I. Careful examination of these pathways reveals that *a priori* there are indeed at least four products of reaction possible. The initiation step involving the

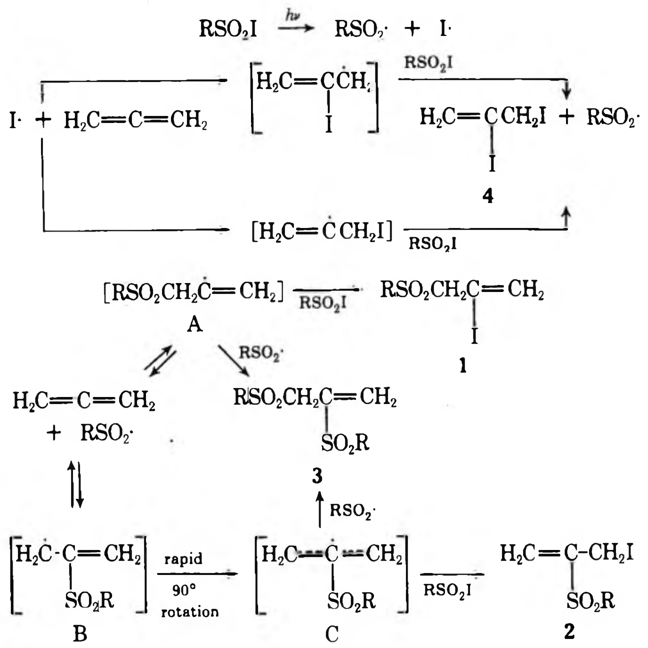
Table III
Addition of Sulfonyl Iodides to Substituted Allenes



1-4	R_1	R_2	R_3	R_4	Yield, %
a	CH_3	C_6H_5	H	H	93
b	CH_3CH_2	C_6H_5	H	H	92
c	$(CH_3)_2CH$	C_6H_5	H	H	43[a]
d	C_6H_5	C_6H_5	H	H	94
e	$p\text{-}CH_3C_6H_4$	C_6H_5	H	H	80
f	CH_3	CH_3	CH_3	H	100
g	CH_3CH_2	CH_3	CH_3	H	96
h	C_6H_5	CH_3	CH_3	H	100
i	$p\text{-}CH_3C_6H_4$	CH_3	CH_3	H	97
j	$p\text{-}CH_3C_6H_4$	CH_3	H	CH_3	45

[a] Separated from remaining phenylallene by elution chromatography.

Scheme I
Diagram of the Addition of a Sulfonyl Iodide to Allene



homolytic cleavage of the sulfur-iodine bond not only produces a chain-initiating sulfonyl radical, but also produces a free iodine atom. In the presence of excess allene, the free iodine atom will undoubtedly add to the allene molecule to give either of the two possible intermediate radicals shown. Either of these radicals should rapidly abstract an iodine atom from another molecule of the sulfonyl iodide to give 2,3-diiodopropene (4) and another sulfonyl radical.[24] Note that to this point two chain-initiating sulfonyl radicals have been produced while the two iodine atoms have been consumed. Therefore, even if all of the rest of the molecules of sulfonyl iodide are consumed in the production of the two 1:1 adducts, two sulfonyl radicals must be left to attack allene and form the 2,3-bis(alkyl/arylsulfonyl)propene (3). This analysis indicates that products 3 and 4 should be formed in equimolar amounts.

The results obtained in Table II were generally as expected, *i.e.*, the calculated yields of allylic iodides 2a-e were higher in every case than the isolated yields of Table I. Perhaps most striking was the detection by nmr of the allylic iodides 2d and 2e, which were not isolated from the crude reaction mixtures represented in Table I, apparently owing to substantial decomposition during fractional crystallization and/or chromatography.

From Table II, the calculated yield of adduct 1e is slightly less than 47%, while previously in Table I the isolated, purified yield of 1e was listed as 60%. This discrepancy may be due to a solvent effect, since the reaction listed in Table I was run in ether, while the reaction listed in Table II was run in benzene. No valid conclusion may be drawn, however, since this is the only addition to allene which was performed in ether.

The low material balance obtained in the addition of 2-propanesulfonyl iodide may be due to decomposition of the intermediate sulfonyl radical according to the following scheme.

$$(CH_3)_2CHSO_2\cdot \longrightarrow SO_2\uparrow + (CH_3)_2\dot{C}H \xrightarrow{(CH_3)_2CHSO_2I} (CH_3)_2CHI + (CH_3)_2CHSO_2\cdot$$

The biting odor of sulfur dioxide was occasionally noted above the crude reaction mixture prior to removal of solvent at reduced pressure. The solvent removal would, of course, also remove any isopropyl iodide produced during the course of the reaction. Since the extrusion of sulfur dioxide from the 2-propanesulfonyl radical would yield a relatively stable secondary radical, this decomposition is likely to occur. Other sulfonyl halides are known to undergo this type of decomposition; for example, benzyl iodide is produced in high yield from α-toluenesulfonyl iodide upon irradiation,[25] and a similar decomposition has been reported for *tert*-butylsulfonyl chloride.[26] Such destruction of the sulfonyl iodide would have no effect on the product ratios, however.

From the data in Table II, the composition of the 1:1 adducts may be calculated to show more clearly the relative ratios of products resulting from central and terminal attack of the intermediate sulfonyl radical. These data are shown in Table IV. The two aromatic sulfonyl iodides add to allene to give very nearly the same ratio of products, the difference being within experimental error. The ratios of 1:1 adducts obtained from the alkanesulfonyl iodides, however, are markedly different from each other and from the ratio obtained for the aromatic sulfonyl iodides. The trend seems to be toward more central attack as the electron-donating power of the alkyl/aryl group increases. Steric factors apparently do not play a major role in determining the orientation of attack, since 2-propanesulfonyl iodide gives a much greater amount of central attack than the arylsulfonyl iodide although the steric requirements would be expected to be similar.

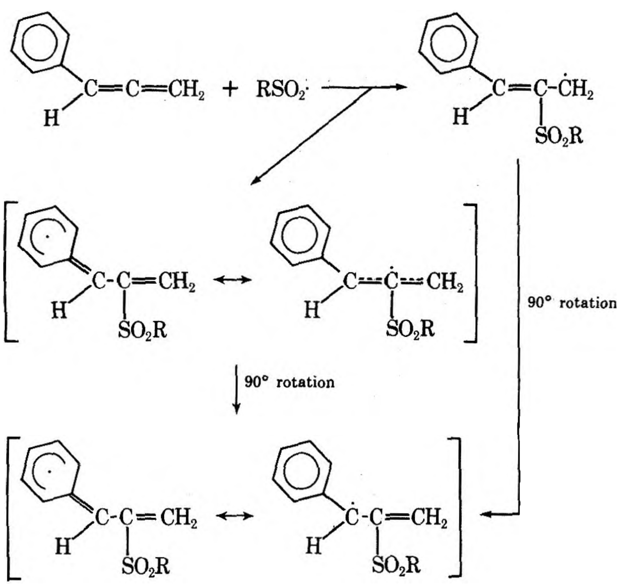
The question of greatest theoretical importance, however, is whether the observed product distribution may be directly related to the selectivity of free-radical attack, *i.e.*, whether the products are formed under strictly kinetic control. By using an excess of the sulfonyl iodide in two cases the product ratios were shifted toward increased terminal attack, indicating that in fact complete kinetic control has probably not been reached. Thus definite conclusions regarding the selectivity of attack of sulfonyl radicals on allene cannot be drawn from these data.

While the vinylic radical resulting from terminal attack of the sulfonyl radical may be comparable in energy to the nonplanar allylic radical derived from central attack, clearly any substitution on the allenic unit will upset this balance. Substitution on the allenic unit would be expected to heavily favor central attack by lowering the activation energy, and therefore should also activate the allene toward free-radical addition. The scheme for phenylallene

Table IV
Composition of the 1:1 Adducts Obtained from the Addition of Sulfonyl Iodides to Allene

Sulfonyl iodide RSO_2I	Product, % 1 (terminal attack)	2 (central attack)
CH_3SO_2I	51	49
$CH_3CH_2SO_2I$	40	60
$(CH_3)_2CHSO_2I$	14	86
$C_6H_5SO_2I$	62	38
p-$CH_3C_6H_4SO_2I$	62	38

Scheme II
Possible Intermediates Involved in the Attack of a Sulfonyl Radical on the Central Carbon of Phenylallene



shown in Scheme II, however, *implies that attack at the central carbon occurs preferentially at one of the two π bonds, i.e.*, the π bond which would yield an incipient benzylic radical rather than an incipient primary radical. Rotation in either case would give the same intermediate radical and the same products, however. The rate of rotation about single bonds is much larger (by a factor of *ca.* 10^8)[27] than chain transfer, and therefore the intermediate radical is almost certainly fully delocalized.

If chain transfer now occurs, *a priori* the iodine may be abstracted at two different positions. The preference for either of these two positions would seem to depend upon steric factors, the relative odd-electron density at the two sites, and the relative stabilities of the final products. From these considerations, the most likely point of attachment of iodine would seem to be at the terminal position. This would seem to be best from a steric point of view, since the terminal position should be more open to attack; the final product also would have the double bond in conjugation with the aromatic ring. The alternative structure $[PhC(I)HC(SO_2R){=}CH_2]$ would seem to be less likely to be observed.

Since the final product is $PhCH{=}C(SO_2R)CH_2I$ as expected, then the question of stereochemistry of the product arises. If preferential attack on one of the π bonds occurs, then the 90° rotation to achieve allylic stabilization can occur in either direction to give either a cis or a trans final product. Given the rather large size of the sulfonyl grouping, the rotation would be expected to occur to place the aromatic ring and the sulfonyl group trans. We believe that this explanation involving the relief of steric strain during the 90° rotation is preferable to the recent suggestion[28] that sulfonyl radicals are selective in the direction of approach.

Similar arguments apply to the addition of other substituted allenes such as 3-methyl-1,2-butadiene and 2,3-pentadiene.

From the experimental results the theoretical picture seems to be reasonable. Certainly substitution on the allenic unit brings about a dramatic shift in products and is the overriding factor. The addition of sulfonyl iodides to allenes would seem to be a useful method of making certain iodine-containing sulfones which could be synthetically useful intermediates. The reaction would be of greatest synthetic utility when substituted allenes are employed, since they are more reactive and, in the substituted ones just described, give a single product in very high yield.

One potential use for the 1:1 adducts is in the synthesis of various unsaturated sulfones. Although further details will be reported later, we would like to report that we have successfully replaced the iodine atom by hydrogen in both the vinyl iodides and the allylic iodides by treatment with zinc–acetic acid. This reduction also served as a proof of the assigned structure, since the reduced adducts could be readily distinguished by their nmr spectra. For example, although the nmr spectrum of 1a $[H_2C{=}C(I)CH_2SO_2CH_3]$ is similar to that of 2a $[H_2C{=}C(SO_2CH_3)CH_2I]$, the nmr spectra of the corresponding reduced adducts $[H_2C{=}CHCH_2SO_2CH_3$ and $H_2C{=}C(SO_2CH_3)CH_3]$ are quite different.

Experimental Section

All melting points and boiling points are uncorrected. The 60-MHz nmr spectra were recorded on a Varian A-60A and the 100-MHz nmr spectra were recorded on a Varian XL-100. Infrared spectra were recorded on a Beckman IR-33. The nmr spectral data are reported in chemical shift from TMS (δ 0), with s, d, t, q, and m referring to singlet, doublet, triplet, quartet, and multiplet, respectively.

Microanalyses were performed by Dr. C. S. Yeh and staff of this department. Sodium benzensulfinate and sodium *p*-toluenesulfinate were purchased from Aldrich Chemical Co. Methane- and ethanesulfonyl chloride were purchased from Aldrich and Eastman, respectively, while 2-propanesulfonyl chloride had to be prepared from Eastman's sodium 2-propanesulfonate. Allene was purchased from J. T. Baker, 3-methyl-1,2-butadiene was obtained from Chemical Samples Co., and 2,3-pentadiene was obtained as a National Bureau of Standards sample (no. 558-5s). Phenylallene was prepared by the method of Skattebøl and Solomon.[32] All sulfonyl iodide addition reactions, unless otherwise stated, were carried out in a flame-dried apparatus using spectral grade benzene as solvent, under the influence of a 250-W General Electric sun lamp, and were performed under nitrogen.

Alternate Preparation of 2,3-Diiodopropene (4). Allene was bubbled into a benzene solution of iodine under illumination from a General Electric sun lamp. The dark purple color of the iodine solution was rapidly discharged and the solution became colorless. Removal of solvent under vacuum gave 2,3-diiodopropene (4), a very unstable oil which liberated iodine upon standing at room temperature, nmr ($CDCl_3$) δ 4.34 (d, 2, $J \simeq 1$ Hz), 5.8 (d, 1, $J \simeq 2$ Hz), 6.47 (m, 1).

Preparation of 2-Propanesulfonyl Chloride. Thionyl chloride (59.50 g, 0.50 mol) was added over a period of 1 hr to a solution of sodium 2-propanesulfonate monohydrate (24.62 g, 0.15 mol) in 150 ml of DMF, the temperature of the mixture rising to approximately 50° during the addition. The mixture was allowed to stir at ambient temperature, then poured onto 300 g of ice. An additional 500 ml of water was added and the aqueous mixture was extracted with ether. The combined ether extracts were dried over $MgSO_4$ and the solvent was removed under vacuum, to give 10.4 g (48.4%) of 2-propanesulfonyl chloride of greater than 95% purity by nmr, nmr ($CDCl_3$) δ 1.58 (d, 6, $J = 6$ Hz), 3.83 (septet, 1, $J = 6$ Hz).

General Procedure for the Preparation of the Sodium Salts of the Sulfinic Acids. The appropriate sulfonyl chloride and sodium bicarbonate were added alternately in small portions to a stirred solution of sodium sulfite in water. The additions were carried out over a period of 30 min and unless stated otherwise the reaction temperatures were maintained at 75–95° throughout the addition. (Caution: In all of these reductions the gas evolution upon addition of sodium bicarbonate was very vigorous after an initial induction period. The bicarbonate must be added in very small portions to prevent much foaming.) The solution was stirred for an additional 30 min and checked to ensure that the solution was mildly basic, and the solvent was removed under reduced pressure. The resulting solid was dried, stirred with boiling absolute ethanol, and filtered. Removal of the solvent from the filtrate under reduced pressure, followed by drying of the white solid product in a vacuum desiccator, gave the sulfinic acid salt.

Sodium methanesulfinate, sodium ethanesulfinate, and sodium 2-propanesulfinate were prepared in this manner in yields ranging from 70 to 72%.

General Procedure for the Preparation of the Sulfonyl Iodides. *p*-Toluenesulfonyl iodide was prepared by adding an equivalent quantity of a concentrated ethanolic solution of iodine to a very dilute solution of the sodium arylsulfinate in water. The sulfonyl iodide precipitated from solution, and was collected and recrystallized from carbon tetrachloride. The sulfonyl iodide began to darken and decompose in a few hours at room temperature, but could be stored for several days at −10°.

The remaining sulfonyl iodides were not isolated, but were used as freshly prepared benzene solutions. When a benzene solution of iodine was vigorously mixed with an aqueous solution containing an excess of the sodium sulfinate, the intense purple color of the iodine rapidly faded and was replaced by the bright yellow-orange color of the sulfonyl iodide. When no further color change was evident, the benzene layer was separated, dried briefly over $MgSO_4$, and filtered to give a clear, yellow-orange solution of the sulfonyl iodide. Delay in using this dried sulfonyl iodide solution or exposure to strong light produced considerable decomposition of the sulfonyl iodide and darkening of the benzene solution. Hence, the solutions were used immediately and were protected from the light until the appropriate allene was present.

Preparation of *p*-Toluenesulfonyl Iodide. A solution of iodine (25.0 g, 0.0985 mol) in approximately 300 ml of absolute ethanol was added with vigorous stirring to a solution of sodium *p*-toluenesulfinate (17.8 g, 0.10 mol) in 1500 ml of water. A flocculent yellow solid rapidly precipitated and was collected and recrystallized from carbon tetrachloride. After this dried in a vacuum desiccator for 30 min, 23.5 g (84.5%) of the sulfonyl iodide was obtained as bright yellow crystals, mp 88–90° dec (lit.[29] mp 90–91° dec).

The *p*-toluenesulfonyl iodide could also be prepared by the above procedure in 74.5% yield by the use of iodine monochloride instead of iodine.

General Procedure for the Addition of the Sulfonyl Iodides to Allenes. The addition reactions were carried out at room temperature in benzene solution with the exception of the *p*-toluenesulfonyl iodide additions, which could be carried out in either benzene or ether.

When 1,2-propadiene was used as the substrate, the gaseous allene was bubbled into the freshly prepared sulfonyl iodide solution at an undetermined rate until allene was being returned by a Dry Ice condenser and the allene was certainly in excess. At this point the solution was exposed to light from a 250-W General Electric sun lamp until the solution became colorless, usually within 15 min. Removal of solvent under reduced pressure gave the crude product.

When the liquid allenes were used as substrates, an equivalent quantity of the allene was added to the sulfonyl iodide solution and the flask was subsequently exposed to illumination until the solution became colorless, usually within 5 min. Removal of solvent at reduced pressure gave the crude product.

Yields of the adducts were generally based on the amount of starting iodine.

General Procedure for the Nmr Analysis of the Addition of Sulfonyl Iodides to 1,2-Propadiene. The additions of sulfonyl iodides to allene were repeated using benzene as solvent in all cases and the crude products obtained were analyzed immediately by nmr to determine the true product ratios. Nmr analysis of the crude products using a Varian A-60A (60 MHz) instrument indicated that in every case 2,3-diiodopropene (**4**) and 2,3-bis(alkyl/arylsulfonyl)propene (**3a–e**) were present in nearly equimolar quantities, as evidenced by the fact that the overall integration of the various regions of the spectrum was nearly perfect for 1:1 adduct. [For example, an equimolar mixture of 2,3-bis(methanesulfonyl)propene and 2,3-diiodopropene would integrate as follows: vinyl region:methylene region:methyl region as 2:2:3 which would be the same as for 2-iodo-3-methanesulfonylpropene (**1a**) or 2-methanesulfonyl-3-iodopropene (**2a**).]

The samples were then further analyzed using a Varian XL-100 (100 MHz) instrument. The scale was expanded to 100 Hz and each area of the spectrum was examined in turn. Peak assignments were based on appearance and chemical shift as determined from the spectra of products which had previously been isolated. Comparison of peak areas on a per hydrogen basis gave the appropriate product ratios. Averages were calculated where appropriate.

Addition of Methanesulfonyl Iodide to Allene. Treatment of methanesulfonyl iodide (0.05 mol) with excess allene afforded 9.1 g of crude product. Purification by elution chromatography using a silica gel column and 1:1 ether–hexane as eluent afforded 2-methanesulfonyl-3-iodopropene (**2a**, 0.4 g, 3.3%), nmr ($CDCl_3$) δ 3.1 (s, 3), 4.27 (d, 2), 6.43 (m, 1), 6.57 (m, 1); 2-iodo-3-methanesulfonylpropene (**1a**, 3.8 g, 30.9%), mp 51–52° or 57–58°, nmr ($CDCl_3$) δ 3.03 (s, 3), 4.20 (s, 2), 6.27 (d, 1, $J \cong 2$ Hz), 6.6 (m, 1); and 2,3-diiodopropene (**4**, 1.5 g, 10.2% based on available iodine), nmr ($CDCl_3$) δ 4.34 (d, 2, $J \cong 1$ Hz), 5.8 (d, 1, $J \cong 2$ Hz), 6.47 (m, 1). A second trial also yielded 9.1 g of crude product. Addition of a small amount of dry ether to this material precipitated 0.9 g (18.2% based on 0.025 mol possible) of 2,3-bis(methanesulfonyl)propene (**3a**), mp 90–91°, nmr ($CDCl_3$) δ 3.04 (s, 3), 3.07 (s, 3), 4.20 (s, 2), 6.47 (m, 1), 6.70 (m, 1).

In a third trial **1a** was isolated in 31.8% yield, **2a** in 19.5% yield, and **4** in 21.5% yield. Thus, the isolated yields of products are not reproducible.

Anal. Calcd for $C_4H_7IO_2S$ (**1a**): C, 19.52; H, 2.87; I, 51.57. Found. C, 19.74; H, 3.00; I, 51.44.

Nmr Analysis of the Addition of Methanesulfonyl Iodide to Allene. Treatment of methanesulfonyl iodide with excess allene, followed by removal of solvent under vacuum, gave a crude product whose 100-MHz nmr spectrum indicated the presence of 2-iodo-3-(methanesulfonyl)propene (**1a**), 2-methanesulfonyl-3-iodopropene (**2a**), 2,3-bis(methanesulfonyl)propene (**3a**), and 2,3-diiodopropene (**4**). The product ratios were calculated from the integration of the vinyl region (*ca.* δ 5.7–6.8) of the spectrum. The results of two separate trials may be tabulated as follows.

Trial	CH_3SO_2I, mol	Crude product, g	Material recovery, %	Product, mol % of product mixture 1a	2a	3a	4
1	0.03	6.90	93.5	34.5	30.9	17.6	17.0
2	0.01	2.30	93.5	35.1	36.8	15.8	12.3
Average			93.5	34.8	33.8	16.7	14.7

A third trial in which the sulfonyl iodide was always in excess gave somewhat different results. In this trial the allene was slowly bubbled into the solution under illumination until the solution became colorless. The results are tabulated as follows.

Trial	CH_3SO_2I, mol	Crude product, g	Material recovery, %	Product, mol % of product mixture 1a	2a	3a	4
3	0.01	2.20	89.5	46.2	22.9	17.6	13.2

Addition of Ethanesulfonyl Iodide to Allene. Ethanesulfonyl iodide (0.05 mol), when treated with excess allene, yielded 9.75 g of crude product. Purification by elution chromatography using a silica gel column with 1:1 ether–hexane as eluent afforded 3.22 g (24.8%) of 2-iodo-3-ethanesulfonylpropene (**1b**), nmr ($CDCl_3$) δ 1.37 (t, 3, $J = 7.7$ Hz), 3.13 (q, 2, $J = 7.7$ Hz), 4.17 (s, 2), 6.25 (m, 1), 6.60 (m, 1); 1.51 g (11.6%) of 2-ethanesulfonyl-3-iodopropene (**2b**), nmr ($CDCl_3$) δ 1.33 (t, 3, $J = 8$ Hz), 3.22 (q, 2, $J = 8$ Hz), 4.27 (s, 2), 6.42 (s, 2); 1.55 g (27.4% based on 0.025 mol theoretical yield) of 2,3-bis(ethanesulfonyl)propene (**3b**), mp 40–43°, nmr ($CDCl_3$) δ 1.32 (t, 3, $J = 8$ Hz), 1.42 (t, 3, $J = 8$ Hz), 3.2 (q, 4, $J = 8$ Hz), 4.17 (s, 2), 6.57 (s, 1), 6.65 (s, 1); 2.3 g (31.3% based on 0.025 mol theoretical yield) of 2,3-diiodopropene (**4**).

Nmr Analysis of the Addition of Ethanesulfonyl Iodide to Allene. Treatment of ethanesulfonyl iodide (0.01 mol) with excess allene afforded 2.15 g (82.7%) of crude material. The product ratios were calculated from the integration of the vinyl region of the 100-MHz nmr spectrum using a sweep width of 100 Hz. The mixture was found to be composed of 27.9 mol % 2-iodo-3-ethanesulfonylpropene (**1b**), 41.8 mol % 2-ethanesulfonyl-3-iodopropene (**2b**), 17 mol % 2,3-bis(ethanesulfonyl)propene (**3b**), and 13.3 mol % 2,3-diiodopropene (**4**).

Addition of 2-Propanesulfonyl Iodide to Allene. When 2-propanesulfonyl iodide (0.01 mol) was treated with excess allene, 2.3 g of a crude oil was obtained. Purification by elution chromatography using a silica gel column with 1:1 ether–hexane as eluent afforded 0.9 g (32.8%) of 2-(2-propanesulfonyl)-3-iodopropene (**2c**), nmr ($CDCl_3$) δ 1.34 (d, 6, J = 7 Hz), 3.1–3.6 (m, 1), 4.23 (s, 2), 6.4 (s, 2); 0.1 g (3.6%) of 2-iodo-3-(2-propanesulfonyl)propene (**1c**), nmr ($CDCl_3$) δ 1.43 (d, 6, J = 7 Hz), 3.10–3.57 (m, 1), 4.13 (s, 2), 6.26 (d, 1, $J \cong$ 2 Hz), 6.63 (m, 1); 0.66 g (52% based on 0.005 mol theoretical yield) of 2,3-bis(2-propanesulfonyl)propene (**3c**), nmr ($CDCl_3$) δ 1.36 (d, 6, $J \cong$ 7 Hz), 1.44 (d, 6, $J \cong$ 7 Hz), 3.07–3.63 (m, 2), 4.10 (s, 2), 6.61 (m, 2); 0.25 g (17% based on 0.005 mol theoretical yield) of 2,3-diiodopropene (**4**).

Nmr Analysis of the Addition of 2-Propanesulfonyl Iodide to Allene. Treatment of 2-propanesulfonyl iodide (0.01 mol) with excess allene gave 1.0 g (36.5%) of crude product. The product ratios were calculated from the integration of the vinyl region of the 100-MHz nmr spectrum using a sweep width of 100 Hz. The relative amount of 2,3-bis(2-propanesulfonyl)propene (**3c**) was less accurately determined owing to incomplete resolution; the relative ratio of 1:1 adducts are the most accurate calculations. The product was found to be composed of 10.6 mol % **1c**, 65.7 mol % **2c**, 15.4 mol % **3c**, and 8.3 mol % **4**.

Addition of Benzenesulfonyl Iodide to Allene. Benzenesulfonyl iodide (0.05 mol), when treated with excess allene, afforded a crude oil whose nmr spectrum showed the presence of 2-iodo-3-benzenesulfonylpropene (**1d**), 2-benzenesulfonyl-3-iodopropene (**2d**), 2,3-diiodopropene (**4**), and 2,3-bis(benzenesulfonyl)propene (**3d**). Addition of a small amount of ethanol induced crystallization; recrystallization from absolute ethanol produced crystals, mp 80–88°. Nmr analysis showed this to be a mixture of **1d** and **3d**. The entire product was recovered from the mother liquors by evaporation under vacuum and combined with the crystals to again obtain a crude oil. Purification of this crude oil by elution chromatography using a silica gel column with 1:1 ether–hexane as eluent afforded 7.0 g (45.5%) of **1d**, mp 89.5–92°, nmr ($CDCl_3$) δ 4.24 (s, 2), 6.08 (d, 1), 6.27 (m, 1), 7.4–8.07 (m, 5); and 1.1 g (13.7% based on 0.025 mol theoretical) of **3d**, mp 129–130°, nmr ($CDCl_3$) δ 4.12 (s, 2), 6.47 (s, 1), 6.67 (s, 1), 7.3–7.83 (m, 10).

Nmr Analysis of the Addition of Benzenesulfonyl Iodide to Allene. Treatment of benzenesulfonyl iodide (0.01 mol) with excess allene gave 3.05 g (99%) of crude product. Product ratios were calculated from the integration of the vinyl region of the 100-MHz nmr spectrum using a sweep width of 100 Hz. The product mixture was found to be composed of 46.2 mol % **1d**, 29.1 mol % **2d**, 10.8 mol % **3d**, and 14.0 mol % **4**. While **2d** had not been isolated from the addition of benzenesulfonyl iodide to allene, the product was visible in the 100-MHz nmr spectrum, nmr ($CDCl_3$) vinyl H *ca.* δ 6.28 (1, overlapped with **1d**) and 6.65 (m, 1). The integration of the vinyl region was consistent with this assignment, which is based solely on the nmr evidence.

Addition of *p*-Toluenesulfonyl Iodide to Allene. When an ethereal solution of *p*-toluenesulfonyl iodide (16.92 g, 0.06 mol) was treated with excess allene, a white solid precipitated from the solution. The solution was concentrated and filtered to give 1.7 g (16.2% based on 0.03 mol possible) of 2,3-bis(*p*-toluenesulfonyl)propene (**3e**): mp 155.5–157°; nmr ($CDCl_3$) δ 2.40 (s, 6), 4.06 (s, 2), 6.47 (m, 1), 6.63 (m, 1), 7.42 (q, 8).

Anal. Calcd for $C_{17}H_{18}O_4S_2$: C, 58.26; H, 5.18; S, 18.30. Found: C, 57.99; H, 4.88; S, 18.52.

The remaining ethereal solution was evaporated to dryness and the residue was crystallized from absolute ethanol to give 11.65 g (60.4%) of 2-iodo-3-(*p*-toluenesulfonyl)propene (**1e**): mp 77–80°; nmr ($CDCl_3$) δ 2.43 (s, 3), 4.17 (s, 2), 6.05 (d, 1), 6.23 (m, 1), 7.58 (q, 4).

Anal. Calcd. for $C_{10}H_{11}IO_2S$: C, 37.28; H, 3.44; I. 39.39; S, 9.95. Found: C, 37.47; H, 3.69; I, 39.30; S, 10.09.

Nmr Analysis of the Addition of *p*-Toluenesulfonyl Iodide to Allene. Treatment of *p*-toluenesulfonyl iodide (0.01 mol) with excess allene gave 3.20 g (99.5%) of crude product. Product ratios were calculated from the integration of the vinyl region of the 100-MHz nmr spectrum using a sweep width of 100 Hz. The product was found to be a mixture of 46.7 mol % **1e**, 28.2 mol % **2e**, 13.3 mol % **3e**, and 11.8 mol % **4**. While **2e** had not been isolated from the addition of *p*-toluenesulfonyl iodide to allene, the product was clearly visible in the 100-MHz nmr spectrum, nmr ($CDCl_3$) vinyl H *ca.* δ 6.26 (1, overlapped with **1e**) and 6.61 (d, 1). The integration of the nmr spectra was consistent with this assignment, which is based solely on the nmr evidence. Use of a limited quantity of allene produced a mixture of 1:1 adducts composed of 82.7% **1e** and 17.3% **2e** (as well as some **3e** and **4**).

Addition of Methanesulfonyl Iodide to Phenylallene. Treatment of methanesulfonyl iodide (0.01 mol) with phenylallene (1.16 g, 0.01 mol) afforded 3.0 g (93.2%) of β-(methanesulfonyl)-β-(iodomethyl)styrene (**5a**), which by nmr was found to be the only product of this reaction. The product was recrystallized from ethanol to give needles, mp 110–111°, nmr ($CDCl_3$) δ 3.22 (s, 3), 4.47 (s, 2), 7.4–7.8 (m, 6).

Addition of Ethanesulfonyl Iodide to Phenylallene. Treatment of ethanesulfonyl iodide (0.01 mol) with phenylallene (1.16 g, 0.01 mol) afforded 3.1 g (92.2%) of β-(ethanesulfonyl)-β-(iodomethyl)styrene (**5b**), which by nmr was found to be the only product of this reaction. The product was further purified by recrystallization from absolute ethanol to give pale yellow-white needles: mp 129–130°; nmr ($CDCl_3$) δ 1.37 (t, 3, J = 7 Hz), 3.34 (q, 2, J = 7 Hz), 4.45 (s, 2), 7.33–7.83 (m, 6). In a second trial, the yield of 1:1 adduct increased slightly to 3.15 g (93.7%) of material which was found to be pure by nmr.

Addition of 2-Propanesulfonyl Iodide to Phenylallene. Treatment of 2-propanesulfonyl iodide (0.01 mol) with phenylallene (1.16 g, 0.01 mol) afforded a mixture of phenylallene and β-(isopropylsulfonyl)-β-(iodomethyl)styrene (**5c**). Purification of this crude product by elution chromatography using a silica gel column with 1:1 ether–hexane as eluent yielded 1.5 g (42.8%) of **5c**, which was further purified by recrystallization from ethanol to give crystals: mp 90.5–92°; nmr ($CDCl_3$) δ 2.40 (d, 6, J = 7 Hz), 3.20–3.90 (m, 1), 4.43 (s, 2), 7.33–7.67 (m, 6).

Addition of Benzenesulfonyl Iodide to Phenylallene. Treatment of benzenesulfonyl iodide (0.01 mol) with phenylallene (1.16 g, 0.01 mol) afforded 3.62 g (94.3%) of pure (by nmr) β-(benzenesulfonyl)-β-(iodomethyl)styrene (**5d**). Recrystallization from absolute ethanol gave crystals: mp 92–93°; nmr ($CDCl_3$) δ 4.28 (s, 2), 7.33–7.73 (m, 8), 7.83–8.10 (m, 3).

Addition of *p*-Toluenesulfonyl Iodide to Phenylallene. Treatment of an ethereal solution of *p*-toluenesulfonyl iodide (11.28 g, 0.04 mol) with phenylallene (4.65 g, 0.04 mol) gave a crude solid product which was recrystallized from ethanol–water to give 12.77 g (80.0%) of β-(*p*-toluenesulfonyl)-β-(iodomethyl)styrene (**5e**): mp 119–120°; nmr ($CDCl_3$) δ 2.35 (s, 3, $C_6H_4CH_3$), 4.21 (s, 2, CH_2I), 7.20–8.00 (m, 10, C_6H_5CH and C_6H_4).

Anal. Calcd. for $C_{16}H_{15}IO_2S$: C, 48.25; H, 3.80, I, 31.86; S, 8.05. Found: C, 48.23; H, 4.06; I, 31.66; S, 7.99.

Addition of Methanesulfonyl Iodide to 3-Methyl-1,2-butadiene. Treatment of methanesulfonyl iodide (0.01 mol) with 3-methyl-1,2-butadiene (1.02 g, 0.015 mol) afforded a quantitative yield of 1-iodo-2-methanesulfonyl-3-methyl-2-butene (**5f**), recrystallized from absolute ethanol: mp 81.5–82.5°; nmr ($CDCl_3$) δ 1.95 (s, 3), 2.23 (s, 3), 3.08 (s, 3), 4.33 (s, 2).

Anal. Calcd for $C_6H_{11}IO_2S$: C, 26.29; H, 4.05; I, 46.29. Found: C, 26.48; H, 4.35, I. 46.02.

Addition of Ethanesulfonyl Iodide to 3-Methyl-1,2-butadiene. Treatment of ethanesulfonyl iodide (0.01 mol) with 3-methyl-1,2-butadiene (1.02 g, 0.015 mol) afforded 2.75 g (95.5%) of pure (by nmr) crystalline 1-iodo-2-ethanesulfonyl-3-methyl-2-butene (**5g**). Attempts to recrystallize this adduct from ethanol or hexane failed, as the adduct decomposed very readily. The nmr spectrum was found to be free of other possible 1:1 adducts and to be consistent with the assigned structure: nmr ($CDCl_3$) δ 1.38 (t, 3, J = 7 Hz), 1.97 (s, 3), 2.23 (s, 3), 3.16 (q, 2, J = 7 Hz), 4.33 (s, 2).

Addition of Benzenesulfonyl Iodide to 3-Methyl-1,2-butadiene. Treatment of benzenesulfonyl iodide (0.01 mol) with 3-methyl-1,2-butadiene (1.02 g, 0.015 mol) afforded a quantitative yield of 1-iodo-2-benzenesulfonyl-3-methyl-2-butene (**5h**): nmr ($CDCl_3$) δ 1.80 (s, 3), 1.98 (s, 3), 4.35 (s, 2), 7.37–7.70 (m, 3), 7.80–8.13 (m, 2). Attempts to recrystallize this material from ethanol or hexane–ethanol failed, substantial decomposition occurring during each attempt.

Addition of *p*-Toluenesulfonyl Iodide to 3-Methyl-1,2-butadiene. Treatment of *p*-toluenesulfonyl iodide (5.64 g 0.02 mol) with 3-methyl-1,2-butadiene (1.5 g, 0.0221 mol) afforded a mixture of 6.8 g (97.4%) of 1-iodo-2-(*p*-toluenesulfonyl)-3-methyl-2-butene (**5i**) and 0.34 g of residual benzene solvent (by nmr). No other products were detected by nmr. Recrystallization from absolute ethanol gave 5.75 g (82.2%) of pure product: mp 66–67° (lit.[28,30] mp 77–80°); nmr ($CDCl_3$) δ 1.83 (s, 3), 2.02 (s, 3), 2.38 (s, 3), 4.35 (s, 2), 7.58 (q, 4).

Addition of *p*-Toluenesulfonyl Iodide to 2,3-Pentadiene. Equivalent quantities (0.0496 mol) of the allene and the sulfonyl iodide were combined in ether. After 30 min, the solution was very dark red-orange in color. Solvent removal and recrystallization of the residue from ethanol-water gave 7.88 g (45%) of 3-(*p*-toluenesulfonyl)-4-iodo-2-pentene (**5j**): mp 114-115° dec; nmr ($CDCl_3$) δ 1.91 (m, 6, $CH_3CH{=}C$ and $CHICH_3$), 2.42 (s, 3, $C_6H_4CH_3$), 4.99 (q, 1, $CHICH_3$), 6.99-7.82 (m, 6, C_6H_4 and $CH_3CH{=}C$).

Anal. Calcd for $C_{12}H_{15}IO_2S$: C, 41.15; H, 4.32; I, 36.24; S, 9.16. Found: C, 41.35; H, 4.51; I, 36.15; S, 9.40.

Zinc-Acid Reduction of β-(*p*-Toluenesulfonyl)-β-(iodomethyl)styrene (5e). The allylic iodide **5e** (1.99 g, 0.005 mol) was dissolved in a mixture of acetic acid (1.5 ml), water (1.5 ml), dioxane (5 ml), and ether (30 ml). Zinc dust (0.654 g, 0.01 mol) was added. Heat was evolved and vigorous bubbling occurred. The mixture was stirred for 2 hr and then poured into water. The aqueous mixture was extracted with ether, the ether layer was dried over $MgSO_4$, and the solvent was removed under vacuum to give the crude solid product. Recrystallization from absolute ethanol gave platelets, mp 116-118°. These platelets were again recrystallized from ethanol and could be induced to crystallize as white needles, mp 119-120°. This material was found by nmr, ir, and mixture melting point to be identical with β-(*p*-toluenesulfonyl)-*cis*-β-methylstyrene, which was alternately prepared from *trans*-β-methylstyrene and *p*-toluenesulfonyl chloride by a method used by Goralski[31] for the synthesis of similar compounds. The nmr coupling constant for trans $HC{=}CCH_3$, J = 1.5 Hz, supported the stereochemical assignment. The yield of reduced product was 74%.

Alternate Synthesis of β-(*p*-Toluenesulfonyl)-*cis*-β-methylstyrene. *trans*-β-Methylstyrene (10.0 g, 0.085 mol), *p*-toluenesulfonyl chloride (16.2 g, 0.085 mol), anhydrous cupric chloride (0.11 g, 0.00085 mol), and triethylamine hydrochloride (0.175 g, 0.00127 mol) were combined in 3.4 g of acetonitrile. The mixture was heated to 110° (reflux) under nitrogen for 2.5 hr and then cooled. Methanol (35 ml) was added and the resulting solution was cooled, but no product crystallized. Removal of solvents under vacuum left a clear, viscous, yellow oil. This oil was dissolved in dry benzene, triethylamine (12.87 g, 0.127 mol) was added, and the mixture was stirred at room temperature overnight. Triethylamine hydrochloride was removed by filtration and aqueous extraction, the benzene layer was dried over $MgSO_4$, and the solvent was removed under vacuum to give a solid residue. This residue was recrystallized from absolute ethanol to yield 16.8 g (72.7%) of β-(*p*-toluenesulfonyl)-*cis*-β-methylstyrene: mp 119.5-121°; nmr ($CDCl_3$) δ 2.09 (d, 3, $J \cong 1.5$ Hz), 2.38 (s, 3), 7.17-7.50 (m, 7), 7.70-7.97 (m, 3).

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Registry No. 1a, 42790-58-9; **1b,** 42790-59-0; **1c,** 42790-60-3; **1d,** 42790-61-4; **1e,** 35890-15-4; **2a,** 42790-63-6; **2b,** 42790-64-7; **2c,** 42790-65-8; **3a,** 42790-66-9; **3b,** 42790-67-0; **3c,** 43790-68-1; **3d,** 2525-55-5; **3e,** 35925-44-1; **4,** 39557-29-4; **5a,** 42790-72-7; **5b,** 42790-73-8; **5c,** 42790-74-9; **5d,** 42790-75-0; **5e,** 42790-76-1; **5f,** 42790-77-2; **5g,** 42790-78-3; **5h,** 42790-79-4; **5i,** 35890-17-6; **5j,** 42790-81-8; methanesulfonyl iodide, 42790-82-9; allene, 463-49-0; ethanesulfonyl iodide, 42790-83-0; 2-propanesulfonyl iodide, 42790-84-1; benzenesulfonyl iodide, 1950-77-2; *p*-toluenesulfonyl iodide, 1950-78-3; phenylallene, 2327-99-3; 3-methyl-1,2-butadiene, 598-25-4; 2,3-pentadiene, 591-96-8; *trans*-β-methylstyrene, 873-66-5; β-(*p*-toluenesulfonyl)-*cis*-β-methylstyrene, 42790-87-4.

References and Notes

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Notes

Preparation and Photodecomposition of α-Toluenesulfonyl Iodide

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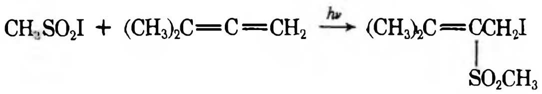
We have recently studied the light-initiated addition of sulfonyl iodides to various allenes and have reported[1,2] that both alkyl- and arylsulfonyl iodides will add to various allenes to give 1:1 adducts. When substituted allenes such as phenylallene or 3-methyl-1,2-butadiene were employed, nearly quantitative yields of the 1:1 adducts resulting from attack by an intermediate sulfonyl radical on the central carbon of the allenic unit were usually obtained. For example, methanesulfonyl iodide would combine very rapidly (within 1-2 min) with 3-methyl-1,2-butadiene under the influence of light to give a quantitative yield of 1-iodo-2-methanesulfonyl-3-methyl-2-butene.



$$CH_3SO_2I + (CH_3)_2C{=}C{=}CH_2 \xrightarrow{h\nu} (CH_3)_2C{=}\underset{SO_2CH_3}{C}CH_2I \quad 100\%$$

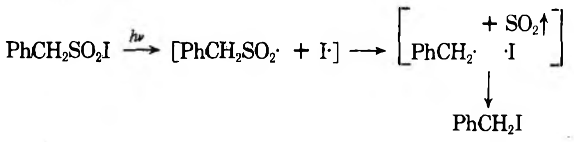
The alkylsulfonyl iodides in this work were not isolated, but were used as freshly prepared benzene solutions owing to the instability of these compounds. Thus, when a benzene solution of iodine was vigorously mixed with an aqueous solution containing an excess of the appropriate sodium alkylsulfinate, the intense purple color of the iodine rapidly faded and was replaced by the bright yellow-orange color of the sulfonyl iodide. When no further color change was evident, the benzene layer was separated, dried briefly over $MgSO_4$, and filtered to give a clear yellow-orange solution of the sulfonyl iodide. Delay in using this dried solution or exposure to strong light produced considerable decomposition of the sulfonyl iodide; hence the solutions were used immediately and were protected from the light until the allene was present. Yields were generally based on starting iodine; from the results quoted it is apparent that the alkylsulfonyl iodides themselves are produced in quantitative or nearly quantitative yields. This technique, used by Truce and Wolf,[3] in the addition of sulfonyl iodides to acetylenes as well as in our work with allenes, has proved to be an extremely useful method of generating and handling unstable sulfonyl iodides.

Since relatively little is known of the chemistry of sulfonyl iodides and few have been prepared owing to their instability, we have attempted to prepare several novel sulfonyl iodides by utilizing the procedure previously described.

Results and Discussion

α-Toluenesulfonyl iodide was successfully generated in benzene solution, but was not isolated. An attempt was made to add this freshly prepared sulfonyl iodide to 3-methyl-1,2-butadiene. Accordingly, a slight excess of 3-methyl-1,2-butadiene was added to a dry benzene solution of the sulfonyl iodide and the solution was exposed to illumination from a 240-W General Electric sun lamp. The color quickly faded and the solution became colorless. Removal of solvent under vacuum gave an 89.4% yield of benzyl iodide, which was pure by nmr. The infrared spectrum of the crude material contained no sulfone bands, and, more importantly, the nmr spectrum of the crude material showed only the presence of benzyl iodide; none of the 3-methyl-1,2-butadiene was involved in this reaction.

This transformation is rather remarkable, in that apparently the intermediate sulfonyl radical is either extruding sulfur dioxide rapidly and the resulting benzyl radical recombining with the iodine atom within the solvent cage, according to the following scheme



$$PhCH_2SO_2I \xrightarrow{h\nu} [PhCH_2SO_2\cdot + I\cdot] \longrightarrow \left[\begin{matrix} & + SO_2\uparrow \\ PhCH_2\cdot & \cdot I \end{matrix}\right] \longrightarrow PhCH_2I$$

or the benzyl iodide is being formed *via* the following chain reaction.

$$PhCH_2SO_2I \xrightarrow{h\nu} PhCH_2SO_2\cdot + I\cdot$$
$$PhCH_2SO_2\cdot \longrightarrow PhCH_2\cdot + SO_2$$
$$PhCH_2\cdot + PhCH_2SO_2I \longrightarrow PhCH_2I + PhCH_2SO_2\cdot$$

We favor the cage mechanism as being somewhat more likely owing to the complete lack of any products involving the allene, although with the information at hand we cannot rigorously distinguish between these mechanisms.

The stability of the benzylic radical provides a driving force for extrusion of sulfur dioxide from the sulfonyl radical, and in fact the carbon-sulfur bond dissociation energy for the process

$$PhCH_2SO_2\cdot \longrightarrow PhCH_2\cdot + SO_2$$

has been calculated at 7.5 kcal/mol,[4] an extraordinarily low value for a bond dissociation energy. Thus it is reasonable that the $PhCH_2SO_2\cdot$ radical should extrude sulfur dioxide very rapidly. A similar extrusion of sulfur dioxide from α-toluenesulfonyl chloride has been observed under radical conditions.[5]

The properties of trichloromethanesulfonyl iodide would be interesting, since the sulfonyl radical would be a particularly polar one owing to the presence of three chlorine atoms. However, all of our attempts to prepare trichloromethanesulfonyl iodide failed. Similar results were obtained in attempts to prepare chloromethanesulfonyl iodide.

The bond strength of the sulfur-iodine bond would appear to be too weak in these two sulfonyl iodides to provide any driving force for the formation of the desired sulfonyl iodide. Indeed, it has been reported[6] that trichloromethanesulfonyl chloride is readily reduced and liberates iodine from an aqueous potassium iodide solution, a point which was readily verified in these laboratories. Studies on the equilibrium constant for formation of the sulfonyl iodides in aqueous solution have shown that the equilibrium constant is very sensitive toward electronegative substituents in the sodium sulfinate.[7] Thus, for the reaction

$$RSO_2^- + I_3^- \rightleftarrows RSO_2I + 2I^-$$
$$K = \frac{[RSO_2I][I^-]^2}{[RSO_2^-][I_3^-]}$$

where R = C_6H_5, K was calculated as 1×10^{-2}, but, when R = 2,5-dichlorophenyl, K was calculated as 4×10^{-7},[7] a difference of over 10^6. In the light of these data, the failure to prepare trichloromethanesulfonyl iodide and chloromethanesulfonyl iodide is not surprising.

Because of the greater stability of the arylsulfonyl iodides (which usually permits their isolation) the preparation of various arylsulfonyl iodides containing an electronegative substituent on the aromatic ring should be possible. We have indeed found that *p*-nitrobenzenesulfonyl iodide can be prepared in the same manner as *p*-toluenesulfonyl iodide,[1,8] by combining an aqueous solution of the sulfinate with an ethanolic solution of iodine. This sulfonyl iodide was found to slowly evolve iodine vapors at room temperature and appeared to be about as stable as *p*-toluenesulfonyl iodide.

Experimental Section

All melting points are uncorrected. Nmr spectra were recorded on a Varian A-60A and ir spectra were recorded on a Beckman IR-33. The nmr spectral data are reported in chemical shift from TMS (δ 0), with s, d, t, q, and m referring to singlet, doublet, triplet, quartet, and multiplet, respectively. Microanalyses were performed by Dr. C. S. Yeh and staff of this department. The α toluenesulfonyl chloride was purchased from Eastman and the 3-methyl-1,2-butadiene was obtained from Chemical Samples Co.

Preparation of Sodium Trichloromethanesulfinate. Trichloromethanesulfonyl chloride (20.5 g, 0.10 mol) was treated with sodium sulfite (25.2 g, 0.20 mol) and sodium bicarbonate (16.8 g, 0.20 mol) in water at 40–45° to give 20.5 g (85.4%) of the sulfinate, ir strong absorption at 790, 1040, and 1085 cm^{-1}. *Anal.* Calcd for CCl_3NaO_2S: Cl, 51.77; Na, 11.19. Found: Cl, 51.63; Na, 11.30. The sulfinate was found to decompose slowly in air. If the reaction temperature was raised to 90°, the yield and purity were greatly reduced.

Preparation of Sodium *p*-Nitrobenzenesulfinate. *p*-Nitrobenzenesulfonyl chloride (22.16 g, 0.10 mol) was treated with sodium sulfite (25.2 g, 0.20 mol) and sodium bicarbonate (16.8 g, 0.20 mol) in approximately 100 ml of water at 75–95° to give 5.0 g (24%) of sodium *p*-nitrobenzenesulfinate: mp 232–233° dec; ir 1510 and 1350 cm^{-1} ($-NO_2$); nmr (D_2O, TMS external standard) δ 7.83 (q).

Preparation of α-Toluenesulfonyl Iodide and Attempted Addition to 3-Methyl-1,2-butadiene. Treatment of α-toluenesulfonyl chloride (38.13 g, 0.20 mol) with sodium sulfite (50.4 g, 0.40 mol) and sodium bicarbonate (33.6 g, 0.40 mol) in 200 ml of water afforded 25.1 g (70.5%) of white solid sulfinate which after a few minutes of exposure to air began to fume and to liberate heat. The material was quickly transferred to a vacuum desiccator and subsequently protected from the air. The nmr spectrum of this product (D_2O, TMS external standard) showed that purity of this material was now not greater than 50%. Because of the apparent instability of the sodium α-toluenesulfinate, the salt was not isolated, but was used as a freshly prepared aqueous solution. Thus, α-toluenesulfonyl chloride was treated with 1 equiv of sodium sulfite and sodium bicarbonate in water at 70–75° and the resulting crude aqueous solution was used without further purification in the following preparation of α-toluenesulfonyl iodide. The α-toluenesulfonyl iodide was generated by vigorously mixing the freshly prepared aqueous solution of sodium α-toluenesulfinate (0.025 mol) with a benzene solution of iodine (5.08 g, 0.02 mol, in *ca.* 200 ml of benzene). The bright yellow benzene solution was separated and dried, then used immediately in the following reaction.

The benzene solution of α-toluenesulfonyl iodide (0.02 mol in *ca.* 200 ml of benzene) was treated with 3-methyl-1,2-butadiene (1.5 g, 0.221 mol). Upon illumination from a 250-W General Electric sun lamp, the bright yellow color rapidly faded and the solution became colorless. Evaporation of the solvent under vacuum gave 3.9 g (89.4%) of benzyl iodide, nmr ($CDCl_3$) δ 4.23 (s, 2), 7.0–7.33 (m, 5). The infrared spectrum of this material contained no sulfone bands, and the nmr spectrum of this material showed only the presence of benzyl iodide; no adducts between 3-methyl-1,2-butadiene and α-toluenesulfonyl iodide could be detected. Further proof of the product identification was obtained as follows.

Treatment of benzyl chloride (1.26 g, 0.01 mol) with sodium iodide (6.0 g, 0.04 mol) in acetone according to the procedure of Coleman and Hauser[9] yielded 1.75 g (80.3%) of benzyl iodide. The benzyl iodide prepared in this manner was compared by ir and nmr and found to be identical with the material produced in the above reaction from α-toluenesulfonyl iodide.

Treatment of the product (1.09 g, 0.005 mol) with sodium benzenesulfinate (1.64 g, 0.01 mol) in methanol at room temperature yielded 1.1 g (94.8%) of the known[10] benzyl phenyl sulfone: mp 149–150° (lit.[5] mp 148°); nmr ($CDCl_3$) δ 4.28 (s, 2), 6.90–7.77 (m, 10).

Preparation of *p*-Nitrobenzenesulfonyl Iodide. When an aqueous solution of sodium *p*-nitrobenzenesulfinate (0.52 g, 0.0025 mol) was treated with a solution of iodine (0.635 g, 0.0025 mol) in ethanol, a yellow solid rapidly precipitated from solution. The solid was collected and recrystallized from CCl_4 to give 0.4 g (51.1%) of *p*-nitrobenzenesulfonyl iodide: mp 96–100° dec; nmr ($CDCl_3$) δ 8.28 (q). The product was found to slowly evolve iodine at room temperature, but was more stable at −10°. The sulfonyl iodide was particularly unstable in chloroform solution.

Attempted Preparation of Trichloromethanesulfonyl Iodide. Treatment of a benzene solution of iodine (0.254 g, 0.001 mol) with an aqueous solution of sodium trichloromethanesulfinate (0.41 g, 0.002 mol) produced no visible reaction. Use of iodine monochloride in place of iodine in the above procedure also failed to produce the sulfonyl iodide (as evidenced by no visible color change) even when a large excess of the sulfinate was employed.

Attempted Preparation of Chloromethanesulfonyl Iodide. Treatment of chloromethanesulfonyl chloride (7.45 g, 0.05 mol) with sodium sulfite (6.3 g, 0.05 mol) and sodium bicarbonate (8.4 g, 0.10 mol) in water at 50–55° yielded 4.1 g (60.2%) of crude sulfinate of approximately 88% purity (by nmr), nmr (D_2O, TMS external standard) δ 4.10 (s), impurity δ 6.07 (s). The impurity is believed to be sodium dichloromethanesulfinate derived from dichloromethanesulfonyl chloride believed to be present in the starting material. Repeated distillation, however, was ineffective in purifying the starting chloromethanesulfonyl chloride. Recrystallization from ethanol was ineffective in purifying the sodium chloromethanesulfinate, thus the sulfinate was used in this purity in the following attempts to prepare chloromethanesulfonyl iodide. The sulfonyl iodide could not be produced by treating an aqueous solution of excess sulfinate with either a solution of iodine in benzene or a solution of iodine monochloride in benzene. In neither case was the dark color (of the iodine or iodine monochloride) discharged.

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Registry No. Sodium trichloromethanesulfinate, 42521-49-3; trichloromethanesulfonyl chloride, 2547-61-7; sodium p-nitrobenzenesulfinate, 15959-31-6; *p*-nitrobenzenesulfonyl chloride, 98-74-8; α-toluenesulfonyl iodide, 42880-77-3; 3-methyl-1,2-butadiene, 598-25-4; benzyl iodide, 620-05-3; *p*-nitrobenzenesulfonyl iodide, 42880-78-4; chloromethanesulfonyl chloride, 3518-65-8; sodium chloromethanesulfinate, 42880-79-5.

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The Crystal Structure of *cis*-2,4-Diphenylthietane *trans*-1-Monoxide[1]

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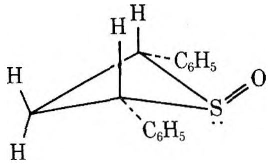
Received August 28, 1973

Dodson, Jancis, and Klose have studied the unusual stereochemistry of small heterocyclic rings containing sulfur in various substituted thietanes and their monoxides and dioxides.[2] The crystal structure analysis of *cis*-2,4-diphenylthietane *trans*-1-monoxide was initially begun to



confirm the stereochemical arrangement of the phenyl groups and the oxygen atom about the four-membered thietane ring. This work also confirms the estimate of ring puckering from planar conformation made by Dodson, Jancis, and Klose[2] from an analysis of proton spin-spin coupling constants of both the *cis*- and *trans*-2,4-diphenylthietane monoxides determined from nuclear magnetic resonance spectra. Using four coupling constants $J_{HH'}$ between protons on adjacent carbon atoms in the trans and two from the cis derivative, they determined values of the three constants A, B, and C in the Barfield–Karplus equation[3]

$$J_{HH'} = A \cos^2 \phi + B \cos \phi + C$$

and three dihedral angles ϕ. Assuming the H–C–H angle at C-2 as the value found in trimethylene oxide of 112°,[4] and assuming bond distances C–C = 1.54 Å and C–S = 1.83 Å, they determined the pucker angle of the ring to be 39.7°, which is the angle between the plane of C-1, C-2, and C-3, and that of the plane determined by C-1, S, and C-3.

Experimental Section

Crystal Data. The crystals were kindly supplied by Dr. Dodson, who had characterized the compound by elemental analysis, infrared and nmr spectra, and thin layer chromatography.[2] The sample was slowly recrystallized from a 3:1 mixture of chloroform and petroleum ether (bp 30–60°). Large, flat, colorless crystals was obtained, and these were cut to obtain suitable crystals for diffraction. Cell dimensions of a = 11.756 (11) Å, b = 10.302 (14) Å, c = 10.721 (10) Å, and β = 98° 49′ (15) were obtained from Si calibrated Weissenberg photographs taken at room temperature with Cu Kα radiation, λ = 1.5418 Å. The density measured by flotation methods of 1.255 g/ml is in agreement with that of 1.255 g/ml calculated for four $C_{15}H_{14}SO$ molecules per cell. Systematic absences for the $h0l$ reflections of $l = 2n + 1$ and for the $0k0$ reflections of $k = 2n + 1$ are consistent with the space group $P2_1/c$. The intensities of 1800 reflections above the detection limit were estimated by visual comparison of multifilm Weissenberg photographs with an intensity standard. The zones photographed include $h0l$ through $h8l$, and these were placed on a common scale by comparisons with measurements on the $hk0$ and $hk1$ photographs. There were 498 reflections below the detection limit.

Determination and Refinement of the Structure. Lorentz and polarization corrections were applied and Fourier synthesis and isotropic diagonal-matrix least-squares calculations were performed on the IBM 1130 computer using programs kindly supplied by Cooper.[5] The structure was resolved by straightforward application of the Patterson function and heavy atom techniques. Least-squares refinement with the program described above gave convergence at R = 0.208. Analysis of a difference synthesis indicated anisotropic thermal motion, and it contained maxima at positions expected for hydrogen atoms. Further least-squares refinements were carried out on the CDC 6600 computer using the program UMLSTSQ.[6] One cycle of block-diagonal refinement and three cycles of full-matrix anisotropic temperature factor refinement reduced R to 0.129. Hydrogen atom scattering was included in the F_c calculations, but the hydrogen positions were not refined.[7]

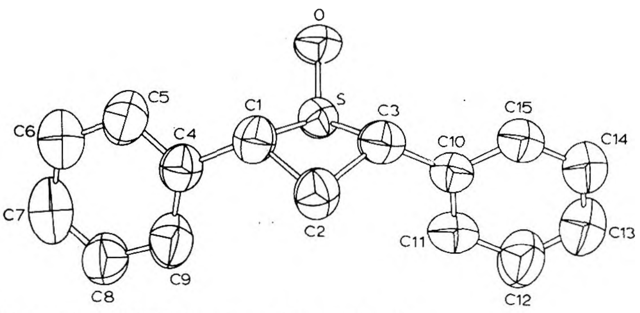


Figure 1. ORTEP drawing of the molecule.

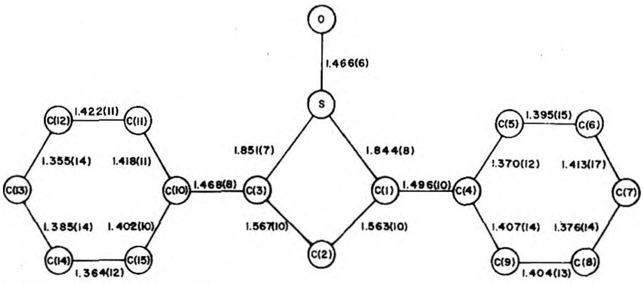


Figure 2. Bond distances.

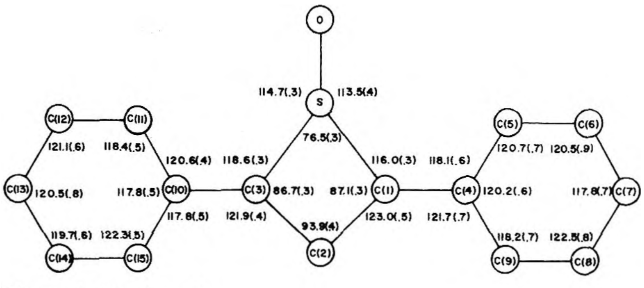


Figure 3. Bond angles.

Table I

	Ref 8	This work
S–O	1.526 (10) Å	1.466 (6) Å
S–C	1.842 (8) Å	1.847 (4) Å
C–C	1.529 (11) Å	1.565 (7) Å
C–S–C	76.6 (5) °	76.5 (3) °
O–S–C	112.0 (4) °	114.1 (3) °
S–C–C	90.2 (4) °	86.9 (3) °
C–C–C	96.6 (9) °	93.9 (4) °
Pucker angle	27°	41.9

Discussion

The general shape of the molecule (Figure 1) is flattened as the benzene rings extend in an equatorial direction from the puckered thietane ring. The molecules pack together with their S–O bonds nearly parallel with the b axis. As no intramolecular bond distances involving O and H are less than 2.3 Å, hydrogen bonds between molecules are not found. The bond distances and angles are shown in Figures 2 and 3. The bond distances and angles found are compared to those reported by Abrahamsson and Rehnberg for *trans*-1-thiacyclobutane-3-carboxylic acid 1-oxide[8] (Table I).

The degree of twist of the thietane ring is evident from the pucker angle of 41.9°, which is the angle between the plane of S, C-1, and C-3, and the plane of C-1, C-2, and C-3. This compares with the estimate of 39.7° made from nmr measurements described above.[2] The probable error in our determination is 0.6°, but the difference is probably not significant considering the approximations in the Barfield–Karplus treatment. Pucker angles in other thietanes are 27° for *trans*-1-thiacyclobutane-3-carboxylic acid 1-oxide[8] and unsubstituted thietane which exhibits a symmetrical double-minimum potential function for ring puckering with minima 32° from a planar structure.[9] The pucker angle in this study of 41.9° may be larger than that of the other compounds cited because of the bulky phenyl groups tending toward equatorial conformation. The measured torsional angles of this study are O-S-C-1-C-4 = 95.7° and O-S-C-3-C-10 = 98.8° indicating the twist of C-1 and C-3. The atoms in the benzene ring C-4-C-9 have a maximum deviation from planarity of 0.04 Å and those in the ring C-10-C-15 have a maximum deviation of a 0.02 Å.

Acknowledgment. We are especially indebted to Dr. Dodson for supplying the crystals, for his continuing encouragement, and for his generous support for the final least-squares calculations on the CDC 6600. We also thank Dr. G. J. Palenik for providing the ORTEP drawing.

Registry No. *cis*-2,4-Diphenylthietane *trans*-1-monoxide, 24605-73-0.

Supplementary Material Available. The atomic coordinates, anisotropic temperature factors, and a packing diagram will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N. W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-246.

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Photochemistry of 4-Cyclooctenone[1a]

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In a preliminary communication we reported on the photochemistry of *cis*-4-cyclooctenone (1), emphasizing the unusual nature of its transformation to 3-vinylcyclohexanone (2).[2] The present report reveals that 1 is reversibly isomerized to the trans isomer 3 upon $n-\pi^*$ irradiation, whereas higher energy light is required for the formation of 2.

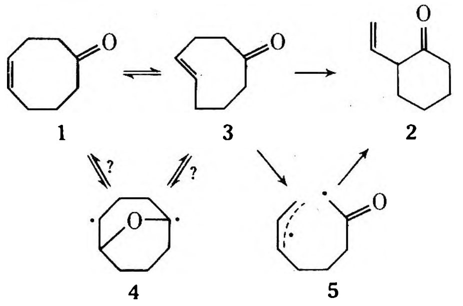
Irradiation of a cyclohexane solution of 1 with a 450-W Hanovia source through a Pyrex filter for 20 hr gave a mixture of 1 and its trans isomer 3 as the only products. Similar results were also obtained with a benzene solution irradiated through a Vycor filter. The identical 60:40 mixture of 1:3 was achieved starting from either isomer in small-scale photolyses conducted in a Rayonet reactor using 3100-Å lamps. Under these conditions prolonged irradiation of an acetone solution of 1 did not result in appreciable reaction. On the other hand, 30 min of irradiation with the Hanovia source directly through a *quartz* probe converted 1 predominantly into cyclohexanone 2. A minor product (6%) in this photolysis had the same glpc characteristics as 3. Irradiation of identical samples of 1 and 3 through quartz test tubes in the Rayonet reactor with 2537-Å bulbs for 15 min resulted in 17% conversion of 3 to 2 but only 3% of 1 to 2. The 3 to 1 isomerization was also more rapid than the conversion of 1 to 3. Cyclohexanone 2 gave only photoreduction to a mixture of isomeric cyclohexanols upon irradiation of a cyclohexane solution with the Pyrex-filtered Hanovia source.

Isolation of a 95% pure sample of 3 was effected by selective extraction into 5% aqueous $AgNO_3$ and preparative glpc at <130°. The assignment of structure 3 follows from the photoequilibration studies and its spectral properties: ir 5.88, 6.09, and 10.1 μ;[3] nmr δ 5.9 (1, m), 5.1 (1, m), and 3.0–1.8 (10, m). A spin-decoupling experiment indicated a 16-Hz coupling constant between the two olefinic hydrogens, consonant only with a trans double bond.[4] The mass spectra of 1 and 3 were similar but not identical. The uv spectrum of 3 was unusual in that exceptional low-wavelength absorption was observed in addition to normal $n-\pi^*$ absorption: λ_{max} 222 nm (ϵ 1000) and 280 nm (24) in ethanol and λ_{max} 287 (11), ϵ_{220} 1120 in cyclohexane. The cis isomer shows λ_{max} 285 nm (ϵ 16) and ϵ_{222} 268 in ethanol and λ_{max} 287 (11), ϵ_{220} 206 in cyclohexane. This feature of 3 is probably attributable to its structural rigidity, which holds the two π systems in close proximity to each other. Many β,γ-unsaturated ketones show such abnormality in their uv spectra.[5]

There was a slow disappearance of 3 upon refluxing in xylene leading to both 1 and uncharacterized higher molecular weight materials, but no 2 was thus produced. Exposure to *p*-toluenesulfonic acid in benzene solution for 4 days did not appreciably transform 3 to either 1 or 2.

This photochemical system presents several noteworthy aspects. Irradiation into the $n-\pi^*$ band of the carbonyl group promotes clean cis–trans isomerization of the transannular double bond at the expense of the normally expected photochemistry of a nonconjugated, medium-ring ketone (Norrish type I and type II cleavages, reductions, etc.).[6] Nor is there any evidence for intramolecular photocycloaddition leading to oxetane formation.[7] More exacting physical studies will be required to demonstrate the mechanism for this conversion, but several potential pathways can be imagined. The photoequilibration of 1 and 3 could involve $n-\pi^*$ excitation, intersystem crossing, triplet-energy transfer from carbonyl to the double bond (either intra- or intermolecularly), and subsequent collapse of the triplet olefin to the isomeric cyclooctenones. This is a well-precedented mechanistic possibility.[6] However, intermolecular energy transfer (and possibly the intramolecular counterpart) is contradicted by the lack of reaction upon photolysis in acetone solution, since the triplet acetone generated under these conditions should also be effective at energy transfer and thus promote the 1 to 3 conversion. A detailed study[8] of the photobehavior of 5-hepten-2-one, an acyclic γ,δ-unsaturated ketone, has led to the conclusion that intramolecular singlet exciplex formation accounts for the nonquenchable oxetane formation and geometrical isomerization, exceptionally short-lived excited singlet, and lack of the normally expected Norrish type II reaction that have been found for this system.[9] A similar intermediate can be invoked for the interconversion of 1 and 3 in the present system, although there is some question regarding the compatibility of the severely restricted geometries of these medium-ring compounds with the necessary relationship of the two π units for intramolecular exciplex formation. Finally, reversible formation of a Schenck-type biradical such as **4** could also explain this isomerization.[10]

Not only is the photoisomerization to **2** a relatively unprecedented type of rearrangement, formally involving 1,3 migration of an acylmethylene group,[11] but reaction appears to require excitation into some higher excited singlet state. This fact indicates that there is some very fast diverting step leading ultimately to product, since this reaction must compete with rapid relaxation by internal conversion and intersystem crossing. The fact that **2** is formed more rapidly from the trans isomer **3** may reflect its additional strain or special conformation, but a more trivial explanation is related to the more efficient absorption of low-wavelength light for **3** relative to **1**. (At 2537 Å the trans isomer has roughly four times the absorptivity of the cis compound.) The two most likely mechanism for this conversion are concerted 1,3-sigmatropic rearrangement or the stepwise equivalent proceeding by photodissociation to biradical **5**, followed by reclosure to **2**.



Experimental Section

General. Nmr spectra were obtained on CCl_4 solutions with Varian A-60 or HA-100 instruments; infrared spectra (ir) were obtained on neat samples with Perkin-Elmer 137 and 137G spectrophotometers. Ultraviolet spectra (uv) were recorded on a Cary 14 spectrophotometer. Gas chromatogrpahy (glpc) was performed on Varian Aerograph A600, A1200 (analytical), and A90-P3 (preparative) instruments. The analytical column was 10 ft × 0.125 in. of 15% Carbowax 20M on 60–80 Chromosorb W and the preparative column was 20 ft × 0.375 in. of 15% Carbowax 20M on 60–80 Chromosorb W. Mass spectra were obtained at 70 eV on AEI-MS9 and Varian-MAT CH-7 instruments. Anhydrous magnesium sulfate was used for all drying operations. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

***cis*-4-Cyclooctenone (1).** To a cooled, stirred solution of 70 g of 4-cyclooctenol[12] in 500 ml of acetone was added dropwise 160 ml of 8 *N* chromic acid. The addition required 1.5 hr, and stirring was continued for an additional 45 min at room temperature. The mixture was poured into 500 ml of water and extracted with five 150-ml portions of pentane. The pentane extracts were combined, washed twice with water, dried, and concentrated. The residue was distilled through an Annular Teflon spinning-band column to give 44 g (64%) of **1**: bp 80–85° (10 mm); ir 5.88, 6.09, 13.6, and 13.8 μ; uv (95% EtOH) end absorption ϵ_{222} 268, λ_{max} 285 nm (ϵ 16); uv (cyclohexane) end absorption ϵ_{220} 206, λ_{max} 287 nm (ϵ 11); mass spectrum *m/e* (rel intensity) 124 (24), 96 (59), 68 (92), 67 (92), 55 (57), 54 (97), 41 (65), 39 (100), 28 (46), 27 (81).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.27; H, 9.72.

***trans*-4-Cyclooctenone (3).** A solution of 12.0 g of **1** in 1200 ml of degassed cyclohexane was irradiated with a Pyrex-filtered 450-W Hanovia lamp for 20 hr. Glpc assay indicated a 60:40 mixture of **1** and **3** as the only important products. The photolysis solution was extracted with two 100-ml portions of 5% $AgNO_3$ solution. Each of these was washed with three 15-ml portions of ether and treated with excess NH_4OH. The resulting mixtures were each extracted with three 50-ml portions of ether, the ether solutions were dried, and the ether was removed. The first extraction gave 2.4 g of **3** as a colorless liquid containing 5% of **1**. The second gave 1.0 g of a mixture of **3** and **1** (85:15). Glpc collection on a 5 ft × 0.375 in. column of 20% Carbowax 20M with injector, detector, and collector temperatures at 130° and a column temperature of 120° gave 95% pure **3** (5% **1**): ir 5.88, 6.09, and 10.1 μ; nmr (neat) δ 5.9 (m, 1), 5.1 (m, 1), and 1.4–3.2 (m, 10); uv (95% EtOH) λ_{max} 222 nm (ϵ 1000), 280 (24); uv (cyclohexane) end absorption ϵ 1120, λ_{max} 285 nm (ϵ 15); mass spectrum *m/e* (rel intensity) 124 (11), 96 (41), 68 (68), 67 (73), 55 (32), 54 (100), 41 (55), 39 (91), 28 (68), 27 (73); exact mass 124.088 (calcd for $C_8H_{12}O$, 124.089).

Photolysis of 1 and 3 at 3100 Å through Pyrex. The following samples were prepared in Pyrex test tubes and irradiated at 3100 Å in a Rayonet reactor using a merry-go-round: (a) 14.7 mg of **1** (96%, no **3**) in 1.47 ml of cyclohexane; (b) 10.1 mg of **3** (95%, 5% **1**) in 1.01 ml of cyclohexane. Glpc analysis showed that after 4 hr both samples had just reached a 60:40 ratio of **1** to **3**.

Photolysis of 1 in Acetone. Irradiation of a dilute acetone solution of **1** in a Pyrex test tube with 3100-Å bulbs in the Rayonet apparatus for 45 hr gave at most 2% conversion to **3**.

Photolysis of 3. A solution of 0.30 g of **3** in 30 ml of cyclohexane was irradiated with 3100-Å lamps through a Pyrex test tube in a Rayonet reactor for 10 hr. Glpc indicated a 55:45 ratio of **1** and **3** with 7% of a much higher retention time component as the only detectable by-product. The residual **3** was extracted from the solution with 10 ml of 5% $AgNO_3$ solution. The cyclohexane solution was dried and the solvent was removed, yielding a product which gave ir and nmr data identical with those of **1**.

Photolysis of 1 in Benzene. A solution of 1.0 g of **1** in 110 ml of benzene was degassed and irradiated with a Vycor-filtered 450-W Hanovia lamp for 2 hr. Glpc assay showed a 54:46 ratio of **1** to **3**. Extraction of the benzene solution with 20 ml of 5% $AgNO_3$ solution followed by the above work-up procedure gave only 0.24 g of **3** containing 9% of **1**. Glpc analysis indicated a 79:21 ratio of **1** to **3** in the remaining benzene solution. Thus, the reaction in benzene gives a higher proportion of **3** more rapidly than the direct irradiation, but does not allow the ease of isolation of **3** observed in cyclohexane.

Low-Wavelength Photolysis of 1. A solution of 0.20 g of **1** (98% purity) in 100 ml of degassed cyclohexane was irradiated under N_2 for 30 min using a quartz probe for a 450-W Hanovia Type L lamp. Glpc analysis revealed one major product and several minor products. One minor product (6%) had the same glpc retention time as *trans*-4-cyclooctenone (**3**). Preparative glpc gave a pure sample of **2**: ir 3.24, 5.81, 6.1, 10.1, and 11.0 μ; nmr δ 5.75 (m, 1), 5.0 (m, 2), and 2.6–1.2 (m, 9); mass spectrum *m/e* (rel intensity) 124 (44), 96 (31), 81 (100), 80 (73), 67 (78), 55 (67), and 54 (70).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.13; H, 9.60.

3-Vinylcyclohexanone (2). To a stirred, cooled solution of 32 g of $Hg(OAc)_2$ in 200 ml of 50% aqueous THF was added dropwise 10.9 g of 4-vinylcyclohexene. The yellow color disappeared before all the olefin had been added. The resulting colorless solution was stirred for an additional 45 min. To this solution was slowly added 100 ml of 3 *M* sodium hydroxide followed by 100 ml of 0.5 *M* sodium borohydride in 3 *M* sodium hydroxide. The resulting mixture was diluted with 100 ml of water and washed with four 100-ml portions of pentane. The combined extracts were washed twice with water, dried, and concentrated. The residue was distilled to give 8 g of a mixture of three components in a ratio of 65:20:15, bp 40–45° (3 mm).

To a cooled, stirred solution of 8 g of this mixture of alcohols in 100 ml of acetone was added 20 ml of 8 *N* chromic acid. The ice bath was removed and stirring was continued for 30 min. The reaction mixture was poured into 150 ml of water and extracted with four 100-ml portions of pentane. The pentane extracts were washed with water, dried, and concentrated. Distillation gave 6 g of a mixture of ketones in a ratio of 62:21:17, bp 45–50° (15 mm). Isolation by glpc gave 3-cyclohexen-1-yl methyl ketone[13] [ir 3.28, 5.88, 6.05, and 11.7 μ; nmr δ 5.6 (m, 2), 2.7–1.4 (m, 7), and 2.1 (s, 3)], 3-vinylcyclohexanone, and 4-vinylcyclohexanone:[14] ir (CCl_4) 3.3, 5.82, 6.1, 10.1, and 11.0 μ; nmr δ 6.2–4.8 (m, 3) and 2.6–1.3 (m, 9); mass spectrum *m/e* (rel intensity) 124 (40), 81 (25), 68 (29), 55 (100), 54 (35).

Photolysis of 2. Photolysis of a 1.0-g sample of **2** in 110 ml of cyclohexane for 10 hr led to formation of two products plus starting material. The solvent was removed and the residue was vacuum transferred (0.1 mm) to give 0.75 g of crude product. Glpc gave bicyclohexyl (25%), starting material (36%), and a third fraction collected as a 30:70 mixture of two components (39%) which was identified as *trans*- and *cis*-3-vinylcyclohexanols: ir 3.0, 3.24, 6.1, 9.6, 10.1, and 11.0 μ; nmr δ 5.7 (m, 1), 4.9 (m, 2), 3.85 (s, 1), 3.5 (m, 1), and 2.3–0.8 (m, 8).

Lithium Aluminum Hydride Reduction of 2. To a cooled, stirred slurry of 250 mg of lithium aluminum hydride in 20 ml of ether was added dropwise 250 mg of **2** in 15 ml of ether. The resulting mixture was stirred at room temperature for 2 hr. Hydrolysis was effected by addition of aqueous HCl. The layers were separated and the aqueous layer was extracted with ether. The ether extract was washed with water and dried, and the solvent was removed by distillation to give 250 mg of a crude mixture of *trans*- and *cis*-3-vinylcyclohexanols identical with the material obtained from photolysis of **2** in cyclohexane. Glpc analysis indicated that the two isomers were present in ratio of 10:90.

Photolysis of 1 and 3 at 2537 Å. The following samples were prepared in quartz test tubes and irradiated at 2537 Å in a Rayonet reactor using a merry-go-round: (a) 10.4 mg of **1** (98%, no **3**) in 1.04 ml of cyclohexane, and (b) 13.0 mg of **3** (96% + 4% **1**) in 1.30 ml of cyclohexane. After 15 min, glpc analysis revealed that 17% of **3** had been converted to **2**, while only 3% of **1** had been converted to **2**. Conversion of **3** to **1** was also more rapid than the conversion to **1** to **3**. The difference in per cent of **2** in these reactions increased until it reached 25% (1 hr), after which time **2** decreased as the per cent of **3** reached the same level in both samples.

Acid-Catalyzed Reaction of 3. A solution of 25 mg of **3** and 3 mg of *p*-toluenesulfonic acid in 2 ml of benzene was allowed to stand for 4 days at 25°. Glpc indicated a decrease of ~20% in the amount of **3** present, but no increase in **1**.

Pyrolysis of 3. A solution of 15 mg of **3** in 1 ml of xylene was heated in reflux for 1 hr. No **2** was observed by glpc, but **1** increased relative to **3**. Quantitative glpc revealed that the increase in **1**, as well as the increase in a higher retention time product, resulted from transformation of **3** both to these compounds and to products not detectable by glpc (presumably polymers). The loss of **3** was divided about evenly between these two processes.

Registry No. 1, 31598-70-6; **2,** 1740-63-2; **3,** 43101-33-3; 4-cyclooctenol, 4277-34-3; 4-vinylcyclohexene, 100-40-3; 3-cyclohexen-1-yl methyl ketone, 7353-76-6; 4-vinylcyclohexanone, 1740-64-3; *trans*-3-vinylcyclohexanol, 43101-34-4; *cis*-3-vinylcyclohexanol, 43101-35-5.

References and Notes

(1) (a) Supported by a research grant from the NSF. (b) Alfred P. Sloan Fellow, 1968–1970; John Simon Guggenheim Fellow, 1970–1971. (c) NDEA Title IV Fellow, 1965–1968; NSF Trainee, 1968–1969. (d) PRF Predoctoral Fellow, 1968–1969.

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Deamination of 1-Adamantylamine

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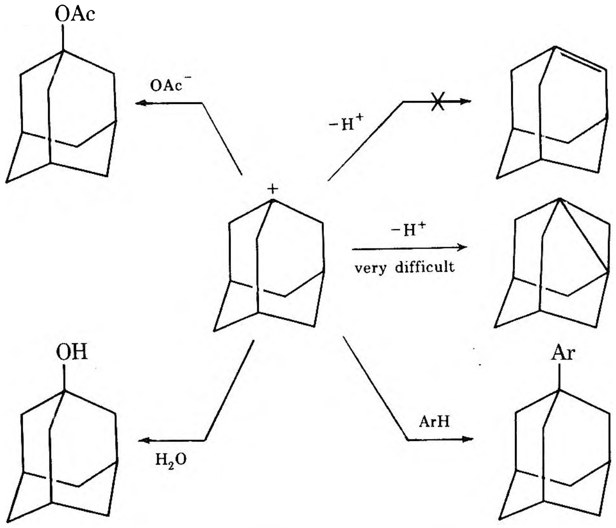
Kazanskii has reported[1] that the deamination of 1-adamantylamine by nitrous acid affords 1-adamantanol and adamantane in 20 and 80% yields, respectively. The adamantane must arise by hydride abstraction, and the necessary stoichiometry of such a process, with adamantane derivatives as the only possible hydride sources, makes the high yield of adamantane surprising. However, intermolecular hydride shifts are known for other adamantane systems[2-4] and therefore this reaction is of mechanistic interest. Accordingly, we decided to examine in detail the deamination of adamantylamines.

Two types of deamination reactions were studied: "normal," with aqueous acid and sodium nitrite;[5] and aprotic, employing isoamyl nitrite and 1 equiv of acetic acid.[6] The product analyses are contained in Table I.

Within our limits of detection (0.1%) no adamantane is formed under any conditions; the only products are 1-adamantanol and 1-adamantyl acetate. We must conclude that intermolecular hydride transfer is not an important reaction pathway in deamination, and therefore that the earlier results[1] are in error. This conclusion is strengthened by our observation that adamantane is not found even when deamination is carried out in the presence of the excellent hydride source, triphenylmethane (Table I).

In examining the literature on aprotic deaminations of alkylamines, one is struck by the minimal amount of alkylation of the aromatic solvents. Typically, only 0.5–2.5% of alkylbenzene is produced, the major products being alkene and cyclopropanes resulting from elimination and rearrangement, and alcohols or acetates.[6,7] Because the 1-adamantyl cation cannot lose a proton (Bredt's rule), and because incorporation of a cyclopropyl ring into the adamantane skeleton can be accomplished only with difficulty,[8] one might expect adamantylamine to yield significantly more alkylbenzenes than other alkylamines.



However, when the aprotic deamination of 1-adamantylamine is carried out in benzene solution, no phenyladamantane at all is detected among the products. When anisole is present, a trace (*ca.* 0.2%) of *p*-anisyladamantane is found. In each case, the only significant products are 1-adamantanol and 1-adamantyl acetate.

Friedman has suggested[9] that a tight diazonium ion–acetate ion pair is the principal intermediate in aprotic deamination in nonpolar solvents. The formation of a tight ion pair would seem to be the best explanation for our results also, with the difference that the cation is more likely the 1-adamantyl ion, because of the known ease of formation of this species.[10,11] We further suggest that the molecule of water formed along with the diazonium ion remains associated with the ion pair. Such an association is consistent with the formation of large amounts of alcohol in the absence of other intermolecular products,

Table I
Deamination Products of 1-Adamantylamine[a]

Run	Reactants	AdH	1-AdOH	1-AdOAc	1-AdAr
		Product composition, %[b]			
1	1-$AdNH_2$, $NaNO_2$ AcOH, H_2O, 5°	0.0 ± 0.1	75.0 ± 0.5	25.0 ± 0.5	
2	1-$AdNH_2$, $NaNO_2$ AcOH, H_2O, 85°	0.0 ± 0.1	70.7 ± 0.5	29.3 ± 0.5	
3	1-$AdNH_2$, $NaNO_2$ AcOH, H_2O, 85°	0.0 ± 0.1	97.0 ± 1.0	3.0 ± 1.0	
4	1-$AdNH_2$, $NaNO_2$ HCl, H_2O, 85°	0.0 ± 0.1	100.0		
5	1-$AdNH_2$, AcOH *i*-AmONO, C_6H_6	0.0 ± 0.1	41.0 ± 0.5	59.0 ± 0.5	0.0 ± 0.1
6	1-$AdNH_2$, AcOH *i*-AmONO, $PhOCH_3$	0.0 ± 0.1	44.3 ± 0.2	55.7 ± 0.2	0.2 ± 0.1
7	1-$AdNH_2$, *i*-AmONO $PhOCH_3$	0.0 ± 0.1	100.0[c]		0.0 ± 0.1
8	1-$AdNH_2$, *i*-AmONO AcOH, Ph_3CH, CCl_4	0.0 ± 0.1	37.5 ± 0.5	62.5 ± 0.5	

[a] Ad = 1-adamantyl; OAc = $OCOCH_3$; Ar = C_6H_5 or *p*-$C_6H_4OCH_3$; AcOH = CH_3COOH; *i*-Am = *i*-C_5H_{11}. [b] See Experimental Section for analytical details. [c] Formed in 24% yield; 76% 1-$AdNH_2$ recovered.

for the collapse of the "solvated" ion pair to alcohol and acetate certainly should be more rapid than its dissociation in the low dielectric aromatic solvents.

In the aqueous systems, the tight ion pair likely is in equilibrium with a solvent-separated one, from which the alcohol product is formed.

Experimental Section

Analytical Procedure. The reaction product (crude, isolated as below) was dissolved in a minimum volume of ether or methylene chloride and analyzed by gas chromatography. The instrument employed was a Perkin-Elmer Model 810 gas chromatograph equipped with dual 12 ft × 0.125 in. columns packed with 10% DC-550 silicone oil on Chromosorb W HMDS, and a flame ionization detector. Helium was the carrier gas, and analyses were conducted at an oven temperature of 195°. Authentic samples were used for peak identification by both absolute retention time and peak enhancement. All peak areas were measured with a planimeter. All percentages reported in Table I are the average of at least three measurements on each of three separate chromatograms.

General Procedure for Deamination. Run 1. A mixture of 2.5 g (0.0165 mol) of 1-adamantylamine, 40 ml of glacial acetic acid, and 10 ml of water was placed in a three-neck flask equipped with a thermometer, a mechanical stirrer, and an addition funnel. The mixture was cooled to 5°, and a solution of 1.26 g (0.0182 mol) of sodium nitrite in 5 ml of water was added dropwise. The resulting mixture was allowed to warm to room temperature and then heated gently until nitrogen evolution ceased. After neutralization with dilute sodium hydroxide, the solution was extracted several times with ether. The combined ether extracts were washed with water and brine and dried over magnesium sulfate. The solution was then concentrated to about 5 ml by careful distillation, and the concentrate was analyzed.

Run 2. The general procedure was followed save that the entire reaction was run at 85°.

Run 3. Conditions for this run were identical with those reported by Kazanskii.[1] A mixture of 2.50 g (0.0165 mol) of 1-adamantylamine, 1.75 ml (0.0307 mol) of glacial acetic acid, and 15 ml of water was placed in a flask. Over 45 min 1.375 g (0.020 mol) of sodium nitrite in 5 ml of water was added. The reaction mixture was heated on the steam bath for 45 min, and the products were isolated as in run 1.

Run 4. The procedure of run 3 was followed, except that 2.5 ml of concentrated hydrochloric acid replaced the acetic acid.

General Procedure for Aprotic Deamination. Run 5. Into a three-neck flask equipped with a mechanical stirrer, a reflux condenser, and an addition funnel were placed 2.513 g (0.0165 mol) of 1-adamantylamine, 0.922 g (0.0165 mol) of glacial acetic acid, and 40 ml of benzene. To this heterogeneous mixture was added dropwise at room temperature a solution of 2.134 g (0.0182 mol) of isoamyl nitrite in 10 ml of benzene. Addition was complete in 45 min. The reaction mixture was heated at reflux on a steam bath for 3 hr. After cooling, it was washed in turn with saturated sodium bicarbonate solution, water, and brine, and dried over magnesium sulfate. The dried extracts were concentrated to about 5 ml by careful distillation, and the concentrate was analyzed.

Run 6. The procedure of run 5 was followed with anisole in place of benzene.

Run 7. The procedure of run 5 was followed, omitting the glacial acetic acid.

Run 8. The procedure of run 5 was followed, employing carbon tetrachloride as the solvent. Triphenylmethane (4.446 g, 0.0182 mol) was added at the beginning of the process.

Registry No. 1-Adamantylamine, 768-94-5.

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A New Synthesis of β,γ-Unsaturated Aldehyde Derivatives. Acid-Catalyzed Rearrangements of 1-Alkylidene-2-alkoxycyclopropanes[1]

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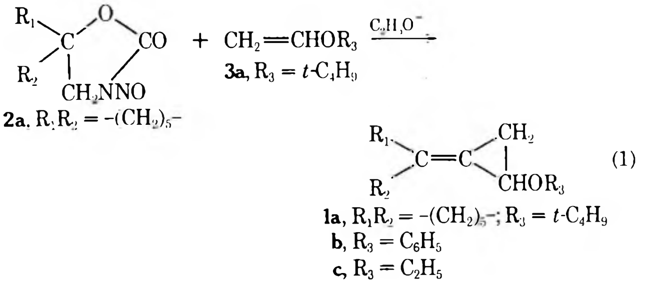
In earlier work the facile synthesis of 1-alkylidene-2-alkoxycyclopropanes (1) by the generation of unsaturated carbenes from *N*-nitrosooxazolidones (2) in the presence of vinyl ethers (3) has been described.[3] The ready availability of such compounds made a study of their chemical reactivity of interest.



2a, $R_1R_2 = -(CH_2)_5-$

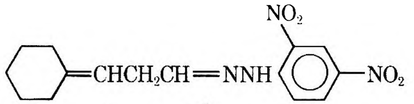
3a, $R_3 = t\text{-}C_4H_9$

(1)

1a, $R_1R_2 = -(CH_2)_5-$; $R_3 = t\text{-}C_4H_9$
b, $R_3 = C_6H_5$
c, $R_3 = C_2H_5$

The synthesis of 1-cyclohexylidene-2-*tert*-butoxycyclopropane (**1a**) in 67% yield was accomplished before the improved method of generation of unsaturated carbenes[4] had been studied. The yields of **1b** and **1c** were 44 and 24%, respectively, but no attempts were made to maximize these yields.

On treatment of **1a** with 2,4-dinitrophenylhydrazine reagent[5] at room temperature an almost quantitative yield of the yellow 2,4-dinitrophenylhydrazone of 3-cyclohexylidenepropanal (4) was obtained. This compound rearranged easily to the red 2,4-dinitrophenylhydrazone of 3-cyclohexyl-2-propenal (5) on recrystallization from alcohol. However, if precautions were taken to wash out all acid with carbonate, 4 could be recrystallized unchanged. All attempts to obtain 3-cyclohexylidenepropanal failed, as this aldehyde is evidently so labile that tarry materials are rapidly produced even in the cold under a variety of acidic conditions.



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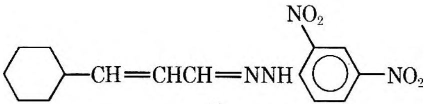

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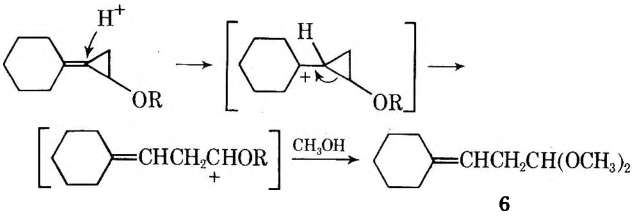
On treatment of a methanolic solution of **1a** with a cation exchange resin at room temperature, the dimethyl acetal of 3-cyclohexylidenepropanal (**6**) was produced in high yield. The fact that a mixed acetal was not found stems from acid-catalyzed ketal exchange with the excess methanol. A likely mechanism is shown in Scheme I. This reaction is unique in that the acetal of a β,γ-unsaturated aldehyde is produced in one step from a readily available intermediate.

Scheme I



6

Experimental Section

N-**Nitroso-1-oxa-3-azaspiro[4.5]decan-2-one (2a).** This compound was prepared as described[6] when needed.

1-Cyclohexylidene-2-*tert*-butoxycyclopropane (1a). To a solution at room temperature of 10.0 g of **2a** in 100 ml of freshly distilled *tert*-butyl vinyl ether,[7] bp 78.5-79.5°, was added 5.5 g of lithium ethoxide ethanolate[8] in one portion. The temperature rose rapidly to 72° and the theoretical amount of nitrogen was collected during the first 10 min. After the reaction mixture was washed with a small amount of dilute acid and saturated salt solution, the organic layer was passed through a cone of anhydrous magnesium sulfate. The filtrate on distillation through a spinning band column yielded 6.97 g (66%) of **1a**: bp 92.8-93.1° (7.0 mm); ir (neat) 5.61 μ (for a double bond exocyclic to a cyclopropane[9]); nmr [$(CH_3)_4Si$ 10.0, CCl_4] τ 6.44 (unresolved triplet, 1, $CHOC_4H_9$), 7.75 (m, 4, allylic cyclohexyl H), 8.43 [m, 6, $-(CH_2)_3-$], 8.77 [s, 9, $(CH_3)_3C-$], and 8.94 (m, 2, cyclopropyl CH_2). This experiment was the best of six varying runs.

Anal.[10,11] Calcd for $C_{13}H_{22}O$: C, 80.4; H, 11.4. Found: C, 80.3; H, 11.4.

1-Cyclohexylidene-2-phenoxycyclopropane (1b). In one similar run involving 10.0 g of **2a**, 75 ml of freshly distilled phenyl vinyl ether,[7] and 5.5 g of lithium ethoxide ethanolate[8] the temperature rose to 78°. After a similar work-up there was isolated 5.1 g (44%) of **1b**, bp 112-113° (0.4 mm), mp 44.0-45.2°. The analytical sample,[11] mp 43.5-45.0°, was obtained after recrystallization from methanol and vacuum sublimation.

Anal.[12] Calcd for $C_{15}H_{18}O$: C, 84.1; H, 8.5. Found: C, 83.8; H, 8.3.

1-Cyclohexylidene-2-ethoxycyclopropane (1c). In a similar run in which ethyl vinyl ether[7] was used a 24% yield of **1c**, bp 69.0-71.5° (2.5 mm),[11] was obtained.

Anal.[10] Calcd for $C_{11}H_{18}O$: C, 79.5; H, 10.9. Found: C, 79.3; H, 11.1.

3-Cyclohexylidenepropanal Dimethyl Acetal (6). A mixture of 4.0 g of **1a** in 50 ml of dry methanol and 15 g of Dowex 50W-4, a cation exchange resin, was stirred at room temperature for 20 hr. After filtration of the resin, most of the methanol was removed under reduced pressure and the residue was dissolved in ether and treated with 10% sodium bicarbonate. After a conventional work-up, distillation afforded 2.90 g (77%) of **6**,[11] bp 92.5-95.0° (6.5 mm).

Anal.[10] Calcd for $C_{11}H_{20}O_2$: C, 71.7; H, 11.0. Found: C, 71.6; H, 11.1.

3-Cyclohexylidenepropanal 2,4-Dinitrophenylhydrazone (4). On mixing 0.80 g of **1a** and 20 ml of 2,4-dinitrophenylhydrazine reagent,[5] a yellow precipitate formed rapidly. This solid was collected after 5 min and washed with cold alcohol. On drying 1.28 g (97%) of crude **4**, mp 120-125° dec, was obtained. This material darkened in the melting point capillary before melting. A solution of this yellow solid in ethyl acetate was washed with 10% sodium bicarbonate. The resulting yellow 2,4-DNPH derivative, **4**, uv λ_{max} 360 mμ (ϵ 24,500),[13] melted at 131.5-134.0° without darkening prior to melting.[11] If the original yellow solid, **4**, was recrystallized from hot ethanol without the alkaline wash a red 2,4-DNPH derivative, **5**, mp 206.0-207.5°, uv λ_{max} 379 mμ (ϵ 28,300),[13] was obtained.[11]

Anal. Calcd for $C_{15}H_{18}N_4O_4$: N, 17.6. Found (**4**):[10] N, 17.6. Found (**5**):[12] N, 17.7.

Similar results were obtained with **1b** and **1c**.

Registry No. 1a, 37150-71-3; **1b**, 37150-69-9; **1c**, 37150-70-2; **2a**, 20498-55-9; **3a**, 926-02-3; **3b**, 766-94-9; **3c**, 109-92-2; **4**, 42880-51-3; **5**, 6556-91-8; **6**, 42880-53-5.

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Synthesis of Mixed Disulfides with Cyanogen Bromide and Its Consequences for Elucidation of Protein Structure

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For a study of the mechanism of a new bacterial enzyme that catalyzes the synthesis of γ-cyanoaminobutyric acid and thiocyanate from a mixture of homocystine (1) and cyanide, a route to γ-thiocyano-α-aminobutyric acid (3) as a possible intermediate was sought.[1] For this purpose homocysteine (4) was treated with cyanogen bromide. During the course of the alkylation, which furnished the desired thiocyanoamino acid in low yield, large amounts of homocystine also formed. This suggestion, that CNBr was acting in effect also as a thiol oxidizing agent, became even clearer when an attempt was made to prepare the starting 4 *in situ* by reduction of the more available 1 with 10 equiv of 2-mercaptoethanol before treatment with CNBr. After 2 hr at pH 9.3 the mixture contained, as determined on the amino acid analyzer,[2] 43% 4, 7% 1, and 39% of the new mixed disulfide of homocysteine and 2-mercaptoethanol, 1-DL-amino-7-hydroxy-4,5-dithiaheptane-1-carboxylic acid (6). Addition of 12.5 equiv of CNBr resulted in a mixture of 9% 4, 12% 1, and 72% 6. Apparently CNBr served to combine 1 equiv of 2-mercaptoethanol with 1 equiv of homocysteine liberated by nucleophilic attack of 2-mercaptoethanol on homocystine, to give a second mole of the mixed disulfide, 6. The effective reaction is the conversion of both alkyl residues of a symmetrical dialkyl disulfide into 2 mol of a mixed disulfide. In this respect it is similar to the excellent method of Schöberl and Gräfje for mixed disulfides,[3] in which the symmetrical disulfide is oxidized first with peracid to a thiolsulfinate ester that is then treated with a mercaptan. When applicable the combined reduction–CNBr procedure may be more convenient than the thiolsulfinate route. Formation of a symmetrical disulfide as a by-product in the synthesis of alkyl thiocyanates from mercaptans and CNBr has been noticed occasionally by others.[4,5] Moreover, in work on antiradiation compounds, Foye and coworkers reported an unexpected synthesis of 2-aminoethyl disulfide and 2-guanidinoethyl disulfide from the mercaptans and CNBr which they stated was applicable to a number of other symmetrical disulfides, including cystine and homocystine.[6]

$$[\mathrm{HOOCCHNH_2(CH_2)_nS}]_2 \qquad \mathrm{HOOCCHNH_2(CH_2)_nSH}$$

$$\mathbf{1}, n = 2 \qquad \mathbf{4}, n = 2$$

$$\mathbf{2}, n = 1 \qquad \mathbf{5}, n = 1$$

$$\mathrm{HOOCCHNH_2(CH_2)_2SCN}$$

$$\mathbf{3}$$

$$\mathbf{1} \xrightarrow{\mathrm{HOCH_2CH_2SH}} \underset{\mathbf{6}}{\mathrm{HOOCCHNH_2CH_2CH_2SSCH_2CH_2OH}} + \mathbf{4} \xrightarrow[\mathrm{CNBr}]{\mathrm{HOCH_2CH_2SH}} \mathbf{6} \qquad (1)$$

DL-Homocysteine-2-mercaptoethanol mixed disulfide, 6, the product of sequence 1, was desalted and purified on a small Dowex 50-X8 resin column and, after crystallization, was obtained in 44% yield. Treatment of the sulfhydryl compound L-4 with excess 2-mercaptoethanol and CNBr furnished 6a in somewhat higher initial yield and purity (88% 6a and 12% 1) than the route starting from the disulfide 1. The product was isolated directly from the reaction mixture by crystallization. Like homocystine and γ-thiocyanoaminobutyric acid (3), 6a is a substrate for the enzymatic synthesis of γ-cyanoaminobutyric acid, presumably by first undergoing cyanolysis to 3.[1]

$$\mathrm{HOOCCHNH_2(CH_2)_nSSR}$$

$$\mathbf{6}, n = 2;\ \mathrm{R = CH_2CH_2OH}$$

$$\mathbf{7}, n = 1;\ \mathrm{R = CH_2CH_2OH}$$

$$\mathbf{8}, n = 2;\ \mathrm{R = CH_2COOH}$$

$$\mathbf{9}, n = 2;\ \mathrm{R = CH_2CHNH_2COOH}$$

$$[\mathrm{HOOCCHNH_2CH_2CH_2CONH\underset{\displaystyle \mathrm{CH_2S}—}{CH}CONHCH_2COOH}]_2$$

10

L-Cysteine (5) with excess 2-mercaptoethanol and CNBr formed in 93% yield the corresponding mixed disulfide of 5 and 2-mercaptoethanol, 1-L-amino-6-hydroxy-3,4-dithiahexane-1-carboxylic acid (7), that was also isolated directly by crystallization. It was chromatographically homogeneous and had the expected nmr spectrum. Its elution volume on the analyzer between proline and glycine was consistent with that reported previously for this compound when tentatively identified in an acid hydrolysate of mercaptoethanol-treated β-mercaptopyruvate transsulfurase.[7] Discrepant constants for 7 appear in the literature. The CNBr product agreed in melting point with 7 prepared by cooxidation of 5 and 2-mercaptoethanol[8] and in optical rotation with 7 prepared by treatment of 2-mercaptoethanol disulfide with 5.[3] The high isolated yields of 6a and 7 are attributed in part to the use of the large excess of 2-mercaptoethanol and to the ready removal by crystallization of the by-product, presumably 2-mercaptoethanol disulfide.

L-Homocysteine-2-mercaptoacetic acid mixed disulfide, 1-L-amino-4,5-dithiahexane-1,6-dicarboxylic acid (8), was also required for the study of the mechanism of the enzymatic utilization of homocystine.[1] It was prepared in a similar way from 4, excess 2-mercaptoacetic acid, and CNBr. DL-8 had been synthesized in 30% yield by reaction of DL-homocystine thiolsulfinate with 2-mercaptoacetic acid.[3]

Treatment of an equimolar mixture of L-homocysteine and L-cysteine with 2 equiv of CNBr in 0.1 *N* HCl gave, along with small amounts of 1 and 2, 59% of L-homocysteine–cysteine mixed disulfide 1-L,7-L-diamino-4,5-dithiaheptane-1,7-dicarboxylic acid (9). Identification of the latter was based on its chromatographic appearance on the analyzer in the "leucine-isoleucine area" previously described for this compound.[9,10] A chromatographic procedure is available for purifying 9 from a similar mixture also containing 1 and 2.[10] This mixed disulfide, which is excreted by individuals with cystinuria and homocystinuria[9,11] and with a derangement of $\mathrm{B_{12}}$ metabolism,[12] had been synthesized before in undisclosed yield by cooxidation in air of a mixture of 4 and 5.[9,10] DL-Homocysteine–L-cysteine mixed disulfide had been synthesized in 60% yield by reaction of DL-homocystine thiolsulfinate with 5.[3]

Symmetrical disulfides were prepared by treating 0.29 *M* mercaptan in 0.1 *N* HCl with approximately 2 equiv of CNBr. L-Cysteine yielded L-cystine (2); after one reprecipitation this product, obtained in 85% yield, had an optical rotation that agreed within 2% with the reported value for 2. 4 yielded 55% 1 and 8% 3; glutathione yielded 91% oxidized glutathione (10) as determined on the amino acid analyzer. CNBr should therefore be added to the group of mild oxidizing agents including $\mathrm{O_2}$, $\mathrm{H_2O_2}$, $\mathrm{I_2}$, $\mathrm{CH_2I_2}$, and

$K_3Fe(CN)_6$ that can be useful for synthesizing mixed and symmetrical disulfides from mercaptans.[13]

CNBr has come into extensive use for elucidation of protein structure for its specific degradation at methionine residues.[14] However, the significance of the disulfide-forming side reaction in this connection seems largely to have gone unnoticed. The early reports of Gross and Witkop on the CNBr degradation of proteins mention only that cysteine reacts slowly at its sulfhydryl group with CNBr[14] and that it is oxidized slowly to cysteic acid.[15] It was suggested that a sulfhydryl-containing protein or peptide be converted to its *S*-carboxymethyl derivative prior to treatment with CNBr,[15] a procedure that should circumvent disulfide formation as well as oxidation of cysteinyl to cysteyl residues. Although this suggestion has generally been followed, *e.g.*, an investigation of the half-cystine containing calf thymus F_3 histone,[16] some cysteine-containing proteins have been treated with CNBr without prior protection and the products have been examined directly. These include the monomeric component of hemoglobin from the bloodworm, *Glycera dibranchiata*,[17] and human serum albumin.[18] The latter, which has a single sulfhydryl group, yielded similar fragment resolution whether or not it had been pretreated with iodoacetate before being subjected to CNBr. However, with the unprotected albumin, aggregation took place and was attributed to incomplete cleavage and disulfide interchange.[18] When myosin, with about 42 sulfhydryl groups,[19] was treated in preliminary studies with CNBr at pH 3 and 6.5, extensive precipitation and gel formation took place, and a soluble macromolecular product could not be isolated.[20] It is clear that disulfide formation could be a factor in the aggregation process for cysteine-containing proteins when treated with CNBr. Such disulfide products would constitute erroneous structures. It has sometimes been the practice to treat an unprotected protein with CNBr and, to obtain still smaller fragments, reduce with dithiothreitol or 2-mercaptoethanol and then to *S*-carboxymethylate. Although the reductive procedure would tend to dissipate disulfides formed by CNBr, to complete the structure elucidation it may be necessary to study unreduced overlap peptides, and interpretation errors due to CNBr-mediated disulfide formation could arise at this point. The advisability of suitably modifying protein sulfhydryl before treatment with CNBr is again evident.

Experimental Section

DL-Homocystine and cysteine·HCl·H_2O were from Mann Research Laboratories, 2-mercaptoethanol (ME) was from Sigma, and oxidized glutathione was from C. F. Boehringer and Sons. Glutathione and cyanogen bromide (99.8% as redetermined by I_2-thiosulfate titrimetry)[21] were from Matheson Coleman and Bell. L-Homocysteine was prepared as described.[22] Thin layer chromatography (tlc) was on strips of Eastman Chromagram 6064 cellulose, and paper chromatography (pc) was on Whatman No. 1 in pyridine–water–*n*-butyl alcohol–acetic acid (1:2:4:1). The strips were treated with ninhydrin.

The nmr spectrum was determined at 60 MHz with a Varian Model EM-360 nmr spectrometer. Chemical shifts are expressed in δ values (parts per million) relative to a Me_4Si external standard. Melting points and optical rotations were taken and amino acid analyses with systems A and B were carried out as described elsewhere.[23] System C refers to system B but at 15°. Elution volumes and ninhydrin color-yield constants were as follows: in system A, **10**, 231 ml, c 31.6; **7**, 280 ml between proline and glycine,[7] *c* 15.9; **9**, 517 ml (45 ml after indication of the change to 4.26 and 50°),[23] *c* 37 (the constant for homolanthionine was assumed; **8**, 5 ml before **1** and 9 ml before Met, *c* 21; in system C, **4**, 48 ml, *c* 21; **1**, 109 ml, *c* 37.6; **6**, 93 ml, *c* 20.3. **1** and **6** did not separate in system B. Reactions were generally under N_2 and were followed by the disappearance of sulfhydryl as determined by the nitroprusside test on paper.[24]

DL-Homocysteine–2-Mercaptoethanol Mixed Disulfide [1-DL-Amino-7-hydroxy-4,5-dithiaheptane-1-carboxylic Acid (6)]. A suspension of DL-**1** (1.34 g, 5 mmol) in 200 ml of deaerated water was adjusted to pH 9 with concentrated NH_3 and stirred under N_2 with ME (3.49 ml, 50 mmol). After 2 hr it was readjusted to pH 9. To the clear solution CNBr (6.47 g, 61 mmol) dissolved in 50 ml of water was added in portions over 10 min at 25°. The solution was taken to dryness and the solid residue, 4.4 g, was collected with the aid of ethanol–ether. This was dissolved in 7 ml of hot water, acidified to pH 2, and applied to a Dowex 50-X8 (H^+) resin column (1.5 × 25 cm). The column was treated with water until the effluent became neutral and then with pyridine acetate buffer, pH 4.45. Fractions of 4 ml were collected. Elution progress was monitored by tlc. Fractions 33–40, R_f 0.52, were combined and lyophilized and yielded 1.28 g of **6**. Subsequent fractions contained **1**, R_f 0.2, as well as **6**. The product was crystallized from 8 ml of 70% ethanol and was recrystallized: 864 mg (41%) of lustrous plates, mp 216–217.5° dec, homogeneous on amino acid analyanalysis and tlc.

Anal. Calcd for $C_6H_{13}NO_3S_2$ (211.3): C, 34.1; H, 6.0; N, 6.63; S, 30.4. Found: C, 34.1; H, 6.32; N, 6.74; S, 30.1.

L-Homocysteine–2-Mercaptoethanol Mixed Disulfide [1-L-Amino-7-hydroxy-4,5-dithiaheptane-1-carboxylic Acid (6a)]. A solution of L-**4** (1.08 g, 8 mmol) in 56 ml of 10% ME (80 mmol) in 0.1 *N* HCl was treated with CNBr (14 g, 133 mmol) as described for **7**. Crystallization from 70% ethanol yielded 765 mg (45%) of **6a** as lustrous needles, homogeneous on amino acid analysis and tlc, mp 229° dec, $[\alpha]^{24.5}{}_D$ +42.6° (*c* 1, 1 *N* HCl).

Anal. Found: C, 34.2; H, 6.16; N, 6.71; S, 30.3.

L-Cysteine–2-Mercaptoethanol Mixed Disulfide [1-L-Amino-6-hydroxy-3,4-dithiahexane-1-carboxylic Acid (7)]. L-Cysteine·HCl·H_2O (1.05 g, 6 mmol) was dissolved in 42 ml of 10% ME (60 mmol) in 0.1 *N* HCl. To it a solution of CNBr (9.47 g, 90 mmol) in 60 ml of 0.1 *N* HCl was added portionwise with magnetic stirring and cooling to maintain room temperature. The mixture was then taken to dryness, 50 ml of water was added, and evaporation was repeated. The residue was taken up in water and adjusted to pH 5, and the solvent was removed. The residue was crystallized from 70% ethanol to give 887 mg, mp 188–189° dec.

Recrystallization yielded 807 mg (68%) of **7**, homogeneous on amino acid analysis: tlc, R_f 0.41; pc, R_f 0.35; mp 182.5–183.5° dec; $[\alpha]^{26}{}_D$ −242° (*c* 1, 1 *N* acetic acid); $[\alpha]^{24}{}_D$ −137° (*c* 0.5, 1 *N* HCl). The reported values are mp 161–162° dec; $[\alpha]^{20}{}_D$ −140.8° (*c* 0.8, 1 *N* HCl);[3] and mp 184–187° dec; $[\alpha]^{20}{}_D$ −92.1° (*c* 0.4);[8] nmr (NaOD) δ 2.95 (2 H, t, $J = 6$ Hz, $^5CH_2$), 3.28 (d, $J = 4$ Hz) and 3.11 (s, sum of 2 H, $^2CH_2$), 3.88 (2 H, d, $J = 6$ Hz, $^6CH_2$), 4.16 (1 H, t, $J = 4$ Hz, ^1CH.

Anal. Calcd for $C_5H_{11}NO_3S_2$ (197.3): C, 30.5; H, 5.62; N, 7.1; S, 32.5. Found: C, 30.2; H, 5.48; N, 7.23; S, 32.7.

L-Homocysteine–2-Mercaptoacetic Acid Mixed Disulfide [1-L-Amino-4,5-dithiahexane-1,6-dicarboxylic Acid (8)]. Prepared as described for **7** from L-**4**, 2-mercaptoacetic acid, and CNBr, **8** was obtained in a crude yield of 91%. It was isolated with Dowex 50-X8 resin as described for **6** and was recrystallized from 70% ethanol: 30% yield; mp 183–185°; $[\alpha]^{24}{}_D$ +6.1° (*c* 0.7, H_2O).

Anal. Calcd for $C_6H_{11}NO_4S_2$ (225.3): C, 32.0; H. 4.92; N, 6.22; S, 28.5. Found: C, 32.0; H, 4.99; N, 6.28; S, 28.2

L-Cystine (2). A solution of L-cysteine·HCl·H_2O (2.63 g, 15 mmol) in 50 ml of 0.1 *N* HCl was treated with CNBr (3.71g, 35 mmol) in 50 ml of 0.1 *N* HCl as described for **7**. After evaporation the residue was dissolved in a minimum of water, and the solution was adjusted to pH 5 with concentrated NH_3 when the product precipitated. After being cooled this was filtered off, resuspended in 10 ml of water, dissolved by the addition of concentrated HCl, and reprecipitated in the same way. **2** was collected and washed with water until halide-free, then with ethanol and ether: yield 1.51 g (85%); $[\alpha]^{24.5}{}_D$ −211° (c 1.1, 1 *N* HCl); reported for **2** $[\alpha]^{25}{}_D$ − 215°.[25] It was homogeneous on amino acid analysis with a quantitative recovery.

L-Homocysteine–L-Cysteine Mixed Disulfide [1-L,7-L-Diamino-4,5-dithiaheptane-1,7-dicarboxylic Acid (9)]. A solution of **4** (13.8 mg, 0.1 mmol) and cysteine·HCl·H_2O (17.9 mg, 0.1 mmol) in 0.35 ml of 0.1 *N* HCl was treated with CNBr (30 mg, 0.28 mmol). After 20 min the solution was taken to dryness and the residue was taken up in water. Amino acid analysis showed 59% **8**, 15% **1**, and 13% **2**.

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Registry No. DL-**1**, 870-93-9; L-**2**, 56-89-3; L-**4**, 6027-13-0; L-**5** HCl, 52-89-1; **6**, 42855-17-4; **6a**, 42855-18-5; **7**, 38254-63-6; **8**, 42855-20-9.

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The Lewis Acid Catalysis of Ene Reactions

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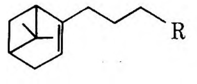
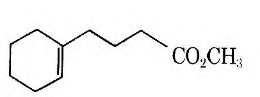
The ene reaction of olefins with highly activated enophiles has been well studied and is a synthetically useful reaction.[2] With less reactive enophiles such as methyl vinyl ketone and methyl acrylate, the ene reaction is of little value, since harsh conditions are required and yields are usually low.[2-4] Since Diels–Alder reactions often proceed in much higher yield and with greater stereospecificity in the presence of Lewis acid catalysts, it was decided to study the ene reaction of olefins with moderately reactive enophiles in the presence of these catalysts.

The reaction of (−)-β-pinene with methyl acrylate in the presence of aluminum chloride at *room temperature* gave the ene adduct **1** in 70% yield. Similarly, (−)-β-pinene with methyl vinyl ketone or acrolein in the presence of zinc bromide at *room temperature* afforded the adducts **2** and **3** in 62 and 32% yields, respectively. In the absence of Lewis acid catalysts, (−)-β-pinene reacted with acrolein at 135° for 17 hr to give a 30% yield of **3**[5] and with acrylonitrile at 230° for 6 hr to give a 41% yield of **4**.[4] From these data it is clear that Lewis acid catalysts greatly accelerate the ene reaction.



1, R = CO_2CH_3
2, R = $COCH_3$
3, R = CHO
4, R = CN



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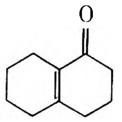
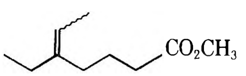


6

The reaction of methylenecyclohexane with methyl acrylate in the presence of aluminum chloride gave the known ester **5**[6] in 70% yield. The reported conversion of **5** to the acid chloride followed by a Friedel–Crafts type acylation results in a very short and efficient synthesis of the octalone **6** (59% from **5**).[6] The reaction of 2-ethyl-1-butene with methyl acrylate under similar conditions afforded a mixture from which the ene adduct **7** and the 2:1 adducts **8** and **9** were isolated in 59 and 9% yield, respectively. The 2:1 adducts are presumably obtained by ene reaction of the original adduct **7** with methyl acrylate. In support of this, it was found that, by allowing the reaction to proceed for a longer time in the presence of excess methyl acrylate, higher yields of **8** and **9** and lower yields of **7** were obtained. The 2:1 adduct mixture was identified by its mass spectra, by the doublet in the nmr spectra at δ 0.98 due to the methyl groups of **8** and **9**, and by the triplet at δ 0.95 due to the second methyl group of **9**. 2-Methyl-1-pentene and methyl acrylate under similar conditions gave a complex mixture of the 1:1 adducts **10** and the 2:1 adducts **11** and **12** which was not investigated further.



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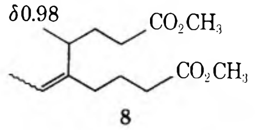

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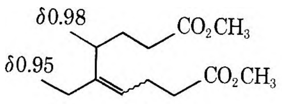

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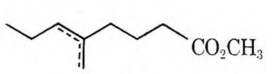

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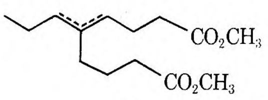

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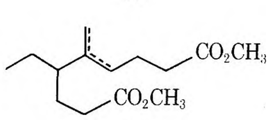

12

It has previously been observed that 1,1-disubstituted olefins give the highest yields in thermal ene reactions.[4] In this study ene reactions were obtained only with 1,1-disubstituted olefins. Preliminary experiments indicated that ene products were not obtained from methyl acrylate and allylbenzene, 1-octene, cyclohexene, or allyl bromide. It was also found that a mixture of products was obtained from (−)-β-pinene and methyl methacrylate or methyl *trans*-crotonate.

The ene reaction of olefins with dienophiles in the presence of Lewis acid catalysts provides an effective synthesis of compounds not readily available by other methods.

Experimental Section

Reaction of (−)-β-Pinene with Methyl Acrylate. To a solution of methyl acrylate (10.3 g, 0.12 mol) in 50 ml of dry benzene was added aluminum chloride (1.4 g, 0.01 mol). After the aluminum chloride had dissolved, (−)-β-pinene (13.6 g, 0.10 mol) was added. The solution was stirred for 48 hr at 25°, 25 ml of saturated sodium bicarbonate solution was added, and the solution was filtered by suction from the precipitated alumina. The organic layer was removed and the aqueous layer was extracted with 3 × 30 ml of ether. The combined organic extracts were dried over sodium sulfate and evaporated, giving 17 g of colorless liquid. Fractional distillation gave 15.38 g (70%) of **1**, bp 90° (0.5 mm). A gc retention time of 4.82 min (6 ft, 5% SE-30, 151°) showed the product to be greater than 98% pure: nmr ($CDCl_3$) δ 5.19 (1 H, br, CH=), 3.76 (3 H, s, OCH_3), 1.5-2.5 (12 H, m), 1.27 (3 H, s, CH_3), and 0.83 (3 H, s, CH_3); ir (neat) 2920, 1740, 1430, 1360, 1200, and 1160 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}O_2$: mol wt, 222.1620. Found: mol wt, 222.1616.

Reaction of Methylenecyclohexane with Methyl Acrylate. To a solution of methyl acrylate (1.3 g, 15 mmol) in 5 ml of benzene were added aluminum chloride (0.14 g, 1 mmol) and methylenecyclohexane (1.25 g, 13 mmol). The solution was stirred for 48 hr at 25° and worked up as described above, giving 1.66 g (70%) of **5**. A gc retention time of 3.15 min (6 ft, 5% SE-30, 143°) indicated that the material was *ca.* 97% pure: nmr ($CDCl_3$) δ 5.4 (1 H, m, CH=), 3.67 (3 H, s, OCH_3), 2.26 (2 H, t, *J* = 6.5 Hz, CH_2CO_2), and 1.3-2.1 (12 H, m, CH_2); ir (neat) 2940, 2850, 1745, 1440, 1250, and 1160 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_2$: mol wt, 182.1307. Found: mol wt, 182.1311.

Reaction of 2-Ethyl-1-butene with Methyl Acrylate. To a solution of methyl acrylate (10.3 g, 0.12 mol) in 50 ml of benzene was added aluminum chloride (1.4 g, 0.01 mol). After the aluminum chloride had dissolved, 2-ethyl-1-butene (8.4 g, 0.10 mol) was added. The solution was stirred for 72 hr at 25° and worked up as described for **1**, giving 14.2 g (83%) of yellow oil. Gc (6 ft, 5% SE-30, 115-190°) indicated this to be a mixture consisting of 83% of **7**, 13% of **8** and **9**, and 4% of two unidentified minor products. A 10-g portion of this was distilled, giving 7 g (58%) of methyl 5-ethyl-5-heptenoate (**7**), bp 78° (6 mm). Gc indicated the distillate to be greater than 95% pure. Gc indicated that the residue (1.3 g, 9%) consisted of 92% of a mixture of diadducts (**8** and **9**) and 8% of **7**.

The spectral data for **7** are ir (neat) 2960, 2870, 1740, 1435, 1245, 1200, and 1150 cm^{-1}; nmr ($CDCl_3$) δ 5.2 (1 H, q, *J* = 6 Hz, CH=), 3.66 (3 H, s, OCH_3), 1.7-2.5 (8 H, m), 1.58 (3 H, d, *J* = 6 Hz, CH_3), and 0.96 (3 H, t, *J* = 7 Hz, CH_3); gc retention time 3.8 min (6 ft, 5% SE-30, 112°).

Anal. Calcd for $C_{10}H_{18}O_2$: mol wt, 170.1303. Found: mol wt, 170.1307.

The spectral data for **8** and **9** are ir (neat) 2900, 2870, 1740, 1435, 1245, 1200, and 1168 cm^{-1}; nmr ($CDCl_3$) δ 4.9-5.5 (1 H, m, CH=), 3.63 (6 H, s, OCH_3), 1.3-2.5 (11 or 14 H, m), 0.98 (3 H, d, *J* = 6.5 Hz, $CHCH_3$), and 0.95 (0 or 3 H, t, *J* = 6 Hz, CH_3); gc retention time 3.2 min (6 ft, 5% SE-30, 185°).

Anal. Calcd for $C_{14}H_{24}O_4$: mol wt, 256.1674. Found: mol wt, 256.1668.

Reaction of 2-Methyl-1-pentene with Methyl Acrylate. To a solution of methyl acrylate (1.03 g, 12 mmol) in 5 ml of benzene was added aluminum chloride (0.28 g, 2 mmol). After dissolution of the aluminum chloride, 2-methyl-1-pentene (0.82 g, 10 mmol) was added and the solution was stirred for 96 hr at 25°. Work-up as for **1** gave 1.2 g (71%) of colorless oil. Gc (6 ft, 5% SE-30, 115-190°) indicated that a complx mixture of the various 1:1 and 2:1 adducts with methyl acrylate were present. These were not separated: ir (neat) 2960, 2870, 1745, 1440, and 1150 cm^{-1}; nmr ($CDCl_3$) δ 5.1 (t, *J* = 7 Hz, CH=), 4.7 (s, CH_2=), 3.65 (s, OCH_3), 1.58 (s, CH_3C=), and 0.89 (t, *J* = 6 Hz, CH_3). The gc characteristics follow: **10**, retention time 3.55 min (6 ft, 5% SE-30, 112°); **11** and **12**, retention times 3.40 and 3.80 min (6 ft, 5% SE-30, 185°).

Anal. Calcd for $C_{10}H_{18}O_2$: mol wt, 170.1307. Found: mol wt, 170.1309.

Reaction of (−)-β-Pinene with Methyl Vinyl Ketone. To a solution of anhydrous zinc bromide (4.0 g, 0.02 mol) in 100 ml of ether were added methyl vinyl ketone (10.5 g, 0.150 mol) and (−)-β-pinene (13.6 g, 0.10 mol). The solution was stirred for 7 days at 25°. It was then poured into water and filtered by suction to remove zinc salts. The ether layer was separated and the aqueous layer was extracted with 2 × 50 ml of ether. The combined ether layers were dried and evaporated. Fractional distillation of the residue gave the ketone **2**, bp 92° (0.5 mm) (13.04 g, 0.062 mol, 62%), which was 95% pure by gc: ir (neat) 2920, 1720, 1450, 1365, and 1165 cm^{-1}; nmr ($CDCl_3$) δ 5.20 (1 H, br, CH=), 1.4-2.6 (12 H, m, CH_2), 2.11 (3 H, s, $COCH_3$), 1.28 (3 H, s, CH_3), and 0.82 (3 H, s, CH_3); gc retention time 4.4 min (6 ft, 5% SE-30, 151°).

Anal. Calcd for $C_{14}H_{22}O$: mol wt, 206.1671. Found: mol wt, 206.1663.

Reaction of (−)-β-Pinene with Acrolein. To a solution of anhydrous zinc bromide (4.0 g, 0.02 mol) in 100 ml of ether were added acrolein (8.4 g, 0.15 mol) and (−)-β-pinene (13.6 g, 0.10 mol). The solution was stirred for 30 hr at 25° and worked up as for **2**. Fractional distillation of the residue gave the aldehyde **3**, bp 86° (0.45 mm) (6.05 g, 0.032 mol, 32%), which was 95% pure by gc: ir (neat) 2920, 2830, 2710, and 1725 cm^{-1}; nmr ($CDCl_3$) δ 9.78 (1 H, t, *J* = 1.9 Hz, CHO), 5.20 (1 H, m, CH=), 1.35-2.7 (12 H, m, CH_2), 1.23 (3 H, s, CH_3), and 0.83 (3 H, s, CH_3); gc retention time 3.25 min (6 ft, 5% SE-30, 145°).

Anal. Calcd for $C_{13}H_{20}O$: mol wt, 192.1514. Found: mol wt, 192.1513.

Acknowledgment. The author is grateful to the National Science Foundation for financial support and to Professor E. J. Corey for his support and encouragement of this work.

Registry No. **1**, 42913-51-9; **2**, 42913-52-0; **3**, 22553-58-8; **5**, 42908-43-0; **7**, 42908-44-1; **8**, 42908-45-2; **9**, 42908-46-3; (−)-β-pinene, 18172-67-3; methyl acrylate, 96-33-3; methylenecyclohexane, 1192-37-6; 2-ethylene-1-butene, 760-21-4; 2-methyl-1-pentene, 763-29-1; methyl vinyl ketone, 78-94-4; acrolein, 107-02-8.

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Preparation of an Optically Active Intermediate for the Synthesis of Prostaglandins

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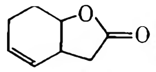
This paper describes the resolution of the (±)-cis-fused lactone **1** and unambiguous demonstration that the levo form possesses the absolute configuration shown in **1a**, which corresponds to the natural prostanoic acid stereochemistry. Since (±)-**1** has been utilized previously for the synthesis of (±)-11-deoxyprostaglandins[1] and also racemic primary prostaglandins,[2] a new route is thus established to these prostanoids in the optically active natural series.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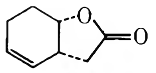
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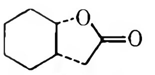
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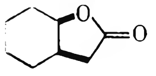
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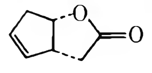
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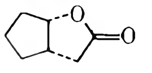
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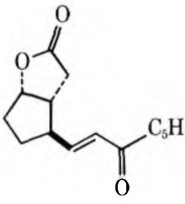
The (±)-lactone **1** was hydrolyzed to the hydroxy acid and treated with (−)-1-(1-naphthyl)ethylamine[3] in ethyl acetate. Three recrystallizations of the resulting salt from ethyl acetate–methanol afforded a product of constant rotation, $[\alpha]^{27}D$ +63°. Conversion of this salt to the dextro lactone **1**, $[\alpha]^{27}\text{D}$ +28°, was effected by acidification with hydrochloric acid and isolation. Use of (+)-1-(1-naphthyl)-ethylamine[3] in the resolution led to the levo lactone **1**, $[\alpha]^{27}\text{D}$ −28°.

The lactone sector rule allows the use of optical rotatory dispersion (ORD) data to assign absolute configuration to optically active bicyclic lactones.[4] Based on this rule the lactone **2a** should have either a plain negative curve or a negative Cotton effect near 225 nm. Hydrogenation of (+)-**1** over palladium on carbon in ethyl acetate gave a dextro lactone which showed a plain positive curve indicating the absolute configuration **2b**.

Additional evidence for the validity of the lactone sector method in these systems was obtained with a lower homolog of **1**. The (−) lactone **3** had earlier been obtained by resolution and converted to natural prostaglandins,[5] thereby demonstrating absolute configuration. Hydrogenation of levo **3** afforded the dihydro derivative **4**, which was found to exhibit a negative Cotton effect as predicted by the lactone sector rule.

Definitive proof for the assignment of **1a** for levo **1** was obtained by chemical correlation with the enone **5**, which was prepared from the (−) iodohydrin **6** of known absolute configuration. Treatment of levo **1** (**1a**) with thallic nitrate gave the (−) aldehyde **7**.[1] This was converted to the (+) enone **5**, $[\alpha]^{27}\text{D}$ +38.7°, by treatment with the sodio derivative of dimethyl 2-oxoheptylphosphonate.[1]

The racemic iodohydrin **6** has earlier been converted to the enone **5**.[6] The (−) iodohydrin **6**, which has the natural prostanoic acid stereochemistry,[7] was transformed to the (+) enone **5** by the following route. The (+) benzyl ether lactone **10** was prepared in quantitative yield from (−)-**6** by treatment with methanesulfonyl chloride and pyridine.[8] Treatment of (+)-**10** with acetic anhydride and boron trifluoride etherate afforded in 94% yield the (+) acetoxy lactone **11**,[8] which was hydrogenated over rhodium on alumina in tetrahydrofuran to provide the (−) saturated lactone **8** in 96% yield. Saponification of (−)-**8** with potassium carbonate in methanol gave the (−) alcohol **9** in 97% yield. Oxidation of (−)-**9** with Collins reagent[9] provided in 83% yield the (−) aldehyde **7**, which was converted to the enone **5**, $[\alpha]^{27}\text{D}$ +39.6°, in 65% yield. It can be concluded, therefore, that the levo lactone **1**, $[\alpha]^{27}\text{D}$ −28°, is fully resolved and has the absolute configuration of natural prostaglandins.



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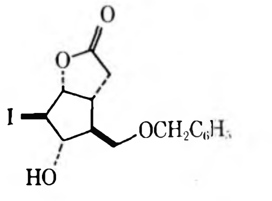

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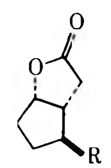
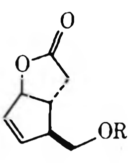


7, R = CHO
8, R = CH_2OCOCH_3
9, R = CH_2OH



10, R = $CH_2C_6H_5$
11, R = $COCH_3$

Experimental Section

Resolution of Lactone 1. The lactone **1**[1] (1.10 g, 8 mmol) was added to a solution of lithium hydroxide (250 mg, 10 mmol) in 5 ml of water and 2 ml of dimethoxyethane. The solution was stirred for 10 hr at 25° and then evaporated to dryness. The white, crystalline residue was taken up in 2 ml of water and 5 ml of ethyl acetate and cooled to 0°. Oxalic acid solution (10% in water) was added at 0° until pH 3.5 was reached. Saturated sodium chloride solution (10 ml) was added, and the reaction mixture was extracted with four portions of ethyl acetate which were dried and evaporated at 10°. The residual hydroxy acid was taken up in 10 ml of ethyl acetate, and (−)-1-(1-naphthyl)ethylamine[3] (1.54 g, 9.0 mmol) was added. After standing for 24 hr at 25° and 12 hr at 0°, white crystals had formed. The crystals were filtered, dried, and recrystallized from ethyl acetate–methanol, giving a salt with $[\alpha]^{27}\text{D}$ +59° (*c* 1.4, CH_3OH). An additional recrystallization gave a product with $[\alpha]^{27}\text{D}$ +62° (*c* 0.8, CH_3OH). A final recrystallization gave 700 mg (53%) of a salt with $[\alpha]^{27}\text{D}$ +63° (*c* 1.2, CH_3OH), indicating completion of the resolution.

Relactonization of the resolved (−)-1-(1-naphthyl)ethylammonium salt was effected by standard procedures. The salt (700 mg, 2.14 mmol) was dissolved in 1.2 equiv of aqueous sodium hydroxide solution. This solution was extracted with two portions of ether to remove the amine. The aqueous layer was acidified with 10 *N* hydrochloric acid and was extracted with five portions of methylene chloride. Tlc analysis of this solution indicated that relactonization had occurred spontaneously. The combined organic extracts were dried and evaporated, giving the lactone **1** (250 mg, 1.82 mmol, 85%) with $[\alpha]^{27}\text{D}$ +28° (*c* 0.6, CH_3OH).

Preparation of (−) Lactone 1. Use of (+)-1-(1-naphthyl)ethylamine instead of the (−) isomer gave after three recrystallizations from ethyl acetate–methanol the white, crystalline salt (730 mg, 2.23 mmol, 56%) with $[\alpha]^{27}\text{D}$ −63° (*c* 0.65, CH_3OH). Relactonization as described above gave the (−) lactone **1** (270 mg, 1.95 mmol, 87%) with $[\alpha]^{27}\text{D}$ −28° (*c* 0.83, CH_3OH).

Reduction of (+) Lactone 1. (+) Lactone **1** (35 mg) and 5% palladium on carbon (35 mg) were placed in 5 ml of ethyl acetate and stirred for 24 hr under hydrogen (1 atm). The solution was filtered and the residue was washed with several portions of ethyl acetate. The combined filtrates were evaporated, giving 33 mg of lactone **2b** as a colorless oil: nmr ($CDCl_3$) δ 4.4–5.0 (1 H, m, CHOCO), 0.8–2.8 (11 H, m); ir (neat) 2930, 2855, 1775, and 1170 cm^{-1}; $[\alpha]^{27}\text{D}$ +45.5° (*c* 0.43, CH_3OH); ORD (*c* 0.033, CH_3OH) 27°; $[\phi]_{350}$ +378°, $[\phi]_{300}$ +588°, $[\phi]_{250}$ +966°, $[\phi]_{220}$ +1680°, $[\phi]_{200}$ +4620°.

Reduction of (−) Lactone 3. (−) Lactone **3** (33 mg) was reduced over 5% palladium on carbon (33 mg) as described above for lactone **1**, giving 29 mg of **4** as a colorless oil: nmr ($CDCl_3$) δ 5.0 (1 H, m, CHOOCO), 1.4–2.8 (9 H, m); ir (neat) 2960, 2870, 1775, and 1175 cm^{-1}; $[\alpha]^{27}\text{D}$ −36° (*c* 0.48, CH_3OH); ORD (*c* 0.145, CH_3OH) 27°; $[\phi]_{350}$ −74°, $[\phi]_{300}$ −139°, $[\phi]_{250}$ −435°, $[\phi]_{225}$ −1164°, $[\phi]_{210}$ −365°.

Oxidation of Lactone 1.[1] To a solution of (−) lactone **1** (236 mg, 1.7 mmol) in 1.5 ml of aqueous 4 *M* sodium perchlorate and 0.5 *M* perchloric acid solution was added thallic nitrate (0.8 g, 1.2 equiv). Stirring was continued for 1 hr at 27° and the mixture was neutralized to pH 7 with solid sodium bicarbonate and then saturated with sodium chloride. The solution was extracted with three 10-ml portions of methylene chloride which were dried and evaporated giving the crude aldehyde **7**, which was converted directly to enone **5**: nmr ($CDCl_3$) δ 9.71 (1 H, s, CHO), 5.05 (1 H, m, CHOOC), 1.4–3.6 (8 H, m); ir (neat) 2720, 1765, 1715, and 1165 cm^{-1}; tlc R_f 0.55 (17:3 benzene–methanol); mass spectrum 154 (M), 126 (M − CO), and 110 (M − CO_2).

Preparation of Enone 5.[1] Sodium hydride (80 mg, 1.6 mmol) was placed under argon in a three-necked flask equipped with an overhead stirrer. Dimethoxyethane (12 ml) was added and the solution was stirred at 25°. Dimethyl 2-oxoheptylphosphonate (378 mg, 1.7 mmol) in dimethoxyethane (8 ml) was then added. After stirring for 1 hr at 25° the reaction was cooled to 0° and the aldehyde **7** (from previous reaction) in dimethoxyethane (6 ml) was added dropwise at 0°. After stirring for 1.5 hr at 0° and for 1.0 hr at 25°, the solution was neutralized with acetic acid. The solvent was evaporated and the residue was chromatographed on 15 g of silica gel (Woelm, activity III) with 97:3 methylene chloride–ethyl acetate to give enone **5** (220 mg, 0.88 mmol, 52% from lactone **1**): nmr ($CDCl_3$) δ 6.80 (1 H, d of d, J = 16, 7 Hz, =CH), 6.16 (1 H, d, J = 16 Hz, =CHCO), 5.06 (1 H, m, CHOCO), 0.65–3.40 (19 H, m); ir (neat) 1770, 1670, 1655, 1630, 1160, and 980 cm^{-1}; uv λ_{max} (methanol) 225 nm (ϵ 14,400); tlc R_f 0.60 (9:1 methylene chloride–ethyl acetate); $[\alpha]^{27}\text{D}$ +38.7° (*c* 3.58, $CHCl_3$).

Anal. Calcd for $C_{15}H_{22}O_3$: mol wt, 250.1569. Found: mol wt, 250.1563.

Preparation of Benzyl Ether Lactone 10.[8] A homogeneous solution of the (−) iodohydrin **6** (800 mg, 2.05 mmol) and dry pyridine (4.0 ml) was treated with methanesulfonyl chloride (0.27

ml). The reaction mixture was stirred for 2 hr at −20° and then for 2 hr at 0°. The reaction was quenched at 0° by addition of a saturated sodium thiosulfate solution (20 ml) followed by extraction of the product with three 20-ml portions of ether. The combined ether extracts were washed with water (2 × 30 ml) and 5% hydrochloric acid (2 × 25 ml). The organic layer was then dried over magnesium sulfate and evaporated, giving the (+) olefin **10** (515 mg, 2.05 mmol, 100%) as a yellow oil which was homogeneous by tlc: nmr ($CDCl_3$) δ 7.33 (5 H, s, aromatic H), 5.80–6.15 (2 H, m, =CH), 5.40–5.60 (1 H, m, HCOCO), 4.52 (2 H, s, CH_2 phenyl), 3.40 (2 H, d of d, J = 6, 3 Hz, CH_2O), and 2.2–3.0 (4 H, m); ir (neat) 1770, 1165, 1100, 1020, 740, and 690 cm^{-1}; tlc R_f 0.48 (1:1 benzene–ether); $[\alpha]^{27}_{D}$ +205.7° (c 0.7, $CHCl_3$).

Anal. Calcd for $C_{15}H_{16}O_3$: mol wt, 244.1100. Found: mol wt, 244.1106.

Preparation of the (+) Acetoxy Lactone 11.[8] The (+) benzyl ether lactone **10** (500 mg, 2.05 mmol) was dissolved in acetic anhydride (10 ml) and cooled to 0° under an argon atmosphere. Boron trifluoride etherate (0.05 ml) was added dropwise with stirring at 0°. After stirring for 15 min at 0° the reaction was quenched with water (1.5 ml). The solvent was then evaporated. The crude product was passed through a column of silica gel (Woelm, activity III, 25 g) to remove benzyl acetate. Elution was carried out with benzene (200 ml), 99:1 benzene–ether (200 ml), 97:3 benzene–ether (200 ml), and 95:5 benzene–ether (500 ml), giving the acetoxy lactone 11 380 mg, 94%): nmr ($CDCl_3$) δ 6.03 (2 H, br s, =CH), 5.45–5.68 (1, H, m, HCOCO), 4.08 (2 H, d, J = 6 Hz, CH_2OAc), 2.1–3.2 (4 H, m), and 2.02 (3 H, s, CH_3CO_2); ir (neat) 1770, 1730, 1240, 1165, 1020, and 755 cm^{-1}; tlc R_f 0.30 (1:1 benzene–ether), 0.50 (17:3 benzene–methanol); $[\alpha]^{27}_{D}$ +226.7° (c 1.73, $CHCl_3$).

Anal. Calcd for $C_{10}H_{12}O_4$: mol wt, 196.0736. Found: mol wt, 196.0723.

Preparation of the Acetoxy Lactone 8. The (+) acetoxy lactone 11 (210 mg, 1.07 mmol) and 5% rhodium on alumina (150 mg) were placed in 10 ml of tetrahydrofuran and stirred for 4 hr at 27° under hydrogen (1 atm). The solution was then filtered and the residue was washed with several portions of ether. The combined filtrates were evaporated, giving the saturated acetoxy lactone 8 (205 mg, 1.03 mmol, 96%): nmr ($CDCl_3$) δ 4.98 (1 H, m, CHOCO), 4.03 (2 H, d J = 6 Hz, CH_2OAc), 2.05 (3 H, s, CH_3CO_2), and 1.2–3.0 (8 H, m); ir (neat) 1770, 1740, 1230, 1165, and 1035 cm^{-1}; tlc R_f 0.30 (1:1 benzene–ether); $[\alpha]^{27}_{D}$ −1.2° (c 0.81, $CHCl_3$); mass spectrum m/e 198 (M, w), 156 (M − CH_2CO, s), and 138 (M − CH_3CO_2H, vs).

Anal. Calcd for $C_{10}H_{14}O_4$: mol wt, 198.0892. Found: mol wt, 198.0890.

Preparation of Alcohol 9. The acetoxy lactone 8 (200 mg, 1.01 mmol) and freshly powdered potassium carbonate (138 mg, 1.0 mmol) were dissolved in methanol (4 ml) under argon. The solution was stirred for 30 min at 25° and neutralized with 10 N hydrochloric acid (0.2 ml). The solvent was evaporated and the resulting slurry was washed exhaustively with ethyl acetate. The combined organic extracts were dried over magnesium sulfate and concentrated to afford the alcohol 9 (154 mg, 0.98 mmol, 97%) which was homogeneous by tlc: nmr ($CDCl_3$) δ 5.00 (1 H, br, CHOOC), 3.92 (1 H, br, OH), 3.54 (2, H, d, J = 6 Hz, CH_2OH), 1.3–3.0 (8 H, m); ir (neat) 3400, 1770, 1170, 1035 cm^{-1}; tlc R_f 0.30 (17:3 benzene–methanol); $[\alpha]^{27}_{D}$ −20.4° (c 0.66, $CHCl_3$); mass spectrum m/e 156 (M, s), 139 (M − OH, m), and 138 (M − H_2O, vs).

Anal. Calcd for $C_8H_{12}O_3$: mol wt, 156.0786. Found: mol wt, 156.0789.

Oxidation of Alcohol 9. Collins reagent (2.34 g, 9 mmol) and dry Celite (4.3 g) were dissolved in 23 ml of dry methylene chloride under argon and cooled to 0°. A solution of alcohol 9 (154 mg, 0.98 mmol) in 5 ml of methylene chloride was added. The solution was stirred for 1 hr at 0° and sodium bisulfate (5.0 g) was added. The solution was stirred for 10 min at 25° and filtered through a pad of anhydrous magnesium sulfate. The residue was washed with several portions of methylene chloride. The combined filtrate was evaporated, giving aldehyde 7 (125 mg, 0.81 mmol, 83%) which was homogeneous by tlc: nmr ($CDCl_3$) δ 9.71 (1 H, s, CHO), 5.05 (1 H, m, CHOCO), 1.4–3.6 (8 H, m); ir (neat) 2720, 1765, 1715, and 1165 cm^{-1}; tlc R_f 0.55 (17:3 benzene–methanol); $[\alpha]^{27}_{D}$ − 41° (c 0.61, $CHCl_3$); mass spectrum m/e 154 (M), 126 (M − CO), and 110 (M − CO_2).

Preparation of Enone 5. The aldehyde 7 (105 mg, 0.68 mmol) was treated as described above giving the enone 5 (110 mg, 0.44 mmol, 65%) which was homogeneous by tlc. This material was identical with an authentic sample by tlc and ir and nmr spectral comparison, $[\alpha]^{27}_{D}$ +39.6° (c 1.59, $CHCl_3$).

Acknowledgment. This work was assisted financially by the National Institutes of Health and the National Science Foundation.

Registry No. (±)-1, 43119-22-8; (−)-1, 43119-23-9; (−)-1 (+)-1-(1-naphthyl)ethylamine salt, 43119-24-0; **1a**, 43119-25-1; **1a** (−)-1-(1-naphthyl)ethylamine salt, 43119-26-2; **2b**, 43119-27-3; **3**, 43119-28-4; **4**, 43119-29-5; **5**, 43119-30-8; **6**, 31767-37-0; **7**, 43119-32-0; **8**, 43119-33-1; **9**, 43119-34-2; **10**, 35761-79-6; **11**, 35761-78-5; (−)-1-(1-naphthyl)ethylamine, 10420-89-0; (+)-1-(1-naphthyl)-ethylamine, 3886-70-2.

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Reduction of Enedicarbonyl Compounds with Titanous Ion

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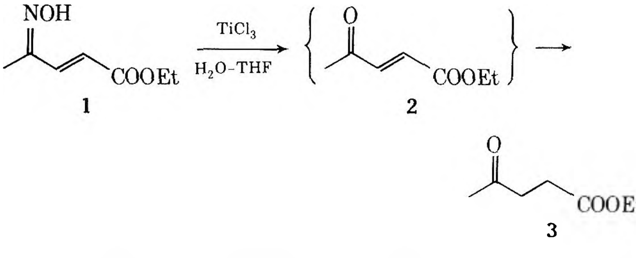
We recently had occasion to treat ethyl 4-oximino-2-pentenoate (**1**) (obtained from ethyl 3-bromolevulinate by Mattox–Kendall reaction with hydroxylamine[1]) with aqueous $TiCl_3$ according to the deoximation procedure of Timms and Wildsmith.[2] Although we expected that ethyl 4-oxo-2-pentenoate (**2**) would result, the sole product of the reaction was the saturated keto ester, ethyl levulinate (**3**).

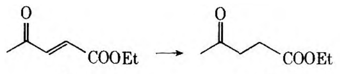
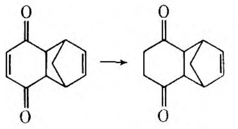
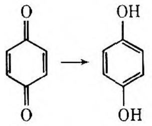
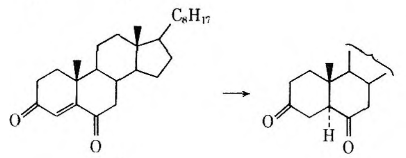
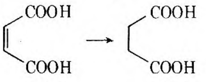
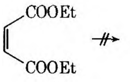


The simplest rationalization of this result is to assume that **2** is in fact formed initially, and that $TiCl_3$ is capable of effecting rapid further reduction of enedicarbonyl compounds to their saturated analogs. This has indeed proved to be the case, and we have carried out a short study of the reaction which suggests that it is a gentle, effective, and remarkably simple method to use. Our results are given in Table I.

As can be seen from Table I, the reaction, which is usually complete within 15 min at room temperature, works quite well for diketones (examples **4**, **6**, **8**), for keto esters (example **2**), and for diacids (example **10**). The reaction fails completely for diesters, however, even when a prolonged reflux is employed. This presumably reflects the undoubted higher reduction potential of **12** *vs.* the other substrates.[3]

Similar methods of reduction of enedicarbonyl compounds have been reported using chromous ion,[4-6] al-

Table I
Reduction of Enedicarbonyl Compounds with TiCl$_3$

Reaction	Yield, %
 2 → 3	84
 4 → 5	95
 6 → 7	98
 8 → 9	86
 10 → 11	45
 12	

though only moderate yields were obtained, and the well-known zinc–acetic acid reagent is also effective.[7] Because of the high yields obtained and mild conditions required by this new TiCl$_3$ method, however, we believe that it will be a useful procedure.

Experimental Section

The titanium(III) chloride was obtained as a 20% aqueous solution (~1.6 *M*) from Matheson Coleman and Bell and was found to be stable for long periods when stored under nitrogen.

Representative Reaction Procedure. Reduction of Cholest-4-ene-3,6-dione (8). A 50-ml, three-neck flask, fitted with a nitrogen inlet, magnetic stirrer, and rubber septum, was charged with cholest-4-ene-3,6-dione[8] (8, 200 mg, 0.5 mmol) and 10 ml of acetone. Cold TiCl$_3$ solution (0.62 ml, 1.0 mmol) was then injected and the reaction mixture was stirred for 7 min at room temperature. The solution was then poured into 50 ml of brine, and the aqueous phase was extracted with ether. The combined extracts were dried (Na$_2$SO$_4$), filtered, and concentrated to give 197 mg (98%) of crude solid product. Two recrystallizations from isopropyl ether gave 173 mg (86%) of pure 5α-cholestane-3,6-dione (9): ir (CHCl$_3$) 1702 cm^{-1}; nmr (CDCl$_3$) no vinyl protons; mp 168-169° (lit.[9] mp 168-170°).

The following reductions were carried out in a similar manner.

Ethyl 4-oxo-2-pentenoate (2) gave ethyl levulinate (84%) identified by comparison with an authentic sample.

Benzoquinone gave hydroquinone identified by comparison with an authentic sample.

Benzoquinone–cyclopentadiene adduct (4) gave the saturated diketone 5: ir (neat) 1705 cm^{-1}; nmr (CCl$_4$) δ 6.14 (t, 2 H, J = 1.6 Hz), 3.40 (m, 2 H), 3.12 (m, 2 H), 2.38 (m, 4 H), 1.35 (m, 2 H).

Maleic acid gave succinic acid (45%), identified as the dimethyl ester, after a reaction time of 24 hr.

Acknowledgment. We thank the National Science Foundation for their support of this work through Grant GP 28173.

Registry No. 2, 6742-53-6; **4,** 1200-89-1; **5,** 21428-54-6; **6,** 106-51-4; **8,** 984-84-9; **9,** 2243-09-6; **10,** 110-16-7; TiCl$_3$, 7705-07-9.

References and Notes

(1) V. R. Mattox and E. C. Kendall, *J. Amer. Chem. Soc.*, **70**, 882 (1948).
(2) G. H. Timms and E. Wildsmith, *Tetrahedron Lett.*, 195 (1971).
(3) Although the reduction potentials of our substrates are not known, we presume that, in accordance with the recent results of House [H. O. House and M. J. Umen, *J. Amer. Chem. Soc.*, **94**, 5495 (1972)], an unsaturated ester would have a reduction potential higher (more *negative*) than would an unsaturated ketone.
(4) W. Traube and W. Passarge, *Chem. Ber.*, **49**, 1692 (1916).
(5) C. E. Castro, R. D. Stephens, and S. Moje, *J. Amer. Chem. Soc.*, **88**, 4964 (1966).
(6) J. R. Hanson and E. Premuzic, *J. Chem. Soc. C*, 1201 (1969).
(7) *Cf.* A. Windaus, *Chem. Ber.*, **39**, 2249 (1906).
(8) L. F. Fieser, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., p 189.
(9) J. S. Moffatt, *J. Chem. Soc.*, 872 (1947).

A New Method for Converting Nitro Compounds into Carbonyls. Ozonolysis of Nitronates

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Thimann Laboratories, University of California,
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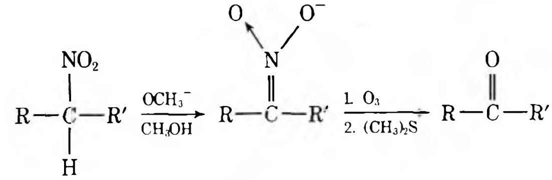
Received August 10, 1973

The nitro group is a function of considerable importance in synthetic chemistry because of the variety of reactions it can undergo. One of the more useful of these reactions is the transformation nitro → carbonyl, and a number of methods have been devised for accomplishing this goal, including the Nef reaction[1] (strongly acidic); permanganate oxidation of nitronate salts[2] (basic, oxidative); persulfate oxidation of nitronates[3] (basic, oxidative); treatment with a mixture of organic and inorganic nitrite[4] (neutral, oxidative); and our own recently introduced method involving treatment of free nitro compounds with TiCl$_3$[5] (neutral, reductive). Of these possibilities, only the TiCl$_3$ method can be considered truly general in that a wide variety of functional groups survive and that both ketones and aldehydes can be produced in good yields. The major drawback to the use of TiCl$_3$ is that a large amount (4 equiv per nitro group) must be used, making the method inconvenient for large-scale use. We therefore sought yet another method for transforming a nitro group into a carbonyl.

It has been known for some time[6] that a C=N (such as a 2,4-DNP) will react with ozone to generate the corresponding ketone or aldehyde, and we therefore examined ozonolysis of nitronate salts as a possible synthetic method.

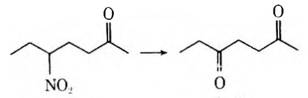
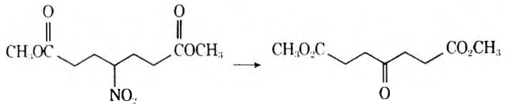
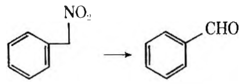


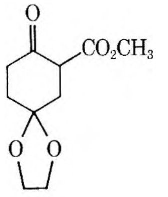
$$R{-}\underset{H}{\overset{NO_2}{C}}{-}R' \xrightarrow[CH_3OH]{OCH_3^-} R{-}\overset{\overset{O\ \ O^-}{\diagdown\ \diagup}}{\overset{N}{\overset{\|}{C}}}{-}R' \xrightarrow[2.\ (CH_3)_2S]{1.\ O_3} R{-}\overset{O}{\overset{\|}{C}}{-}R'$$

The desired reaction does in fact proceed rapidly and cleanly. Some examples we have run are listed in Table I.

Both aldehydes and ketones can be produced in good yields, and of course a wide variety of functional groups are stable to ozone. One of the more useful examples in Table I is the preparation of dimethyl 4-oxopimelate (4) from the readily available[7] nitro diester 3, in 88% yield. Diester 4 can be ketalized and Dieckmann cyclized to diketone 9, a compound much used in natural product synthesis, but heretofore obtained only by a tedious route from furfural.[8] This new method should therefore prove of considerable use in synthetic chemistry.

Table I
Ozonolysis of Nitronate Salts

Reaction	Yield, %
 1 → 2	83
 3 → 4	88
 5 → 6	68
$CH_3(CH_2)_6CH_2NO_2 \rightarrow CH_3(CH_2)_6CHO$ 7 → 8	65



9

Experimental Section

General Reaction Procedure. The nitro compound (0.020 mol) in 50 ml of anhydrous methanol was treated with 1 equiv of sodium methoxide (1.08 g, 0.020 mol) and stirred for 10 min to form the nitronate salt. This methanolic solution was then cooled to −78°, and a stream of ozone-oxygen was passed through.[9] For secondary nitro compounds, ozonolysis was continued until the reaction mixture was light blue (excess O_3). For primary nitro compounds, however, it was found necessary to meter in only 1 equiv of O_3 since an excess led to further reaction and consequent lower yields of aldehyde product.

After 30 min, the reaction mixture was purged with a nitrogen stream to remove excess ozone, and was then treated with 5 ml of dimethyl sulfide at −78° and slowly allowed to come to room temperature. After standing for 16 hr, volatile material was removed at the rotary evaporator. The residue was taken up in ether and washed with water and brine, then dried (Na_2SO_4), concentrated, and purified either by distillation or crystallization.

In this manner, the following compounds were prepared.

Heptane-2,5-dione (2) was prepared from 5-nitroheptan-2-one,[5] and identified by spectral comparison with an authentic sample,[5] 83% yield.

Dimethyl 4-oxopimelate (4) was prepared from dimethyl 4-nitropimelate,[7] and purified by crystallization from hexane, mp 49–50° (lit.[8] mp 49–50°), 88% yield.

Benzaldehyde (6) was prepared from α-nitrotoluene,[10] purified by distillation, and identified by spectral comparison with an authentic sample, 68% yield, bp 70–75° (20 mm).

Octanal (8) was prepared from 1-nitrooctane,[11] purified by distillation, and identified by spectral comparison with an authentic sample, 65% yield, bp 80° (30 mm).

Acknowledgment. We thank the National Science Foundation for their support of this work through Grant GP 28173.

Registry No. 1, 42397-25-1; **2,** 1703-51-1; **3,** 7766-83-8; **4,** 22634-92-0; **5,** 622-42-4; **6,** 100-52-7; **7,** 629-37-8; **8,** 124-13-0.

References and Notes

(1) W. E. Nolan, *Chem. Rev.*, **55**, 137 (1955).
(2) H. Shechter and F. T. Williams, *J. Org. Chem.*, **27**, 3699 (1962).
(3) A. H. Pagano and H. Shechter, *J. Org. Chem.*, **35**, 295 (1970).
(4) N. Kornblum and P. A. Wade, *J. Org. Chem.*, **38**, 1418 (1973).
(5) (a) J. E. McMurry and J. Melton, *J. Amer. Chem. Soc.*, **93**, 5309 (1971); (b) *J. Org. Chem.*, in press.
(6) *Cf.* G. A. Fleisher and E. C. Kendall, *J. Org. Chem.*, **16**, 556 (1951).
(7) S. Kambe and H. Yasuda, *Bull. Chem. Soc. Jap.*, **39**, 2549 (1966).
(8) R. M. Lukes, G. I. Poos, and L. H. Sarett, *J. Amer. Chem. Soc.*, **74**, 1401 (1952).
(9) Ozone was generated with a Welsbach ozonator.
(10) W. Emmons, *J. Amer. Chem. Soc.*, **77**, 4558 (1955).
(11) N. Kornblum and J. W. Powers, *J. Org. Chem.*, **22**, 455 (1957).

Ruthenium-Catalyzed Hydrogen–Deuterium Exchange in Alcohols. A Convenient Method for Deuterium Labeling of Primary Alcohols

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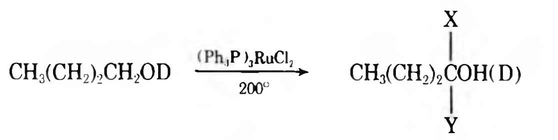
Received August 14, 1973

The most commonly used method for deuterating primary alcohols in the C-1 position is oxidation of the alcohol to either the corresponding aldehyde or carboxylic acid followed by reduction with lithium aluminum deuteride.[1] Although this approach works well in most instances, it requires two separate reactions and uses an expensive reagent (lithium aluminum deuteride).

We wish to report a unique transition metal catalyzed hydrogen–deuterium exchange reaction which provides the basis for a convenient alternate procedure for the introduction of deuterium into certain primary alcohols and which uses deuterium oxide as the isotopic source.

When 1-butanol-*d* was heated to 200° for 1 hr in the presence of 0.2 mol % of tris(triphenylphosphine)ruthenium dichloride, deuterium bound to oxygen exchanged with hydrogen exclusively at the C-1 carbon atom;[2] the distribution of deuterium at the C-1 position is that shown below.[3]



$$CH_3(CH_2)_2CH_2OD \xrightarrow[200^\circ]{(Ph_3P)_3RuCl_2} CH_3(CH_2)_2\overset{X}{\underset{Y}{C}}OH(D)$$

1a, X = Y = H (55%)
b, X = H; Y = D (35%)
c, X = Y = D (10%)

In an effort to determine whether the ruthenium complex is a unique catalyst for exchanging hydrogen with deuterium in 1-butanol-*d*, we have tried the same procedure, substituting each of the following metallic catalysts for the ruthenium complex: $(Ph_3P)_3RhCl$, $(Ph_3P)_2PtCl_2$, Pd/C, $(Ph_3P)_2IrCOCl$, Raney nickel, and K_2PtCl_4. While the ruthenium complex proved most effective for this conversion, all of the other metals exhibited no detectable catalytic activity.

Although we have found that primary alcohols readily undergo hydrogen exchange, those secondary alcohols investigated gave poor results (Table I). Little exchange was detected in the case of 2-propanol and cyclododecanol, and prolonged heating resulted in considerable dehydration. For primary alcohols, we detected no decomposition (<0.1%) under the reaction conditions described.[4]

We have found that, by adding deuterium oxide to a mixture of the ruthenium catalyst and any one of the primary alcohols tested, this exchange reaction becomes a synthetically useful method for deuterium labeling. For example, when 1-decanol and deuterium oxide were heated in the presence of the ruthenium catalyst, the recovered alcohol contained a significant amount of deuterium incorporated in the C-1 position. The amount of deuteri-

Table I
Ruthenium-Catalyzed Hydrogen–Deuterium Exchange in Alcohols[a]

Alcohol	Isotopic composition, %		
	d_0	d_1	d_2
Ethanol-*d*[b]	42	43	15
1-Butanol-*d*[b]	55	35	10
2-Propanol-*d*[b]	>98	<2	
1-Decanol[c]	7	35	58
1-Decanol	0	5	95
1-Dodecanol	0	6	94
1-Octanol	0	3	97
Cyclododecanol	95	5	

[a] The percentage of deuterium indicated represents the isotopic distribution at the C-1 carbon atom. Unless noted otherwise, reactions were carried out using procedures similar to that described for the deuteration of 1-decanol; the reaction temperature was 200°. The molar ratio of deuterium oxide to alcohol used was 50:1. [b] The alcohol was heated directly with the ruthenium catalyst in the absence of deuterium oxide. [c] The molar ratio of deuterium oxide to alcohol used was 5:1.

um introduced into the alcohol was dependent upon the molar ratio of deuterium oxide to alcohol employed.

The advantages of this procedure for isotopic labeling of primary alcohols in the C-1 position lie in its simplicity, its low cost, its avoidance of reactive oxidants and reductants, and its ability to be carried out under neutral pH.

Experimental Section[5]

General Methods. Unless stated otherwise, all reagents were obtained commercially and were used without further purification. Deuterated alcohols (Aldrich Chemical Co.) were greater than 99% pure. Tetrahydrofuran was dried by distillation from calcium hydride under a nitrogen atmosphere. Commercial catalysts were obtained from the following sources: $(Ph_3P)_3RuCl_2$, $(Ph_3P)_3RhCl$, and $(Ph_3P)_2IrCOCl$ (Strem Chemical Co.); K_2PtCl_4 (Alfa Inorganics); Pd/C and Raney nickel (K & K Laboratories).

General Procedure for Hydrogen–Deuterium Exchange in Deuterated Alcohols. Procedures similar to that described for the hydrogen–deuterium exchange in 1-butanol-*d* were followed for all deuterated alcohols. A mixture of 2 mg (0.002 mmol) of tris(triphenylphosphine)ruthenium dichloride and 150 μl (1.6 mmol) of 1-butanol-*d* was sealed under a nitrogen atmosphere in a 4-in. 5-mm Pyrex glass tube. The tube was placed in an oil bath, maintained at 200° for 1 hr, withdrawn, and cooled. The purity of the alcohol was determined by glpc using both a UC-W98 on Chromosorb W column and a Carbowax on Chromosorb W column. Alcohols were collected for mass spectral analysis by glpc using a F & M Model 720 thermal conductivity instrument. Isotopic compositions were determined from $(M - H_2O)^+$ peaks and were corrected for contributions from ^{13}C.[6]

1-Decanol-*1,1-d*$_2$. A mixture of 100 mg (0.1 mmol) of tris(triphenylphosphine)ruthenium dichloride, 1.58 g (10.0 mmol) of 1-decanol, and 10.0 g (0.5 mol) of 99.7% deuterium oxide was sealed under a nitrogen atmosphere in a 14-in. 12-mm Pyrex glass tube. The tube was placed in an oil bath, maintained at 200° for 0.5 hr, withdrawn, and cooled to room temperature. The contents of the tube was poured into 50 ml of ether and the organic phase was dried (Na_2SO_4), concentrated, and distilled (short-path distillation), giving 1.47 g (93%) of 1-decanol, bp 123-125° (20 mm). Mass spectral analysis indicated that the recovered alcohol was a mixture of 95% d_2, 5% d_1, and 0% d_0 material.

Acknowledgment. We are grateful to the Marquette University Committee on Research and Chemistry Department for their financial support.

Registry No. Tris(triphenylphosphine)ruthenium chloride, 15529-49-4; 1-decanol, 112-30-1; 1-decanol-*1,1-d*$_2$, 42006-99-5.

References and Notes

(1) A. Murray and D. L. Williams, "Organic Synthesis with Isotopes," Interscience, New York, N. Y., 1958, p 1341.

(2) We have found that temperatures in excess of 180° are necessary for rapid exchange to occur. Thus, when 1-butanol-*d* was heated in the presence of the ruthenium catalyst for 15 hr at 140°, the ^1H nmr spectrum of the resulting alcohol showed no evidence of hydrogen–deuterium exchange.

(3) The ^1H nmr spectrum of the resulting isotopic mixture of alcohols confirmed that only the C-1 carbon atom had become deuterated.

(4) The purity of the alcohol was measured by glpc using both a UC-W98 on Chromosorb W column and a Carbowax on Chromosorb W column.

(5) Boiling points are uncorrected. Mass spectra were recorded on a Consolidated Electrodynamics Corp. mass spectrometer, Type 21-103 C. All ^1H nmr spectra were recorded using a Varian A-60 spectrometer. The alcohols were analyzed by glpc on a Beckman GC-2A flame ionization instrument.

(6) Biemann has established that aliphatic alcohols, under electron impact, lose water exclusively *via* 1,3, 1,4, and 1,5 eliminations: W. Benz and K. Biemann, *J. Amer. Chem. Soc.*, **86**, 2375 (1964).

The Chemistry of Flavandiones.[1] Reaction with Base[2]

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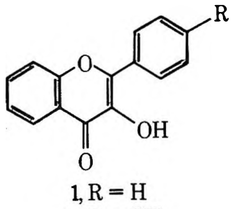
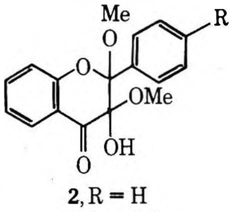
Received May 31, 1973

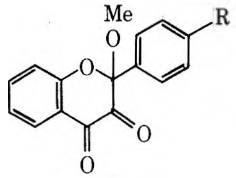
Flavolon (**1**) is oxidized by 1 mol of periodic acid. From the reaction in methanol, the methyl 3-hemiketal **2** of 2-methoxy-3,4-flavandione (**3**) can be isolated.[3] Solutions of **2** are always yellow, indicating that some **3** is always present. We have found that the hemiketal **2** undergoes a normal benzilic acid rearrangement. In aqueous methanol, the product is the hydroxy acid **4**; in anhydrous methanol, the methyl ester **5**. These products are readily accounted for in terms of the ionic reaction mechanism usually formulated for the benzilic acid rearrangement.[4] This result was not entirely predictable. Compound **2** is a mixed ketal of an o-hydroxydiphenylpropanetrione, and the reactions of 1,2,3-triketones with base are more complex.[5,6]



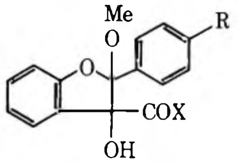
1, R = H
9, R = CH$_3$



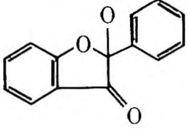
2, R = H
10, R = CH$_3$



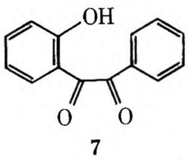
3



4, R = H; X = OH
5, R = H; X = OCH$_3$
11, R = CH$_3$; X = OH
12, R = CH$_3$; X = OCH$_3$



6



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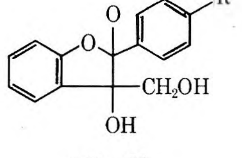

8, R = H
13, R = CH$_3$

The ester **5** is obtained by the reaction of **2** with a solution of sodium methoxide in anhydrous methanol or by passing a methanol solution of **2** through the hydroxide form of an anion exchange resin. The assigned structure is supported by spectra and analyses. The saponification of **5** yielded **4** from which **5** could be regenerated with diazomethane.

When the rearrangement of **2** was carried out in aqueous methanol, the product was the free acid **4**. However, this product, while a pleasant-looking solid, failed to give satisfactory elemental analyses and equivalent weights. Unless care was taken, it separated from the solution as a firm gel. Furthermore, the nmr spectrum was not characteristic for a carboxylic acid (see Experimental Section). However, its reversible conversion into the methyl ester **5** leaves little doubt that it is some form of the acid **4**. Cleavage with 1 mol of lead tetraacetate converted **4** to 2-methoxy-2-phenyl-3(2*H*)-benzofuranone (**6**). The hydrolysis of **6** afforded the known 2-hydroxybenzil **7**.[7] Both the acid **4** and its methyl ester **5** were reduced with lithium aluminum hydride to 2,3-dihydro-3-hydroxy-3-hydroxymethyl-2-methoxy-2-phenylbenzofuran (**8**). The structure of **8** is supported by spectra and elemental analyses.

The study was extended to the hemiketal **10**, prepared from 4′-methylflavonol (**9**). Compounds **11**, **12**, and **13** were prepared.

Experimental Section

All ir spectra were taken as Nujol mulls on a Perkin-Elmer Infracord, Model 137 (NaCl prism). All nmr spectra were obtained in $CDCl_3$ using a Varian A-60A spectrometer. All melting points were uncorrected. Analyses were carried out by Schwarzkopf Analytical Laboratory. The hydroxide form of the anion exchange resin was prepared by stirring 1 lb of Dowex 1X8 resin (20-50 mesh, chloride form) with 1 l. of cold 10% sodium hydroxide and washing with water until neutral.

2-Methoxy-4′-methyl-3,4-flavandione Methyl 3-Hemiketal (10). This is a new compound prepared in the usual way[3] from **9** and HIO_4 in MeOH. The yield of **10** was 50%: mp 152-153° dec; ir (mull) 2.90 (OH), 5.85 μ (C=O); nmr ($CDCl_3$) δ 2.44 (s, 3, CCH_3), 3.02, 3.08 (s, 6, OCH_3), 4.70 (s, 1, OH), 7.0-8.1 (m, 8, aryl H).

Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77; OCH_3, 19.75. Found: C, 68.74; H, 6.06; OCH_3, 21.64.

2,3-Dihydro-3-hydroxy-2-methoxy-2-phenylbenzofuran-3-carboxylic Acid (4). The hemiketal **2**[3] (5.0 g, 1.67 mmol), suspended in 50 ml of MeOH, was stirred with 5.0 g of KOH in 50 ml of H_2O. Compound **2** quickly dissolved, yielding a clear yellow solution. After standing overnight, the solution was poured into 200 ml of H_2O containing 10 ml of concentrated HCl. The cloudy solution was extracted with 200- and 100-ml portions of Et_2O. This ether extract was washed with saturated brine and allowed to stand over $CaSO_4$. Evaporation of the Et_2O afforded about 5 g of a foamy solid. This product was purified by dissolving it in 30 ml of warm $CHCl_3$ and adding 250 ml of hot petroleum ether (bp 60-68°). On standing, the clear solution set to a loose gel which was easily broken up and filtered, yielding 3.6 g (1.31 mmol, 78%) of **4** as a white solid, mp 113-115° dec. Work-up of the filtrate afforded an additional 0.4 g of product, total yield 84%. The product is particularly low in per cent C and does not titrate readily. It dissolves slowly in $NaHCO_3$ and quickly in NaOH. It is stable for several days in NaOH. The solid itself slowly acquires a yellow color. The following spectra data are on a fresh batch of the acid: ir (mull) 2.9, 3.2 (OH), 5.8 μ (C=O); nmr ($CDCl_3$) δ 3.25 (s, 3, OCH_3), 6.9-7.7 (m, 11+, aryl H + 2 OH). The actual ratio of the integrals for the aryl region and OCH_3 was 11.7:3. After D_2O, this ratio fell to 9.6:3, indicating that the two hydroxyl bands were hidden under the aryl signals. The excess OH signal may have been due to H_2O.

Satisfactory elemental analyses could not be obtained on the acid **4**. When heated to its melting point in a stream of N_2, **4** yielded methanol and 0.96 mol of CO_2.[8]

Methylation of 4 to 5. A 30% excess of CH_2N_2 in Et_2O was mixed with 500 mg of **4** in Et_2O. Evaporation yielded a crude product from which 370 mg (70%) of the methyl ester **5**, mp 117-120°, could be obtained, identified by comparison with **5** prepared as detailed below.

Saponification of 5 to 4. The ester **5** was hydrolyzed with 2 g of KOH in 8 ml of H_2O and 10 ml of MeOH. Tlc indicated that all the ester had reacted in 10 min. After 30 min, the solution was diluted with 50 ml of H_2O and acidified. Extraction with ether afforded 370 mg (84%) of **4** as a foamy solid. The crude product was recrystallized from $CHCl_3$-hexane (1:2) affording **4**, mp 110-111° dec.

2-Methoxy-2-phenyl-3(2*H*)-benzofuranone (6). A mixture of 2.03 g (4.58 mmol) of $Pb(OAc)_4$ and 100 ml of AcOH was stirred and to this 1.35 g (4.72 mmol) of the hydroxy acid **4** was added. It dissolved, yielding a pale yellow solution. After 12 hr, the AcOH was removed on a film evaporator. The resulting oil was taken up in 200 ml of Et_2O and washed with 200 ml of water. The water layer was shaken with 50 ml of Et_2O. The combined ether layers were dried with brine and $CaSO_4$ and upon evaporation yielded 1.1 g of an oil (100%) which soon solidified. Recrystallization was effected with 20 ml of petroleum ether, 0.80 g (73%) of **6**, mp 66.5-68°, being obtained: ir (mull) 5.80 μ (C=O); nmr ($CDCl_3$) δ 7-8 (m, 9, aryl H), 3.41 (s, 3, OCH_3).

Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.98; H, 5.03. Found: C, 75.08; H, 5.28.

The hydroxy acid **4** was oxidized at room temperature with a 0.04 *M* solution of $Pb(OAc)_4$ in AcOH, 2.2 mol of the oxidant being present. The excess Pb^{IV} was determined iodometrically.[9] These results were obtained [given as time (hours), moles of Pb^{IV} consumed/mole of **4**]: 0.5, 0.37; 1.25, 0.76; 2.5, 0.88; 3.5, 0.91; 4.5, 0.93; 13, 0.95.

2-Hydroxybenzil (7). The hydrolysis of **6** was effected by prolonged refluxing of **6** (600 mg) in a mixture of dioxane (8 ml), H_2O (8 ml), and concentrated H_2SO_4 (1 ml). After 2 days, water (100 ml) was added and the cloudy mixture was extracted with ether. **7** was removed by 2% sodium hydroxide and recovered by acidification and ether extraction. Evaporation of the ether left 400 mg (71%) of a yellow oil which soon solidified. A recrystallization from petroleum ether yielded pale yellow crystals, mp 73-75° (lit. mp 74°),[7] ir, broad weak band at 2.2-2.4 (chelated OH), 5.9 μ (C=O).

Methyl 2,3-Dihydro-3-hydroxy-2-methoxy-2-phenylbenzofuran-3-carboxylate (5). A. *Via* Sodium Methoxide. A solution of 1.5 g of Na in 75 ml of MeOH was refluxed for 1 hr with 1.5 g of the hemiketal **2**. The reaction mixture was poured into about 500 ml of an ice-water mixture. After acidification, the solution was extracted with two 50-ml portions of Et_2O. The combined Et_2O layers were washed with water and saturated brine before drying with $CaSO_4$. Evaporation of the Et_2O yielded 1.2 g of a mixture of oil and crystals. Recrystallization was effected with 75 ml of petroleum ether, 0.83 g (55%) of white crystals of **5**, mp 121-122°, being obtained. An additional 0.1 g (7%) of **5** could be obtained from the petroleum ether filtrate.

B. *Via* Anion Exchange Method. A solution of 3 g of the hemiketal **2** in 400 ml of anhydrous MeOH was slowly passed down a column of 100 ml of Dowex 1 × 8 (50-100 mesh, OH form). The rate must be very slow; in this particular run it was 1 drop every 10 sec. Once the solution of **2** was through the column, the resin was washed with 100 ml of MeOH. The effluent plus the washings were evaporated to about 2.5 g of a white solid. Recrystallization was effected with a mixture of 12 ml of CCl_4 and 15 ml of hexane, 2.03 g (67%) of **5** being obtained, mp 121-122°. The analytical sample melted at 122-123° (petroleum ether): ir (mull) 2.85 (OH), 5.70 μ (C=O); nmr ($CDCl_3$) δ 3.11, 3.27 (s, 6, OCH_3, $COOCH_3$), 4.2 (s, 1, OH), 7-8 (m, 0.9, aryl H).

Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37; OCH_3, 20.67. Found: C, 67.88; H, 5.63; OCH_3, 20.90.

2,3-Dihydro-3-hydroxy-3-hydroxymethyl-2-methoxy-2-phenylbenzofuran (8). A. From the Acid 4. A solution of 1.0 g of **4** in 100 ml of Et_2O was added slowly (2 hr) to a stirred suspension of 0.30 g of $LiAlH_4$ in 50 ml of Et_2O, the solution being warmed enough to reflux gently. The refluxing was continued for another 3 hr. After the solution stood overnight, the $LiAlH_4$ was decomposed by successive additions of 0.3 ml of H_2O, 0.3 ml of 15% NaOH, and 0.9 ml of H_2O.[10] The resulting slurry was readily filtered and evaporation of the ether afforded 0.8 g (84%) of a tough oil. Recrystallization from 5 ml of CCl_4-5 ml of hexane yielded 0.45 g (47%) of **8**, mp 115-116°. The analytical sample melted at 119-120°.

B. From the Ester 5. The same procedure on the ester **5** yielded **8** in 56% yield: ir (Nujol) 2.85 μ (OH); nmr ($CDCl_3$) δ 1.66 (broad s, 1, OH), 3.24 (s, 5, OCH_3 and $-OCH_2-$), 3.78 (broad s, 1, OH), 6.9-7.0 (m, 9, aryl H). The signals of OCH_2- and $-OCH_3$ at δ 3.24 were readily resolved by the use of the chemical shift reagent, $Eu(dpm)_3$.[11] At a concentration of 25 mg of **8** and 6.5 mg of $Eu(dpm)_3$ in 1 g of $CDCl_3$, the OCH_3 was a sharp singlet at δ 3.18 and the $-OCH_2-$ was a broader signal at δ 3.25.

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.52; H, 5.75.

2,3-Dihydro-3-hydroxy-2-methoxy-2-*p*-tolylbenzofuran-3-carboxylic Acid (11). The procedure followed that for **4**. Crystallization of the crude product from **10** was effected by dissolving it in CH_2Cl_2 (10 ml/g **11**) and adding 5 vol. of hot petroleum ether (bp 60–68°). From 5 g of **10**, 2.9 g (60%) of the acid **11** was obtained. An additional 0.7 g (14%) could be isolated from the mother liquor: mp 112–113° dec; ir (mull) 2.90, 3.20 (OH), 5.80 μ (C=O); nmr ($CDCl_3$) δ 2.35 (s, 3, CCH_3), 3.25 (s, 3, OCH_3), 7–7.7 (m, 10, aryl H + 2 OH). The actual ratio of integrals for the aryl region to the two methyl signals was 9.8:6 before D_2O and 8.2:6 after D_2O.

On melting under N_2, **11** yielded 0.93 mol of CO_2.[8] Methylation of **11** with a slight excess of CH_2N_2 in ether afforded the ester **12**, identified by comparison with **12** prepared as described below. However, as was the case with **4**, satisfactory analyses could not be obtained on **11**.

Methyl 1,2,3-Dihydro-3-hydroxy-2-methoxy-2-*p*-tolylbenzofuran-3-carboxylate (12). The procedure followed the sodium methoxide preparation for **5**. From 1 g of the hemiketal **10**, 0.8 g of a soft white solid was obtained. Recrystallization was effected with a mixture of 10 ml of CCl_4–40 ml of petroleum ether, yielding 0.52 g (52%) of white crystals of **12**, mp 144–146°. The analytical sample (from CCl_4) melted at 145.5–146.5°: ir (mull) 2.85 (OH), 5.75 μ (C=O); nmr ($CDCl_3$) δ 2.37 (s, 3, CCH_3), 3.17, 3.25 (s, 6, OCH_3, $COOCH_3$), 4.1 (broad, 1, OH), 6.8–7.7 (m, 8, aryl H).

Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77, OCH_3, 19.75. Found: C, 68.26; H, 5.74; OCH_3, 19.01, 19.07, 19.66.

2,3-Dihydro-3-hydroxy-3-hydroxymethyl-2-methoxy-2-*p*-tolylbenzofuran (13). Following the procedure for **8**, a 1.0 g sample of the acid **11** was reduced with $LiAlH_4$. The crude product was obtained in 62% yield. Purification was effected from CCl_4-hexane (1:1), the analytical sample of **13** melting at 94–95°, ir (mull) 2.85 μ (OH).

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34; OCH_3, 10.84. Found: C, 71.31; H, 6.40; OCH_3, 10.70.

Registry No. 2, 1603-46-9; **4,** 42856-76-8; **5,** 42856-77-9; **6,** 42856-78-0; **8,** 42856-79-1; **9,** 19275-68-4; **10,** 42856-81-5; **11,** 42856-82-6; **12,** 42856-83-7; **13,** 42856-84-8.

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(1) For the preceding paper in this series, see *J. Org. Chem.*, **37**, 2774 (1972).

(2) Supported in part by the National Institute of General Medical Sciences, National Institutes of Health, U. S. Public Service (Grant No. 11830) and a grant to Bucknell University from the Dreyfus Foundation.

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Citrus Bitter Principles. XII.[1] Photochemistry of Limonin

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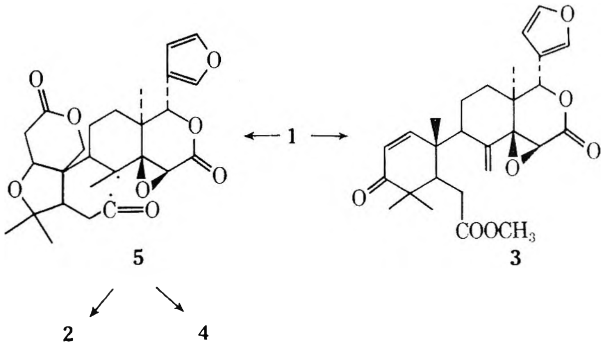
Limonin, a C_{26} triterpene occurring in some species of the Rutaceae, sometimes is responsible for bitterness in processed citrus products.[3] Specific reactions of limonin (**1**) are of interest as the basis of possible debittering methods. As part of such a study this paper describes photolysis studies of limonin.

Because of the complex and polyfunctional nature of limonin (**1**), prediction of the structure of possible limonin photoproducts was difficult. Irradiation of **1** in dioxane or methylene chloride with a high-pressure mercury-vapor lamp using a Pyrex filter gave low yields of two crystalline photoproducts. Only two products were obtained crystalline but tlc indicated the presence of further minor limonoid products, some of which were acidic but which could not be obtained crystalline.

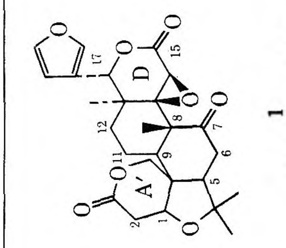
The nonpolar photoproduct, called photolimonin I (**2**), possessed typical limonoid properties. It had the usual furan bands[4] in its ir spectrum and gave a positive Ehrlich's test,[5] indicating the presence of an intact furan ring. The nmr spectrum of photolimonin I, summarized in Table I, showed the usual furan resonances and signals assignable to H-1, H-19, H-15, and H-17.[6] The chemical shifts and multiplicity of these resonances indicated that the A, A′, and D rings were intact and unchanged from those in limonin. The nmr spectrum showed only *three* *C*-methyl resonances, whereas the starting limonin (**1**) has four *C*-methyl groups. A special feature of the nmr spectrum was an aldehyde resonance[7,8] at δ 9.78 and singlets at δ 5.37 and 5.44 which are assignable to an exocyclic methylene group. These results are best interpretable in terms of structure **2** and are compared in Table I with the nmr data of andirobin (**3**), a limonoid, having a similarly cleaved B ring, isolated from *Carapa guayanensis* Aubl. (Meliaceae).[9-11] The aldehyde resonance was a broadened singlet which could not be resolved into the expected triplet. However, irradiation of δ 2.80 gave a much sharper aldehyde resonance. Small, 1 Hz and less, coupling constants are not unusual in such systems.[11-13]



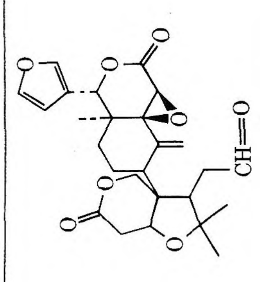
Photolimonin I showed a very low-amplitude negative Cotton effect ($a = -3.7$), consistent with the flexible conformations of the aldehyde group and its distance from an asymmetric center.[13,14]

A second photoproduct, photolimonin II (**4**), was obtained crystalline in low yield from the more polar chromatographic fractions. Photolimonin II showed physical properties (solubility, melting point, R_f on tlc) very similar to those of limonin (**1**) and gave an nmr spectrum (Table I) very similar to that of **1** with some differences in the chemical shifts. Nmr studies of limonoids[6] have shown that H-15 falls in the deshielding region of the 7-keto group, causing its resonance to occur relatively far downfield. In **4** the sharp singlet for H-15 falls further upfield out of the shielding region of the 7-keto group. Moreover, the C-19 methylene group now falls in the deshielding region of the epoxy group, causing its resonance to occur further downfield than it does in limonin. The decreased crowding of H-19 in photolimonin II also may contribute to its downfield position relative to limonin.

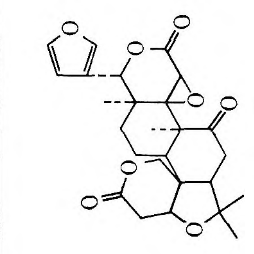
Table I
Nmr Data on Limonin Photoproducts in Deuteriochloroform



1



2


4

Compd	α-Furan	β-Furan	H-17	H-19	H-1	H-15	H-2	C-Methyls			Other	
Limonin (1)	7.36 (d) (J = 1 Hz)	6.30 (t) (J = 1 Hz)	5.45	4.42 4.75	4.03	4.03		1.30	1.17 1.08	1.17		
Photolimonin II (4)	7.44 (d) (J = 1 Hz)	6.37 (t) (J = 1 Hz)	5.51	4.90	3.97 (t) (J = 3 Hz)	3.78	2.95 (d) (J = 3 Hz)	2.48	1.27 1.13	1.27		
Photolimonin I (2)	7.44	6.37 (t)	5.51	4.35	4.33[a]	3.98	2.80	1.37	1.12	1.00	-CH=O >C=CH$_2$	9.78 5.44 5.37
Andirobin (3)[b]	7.46	6.38	5.53			4.08		1.12	1.12 0.95	0.99	>C=CH$_2$	5.44 5.33

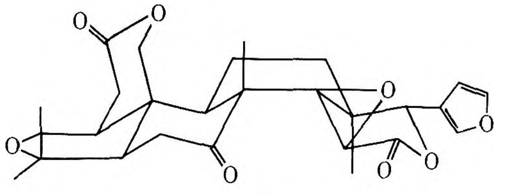
[a] Multiplicity obscured by H-19. [b] Data taken from ref 9.

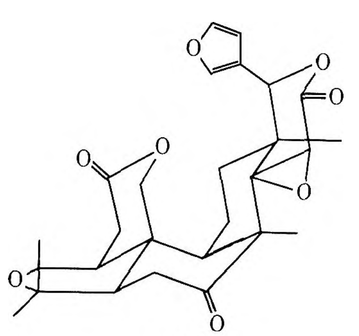
The ORD curve of 4 exhibited a negative Cotton effect ($a = -19.4$) similar to, but not identical with, that of limonin.[15] These data are consistent with the identification of photolimonin II as 4, a C-8 stereoisomer of 1 in which the 8-methyl is α instead of β as in limonin. The sign of the Cotton effect for the 7-keto group of limonin is difficult to predict from the octant rule, since most of the D ring falls in a front octant. In photolimonin II most of the D ring falls in an upper right, back (negative) octant. Thus a negative Cotton effect is predicted.

The two photoproducts isolated in this study are those which would result from 7,8-bond cleavage of 1. Both photolimonins are the classical products expected from photolysis of saturated ketones.[13,16] The formation of 4 results from recombination of the diradical 5 on the α side of the planar C-8. This suggests that 1 and 4 might exist in a photochemical equilibrium. In an attempt to demonstrate the presence of a photochemical equilibrium between limonin (1) and photolimonin II (4), compound 4 was reirradiated. However, it was not possible to detect the formation of 1 among the reaction products even with a tlc system which could resolve compounds 1 and 4.

The nonbonded interactions in both limonin and photolimonin II appear to be of about the same magnitude. The boat C ring in limonin (I) is converted into a chair conformation in 4; however, a new axial 1,3-dimethyl interaction involving 8- and 13-methyls has been created.

The conversion of limonin to its C-8 stereoisomer (4) results in a significant conformational change. Limonin (**1a**) is a fairly planar, extended molecule while photolimonin II (**4a**) is a much more compact ball-shaped system. This structural change results in the loss of biological activity. In contrast to the extreme bitterness of limonin, photolimonin II is completely tasteless while photolimonin I is only slightly bitter.


1a


4a

The close structural similarity between photolimonin I (2) and andirobin (3) provides further laboratory analogy for the conversion of limonoids of the 7-deacetyl-7-oxogedunin type to the andirobin series.[9,10,17] Finally, the photolysis of the 7-keto group has not involved the β,γ-epoxy group.[18]

Experimental Section[19]

Photolimonin I (2). A saturated solution of limonin in methylene chloride (dioxane was used in some runs) was irradiated with a high-pressure mercury-vapor lamp in an immersion cell using a Pyrex filter. The solution was irradiated under nitrogen, with stirring, for 12 hr. Solvent was removed in a rotary evaporator and the residue was recrystallized from methylene chloride-ethanol to give several crops of limonin. Solvent was removed from the mother liquors and the residue was chromatographed on acid-washed alumina. The content of the fractions was monitored by tlc using a 1:1 chloroform-ethyl acetate solvent system with Ehrlich's reagent to detect limonoids as described previously.[5] Those fractions containing a new nonpolar limonoid spot were combined, solvent was removed, and the residue was crystallized from methanol: mp 222-224°; ir (Nujol) ν 1758, 1718 (carbonyl), 1503, 879 (β-substituted furan), 904 cm^{-1} (exocyclic methylene); λ_{max} (EtOH) 215 mμ (ϵ 5200), 280 (16); R_f on tlc[10] 1.3 that of limonin; ORD in dioxane (c 0.15) at 22° $[\alpha]_{600}$ +27°, $[\alpha]_{370}$ +53°, $[\alpha]_{318}$ −107°, $[\alpha]_{281}$ +270°, $[\alpha]_{256}$ −340°, $[\alpha]_{246}$ +200° (last reading).

Anal. Calcd for $C_{26}H_{30}O_8$: C, 66.35; H, 6.42. Found: C, 65.8; H, 6.41.

Photolimonin II (4). Further work-up of the more polar fractions from the column by concentration gave several crops of impure limonin. Finally, solvent was removed and the residue was filtered through a short column of acid-washed alumina with chloroform to remove polar impurities. Solvent was removed from the eluents and the residue was crystallized from ethanol and then from chloroform-ethanol: mp 299-300° dec; ir (Nujol) ν 1753, 1698 (carbonyl), 1504, 879 cm^{-1} (β-substituted furan); λ_{max} (EtOH) 209, 283 mμ; R_f on tlc identical with that of limonin. Limonin and **4** could be resolved on silicic acid using a 1:1 benzene-nitromethane solvent system: ORD in dioxane (c 0.505) at 22° $[\alpha]_{600}$ −59.5°, $[\alpha]_{323}$ −1290°, $[\alpha]_{319}$ −1250°, $[\alpha]_{314}$ −1330°, $[\alpha]_{302}$ −690° (sh), $[\alpha]_{279}$ +615°, $[\alpha]_{260}$ −400° (last reading).

Anal. Calcd for $C_{26}H_{30}O_8$: C, 66.35; H, 6.42. Found: C, 65.8; H, 6.40.

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Registry No. 1, 1180-71-8; **2,** 42867-82-3; **4,** 42867-83-4.

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Phenylsilane Reduction of Phosphine Oxides with Complete Stereospecificity

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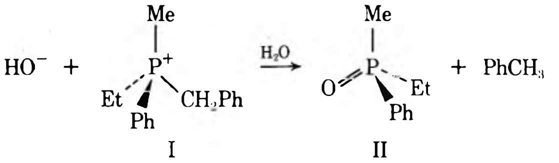
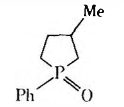
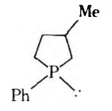
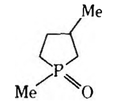
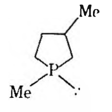
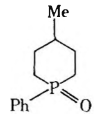
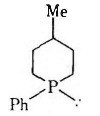
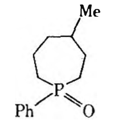
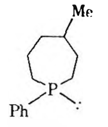
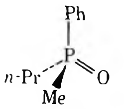
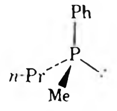
The resolution of racemic benzylethylmethylphenylphosphonium iodide into its enantiomers (I = *R*) by McEwen, *et al.*,[1] in 1959 made possible the first stereochemical studies of nucleophilic substitution reactions at phosphorus.[2] Since substitution of benzyl by hydroxyl occurs stereospecifically with inversion giving rise to optically pure phosphine oxide (II) from optically pure phosphonium salt (eq 1), the reaction provides access to optically active oxides for stereochemical studies.[3] Although attempts to prepare optically active phosphines by hydride reduction of optically active phosphine oxides produced only racemic mixtures,[4] Horner, a short time later, announced that cathodic reduction of optically active salts such as I yielded the corresponding phosphines with retention and high optical purity.[5] More recently, optically active phosphines have been successfully obtained from optically active oxides by amine-moderated reductions with trichlorosilane, which affords predominant retention or inversion of configuration depending upon the choice of amine.[6] One geometric isomer of 3-methyl-1-phenylphospholane 1-oxide (III) has been reduced with predominant inversion of configuration by use of hexachlorodisilane.[7]



(1)

In 1969 the use of phenylsilane to reduce one isomer of 1,3-dimethylphospholane 1-oxide (IV) with *complete* retention of configuration was noted by us.[8] Subsequently, other examples of the conversion of racemic cis and trans isomers of cyclic phosphine oxides to the corresponding phosphines with complete retention of configuration at phosphorus were demonstrated in our laboratories.[9-11] Since the synthetic utility of phenylsilane was not elaborated upon in previous publications[8-11] and since we have now shown that acyclic optically active phosphine oxides are subject to phenylsilane reduction giving rise to optically active phosphines, also with *complete* retention of configuration, we wish at this time to make more extensive comment on this very useful reagent. In fact, we believe it to be the reducing agent of choice when stereochemically pure phosphines are required from stereochemically pure phosphine oxides. This method of reduction is especially important because optically active phosphine oxides are now more generally and conveniently available than optically active phosphonium salts as a result of Mislow's procedure involving conversion of diastereomerically pure menthyl phosphinate esters to optically active phosphine oxides with Grignard reagents.[12] Too, the interest in phosphine-metal complexes in homogeneous catalysis and the possibilities of asymmetric synthesis using chiral phosphines in such complexes[13] add a further dimension of importance to this reductive technique. Yields surpass those of any other reductive method, averaging over 90%, and as far as we have been able to determine (Table I) the reaction is 100% stereospecific for the variety of oxides studied.

Table I
Examples of Phosphine Oxide Stereoisomers Reduced with Phenylsilane

Phosphine oxide (isomer of given mp)	Registry no.	Phosphine (isomer of given bp)	Registry no.	% yield of phosphine	Stereochemical proof
 III, mp 60–61°	34868-22-9	 49–51° (0.01 mm)	24901-29-9	92	*f*
 IV, mp 72–73.5°[a,b]	43140-03-0	 139° (760 mm)	21382-81-0	85	*f*
 mp 148–149°[c]	29782-17-0 (cis) 29782-18-1 (trans)	 76° (0.15 mm)	43140-04-1 (cis) 43140-05-2 (trans)	87	*f*
 mp 80–82°[d]	43140-06-3	 115° (0.05 mm)	43140-07-4	91	*g*
 mp 57–58°[c,e] $[\alpha]_D$ +17.5° (benzene)	17170-48-8	 <70° (0.25 mm)	701-03-1	96	*h*

[a] *Cf.* ref 11. [b] *Cf.* ref 8. [c] *Cf.* ref 9. The other geometric isomer of mp 60–61° is also reduced to the phosphine with retention of configuration. [d] *Cf.* ref 10. This compound was 92% isomerically pure. [e] For preparation see ref 12b; reported[12b] rotation +17° (benzene). [f] The phosphines were stereospecifically reconverted to their oxides with *tert*-butyl hydroperoxide [D. B. Denney and J. W. Hanifin, Jr., *Tetrahedron Lett.*, 2177 (1963)]. [g] A stereochemical cycle was used (*cf.* ref 10). [h] The phosphine was quaternized with benzyl bromide (retention). The salt gave $[\alpha]_D$ +37.9° (methanol) and is known to have the same configuration as the dextrorotatory oxide.[5]

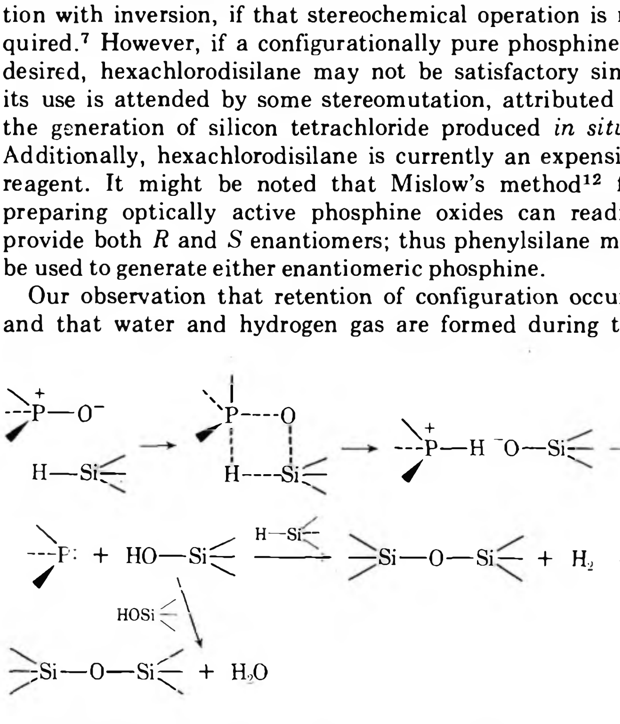
Phenylsilane was first used to reduce phosphine oxides to phosphines by Fritsche, *et al.*,[14] but its use was not noted again in the literature until our discovery of its stereochemical properties as a reducing agent.[8] In addition to superior yields and clean stereochemistry, there are many other advantages to its use. Phenylsilane is commercially available or may be made readily from phenyltrichlorosilane by lithium aluminum hydride reduction.[15] The reaction is normally carried out by mixing the phosphine oxide and phenylsilane together under nitrogen without a solvent and in a molar proportion of 3:2, respectively. Since phenylsilane is reasonably volatile (bp 120°) and siloxane polymers are nonvolatile, the resulting phosphine is obtained in high yield, usually in analytical purity, by simple vacuum distillation. If the phosphine and phenylsilane have similar boiling points, the ratio of phosphine oxide to phenylsilane may be increased to convert phenylsilane completely to polymeric material.

Unlike Horner's method,[5] which requires the construction of an electrochemical cell, no special equipment is needed. Furthermore, cathodic reduction requires the less accessible phosphonium salt enantiomers (usually as one of the halides) and is often complicated by anodic oxidation of bromide or iodide ion to the corresponding halogen which in turn may cause chemical oxidation of the phosphine.

Phenylsilane offers advantages over trichlorosilane[6] as a reducing agent since the later method employs the use of an amine which may be somewhat difficult to separate from the phosphine when the two have similar boiling points. Moreover, some racemization always accompanies the use of trichlorosilane and typical yields are only 50–60%.

Hexachlorodisilane does offer the advantage of reduction with inversion, if that stereochemical operation is required.[7] However, if a configurationally pure phosphine is desired, hexachlorodisilane may not be satisfactory since its use is attended by some stereomutation, attributed to the generation of silicon tetrachloride produced *in situ*.[7] Additionally, hexachlorodisilane is currently an expensive reagent. It might be noted that Mislow's method[12] for preparing optically active phosphine oxides can readily provide both *R* and *S* enantiomers; thus phenylsilane may be used to generate either enantiomeric phosphine.

Our observation that retention of configuration occurs, and that water and hydrogen gas are formed during the course of the reduction, leads us to the preliminary belief that mechanism 2 may be operative.



(2)

Experimental Section

Typical Reaction of Phenylsilane with Phosphine Oxides. The phosphine oxide (10 mmol) and 6.7 mmol of freshly distilled phenylsilane[15] are added together in a 10-ml pear-shaped flask fitted with a small condenser. (The system is previously purged with nitrogen, and the condenser connected to a small nitrogen-filled balloon to maintain atmospheric pressure.) If the reaction does not commence spontaneously, the mixture is heated carefully with an oil bath. Heating is especially necessary if the oxide is a solid to effect solution of the oxide with phenylsilane. Initial slow evolution of hydrogen signals the onset of the reaction. The reaction may become quite vigorous and exothermic, especially with trialkylphosphine oxides; so it is best to have an ice bath available to control the reaction temperature if necessary. After spontaneous evolution of hydrogen subsides, the reaction is heated, usually for 1 hr longer, at 80–100°. Occasionally the contents of the flask form a porous, glass-like solid at this point. At other times an opalescent, viscous liquid is seen. The phosphine may be distilled from the reaction mixture either at atmospheric pressure or at reduced pressure depending upon its boiling point. During atmospheric distillations a small amount of water codistills with the phosphine. The water may be conveniently removed by azeotropic distillation with benzene or other low boiling azeotrope-forming solvents. The pot residue is a brittle, glass-like material which is easily dissolved with alcoholic potassium hydroxide.

(+)-(*R*)-Methylphenyl-*n*-propylphosphine Oxide. This compound was prepared by reaction of 2 *M* *n*-propylmagnesium bromide with (−)-$(S)_P$-methyl methylphenylphosphinate ($[\alpha]_D$ −93°) according to the procedure of Mislow:[12b] oxide, $[\alpha]_D$ +17.5° (benzene); lit.[12] $[\alpha]_D$ +17° (benzene).

(+)-(*S*)-Benzylmethylphenyl-*n*-propylphosphonium Bromide. The optically active oxide from the above procedure was reduced with phenylsilane in the manner described. However, because of the reported thermal isomerization of optically active methylphenyl-*n*-propylphosphine,[5] the external bath temperature during the reduction process was kept below 80° and the reaction mixture was allowed to remain at this temperature for 3 hr. The phosphine was distilled (kugelrohr) below 70° (0.25 mm) and collected in a Dry Ice cooled receiver: yield 96% based on the oxide. The phosphine was dissolved in deoxygenated benzene and quaternized with twice the molar quantity of benzyl bromide. After the reaction mixture was allowed to stand overnight, the solvent and excess benzyl bromide were removed *in vacuo* and the resulting oily residue was triturated with ether, whereupon it immediately crystallized. The crystals were washed twice more with ether to furnish an 89% yield of phosphonium salt: $[\alpha]_D$ +37.9° (methanol); reported[5] $[\alpha]_D$ +36.8° (methanol).

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Registry No. Phenylsilane, 694-53-1; (+)-*S*-benzylmethylphenyl-*n*-propylphosphonium bromide, 5137-89-3.

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Carbon-Phosphorus Bond Cleavage in the Reaction of Tertiary Phosphines with Boron Trihalides

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The reaction of tris(*o*-methoxymethylphenyl)phosphine with boron trichloride has been reported to produce tris(*o*-chloromethylphenyl)phosphine.[2] The analogous reaction of methoxymethyldiphenylphosphine with boron trichloride was investigated in the course of some synthetic work. It was found that this reaction unexpectedly resulted in carbon–phosphorus bond cleavage to yield either diphenylphosphine oxide or diphenylphosphinic acid depending upon the method of work-up (eq 1). The addition of H_2O_2 to the reaction mixture was employed as a means to simplify the work-up in that diphenylphosphinic acid is more easily isolated than diphenylphosphine. Carbon–phosphorus bonds are of comparable strength to that of carbon–carbon bonds and only a few reactions are known, generally under basic conditions, which give rise to carbon–phosphorus bond breaking. The alkaline hydrolysis of quaternary phosphonium salts,[3] the reaction of tertiary phosphines with alkali metals,[4] and the Wittig reaction are examples of reactions of this type. There have been no reported reactions of organophosphorus compounds with any boron trihalide which resulted in carbon–phosphorus bond breaking. A study of the reaction of a series of tertiary phosphines with the boron trihalides was initiated.

$$Ph_2PCH_2OCH_3 + BCl_3 \xrightarrow{H_2O} Ph_2P(O)H \xrightarrow{H_2O_2} Ph_2P(O)OH \qquad (1)$$

It was found that tertiary phosphines substituted with various electronegative functional groups on the carbon α to the phosphorus reacted with boron trichloride to give diphenylphosphinic acid in high yield. Phosphines substituted with similar functional groups on the β carbon gave much lower yields of the cleavage product. Phosphines containing only hydrocarbon substituents did not undergo phosphorus–carbon bond cleavage. These results are listed in Table I.

It is possible that bond cleavage was not a result of reaction with boron trichloride but a consequence of the reaction work-up with alkaline hydrogen peroxide. This possibility was eliminated by control experiments. The reaction of all the starting compounds with only basic hydrogen peroxide gave the corresponding tertiary phosphine oxides and no evidence of any cleavage product.

Boron trifluoride etherate also reacted with the same phosphines in a similar manner, but the resulting yields were generally much lower than that observed with boron trichloride. Boron tribromide reacted with methoxymethyldiphenylphosphine in the same manner. The reaction was very vigorous and extensive decomposition of the compound occurred, but about 20% of the cleavage product was isolated.

Table I
Product Distribution for Reactions of Tertiary Phosphines with Boron Trihalides

Registry no.[g]	Reaction	% $Ph_2P(O)OH$[f]	Other products (%)	Registry no.
43139-94-2	$Ph_2PCH_2OCH_3$[5] + BCl_3[c]	68	$Ph_2P(O)CH_2OCH_3$ (30)	4455-77-0
	$Ph_2PCH_2OCH_3$ + $BF_3 \cdot OEt_2$[d]	7	$Ph_2P(O)CH_2OCH_3$ (78)	
	$Ph_2PCH_2OCH_3$ + BBr_3[e]	28	$Ph_2P(O)CH_3$[b]	2129-89-7
13119-14-7	$Ph_2PCH_2SCH_3$[5] + BCl_3	85	$Ph_2P(O)CH_2SCH_3$ (11)	13119-15-8
	$Ph_2PCH_2SCH_3$ + $BF_3 \cdot OEt_2$	22	$Ph_2P(O)CH_2SCH_3$ (69)	
18629-57-7	Ph_2PCOCH_3[6] + BCl_3	77		
36838-04-7	Ph_2PCOPh[6] + BCl_3	87		
13119-19-2	$Ph_2PCH_2N(CH_3)_2$[5] + BCl_3	4		
607-01-2	$Ph_2PCH_2CH_3$[7] + BCl_3	0	$Ph_2P(O)CH_2CH_3$ (96)	1733-57-9
7650-91-1	Ph_2PCH_2Ph[7] + BCl_3	0	$Ph_2P(O)CH_2Ph$ (70)	2959-74-2
603-35-0	Ph_3P + BCl_3	0	$Ph_3P(O)$ (100)	791-28-6
794-39-8	$Ph_2PCH{=}CHPh$[8] + BCl_3	0	$Ph_2P(O)CH{=}CHPh$ (95)	795-47-1
7608-17-5	$Ph_2PC{\equiv}CPh$[8] + BCl_3	0	$Ph_2P(O)C{\equiv}CPh$ (97)	7608-18-6
5055-12-9	$Ph_2PCH_2CH_2OCH_2CH_3$[9] + BCl_3	0	$Ph_2PCH_2CH_2OH$ (91)	2360-04-5
4848-43-5	$Ph_2PCH_2CH_2NH_2$ + BCl_3	5		
24744-62-5	$Ph_2PCH_2CH(OCH_3)_2$[10] + BCl_3	8[a]		

[a] This reaction produced primarily dark-colored tar. [b] This product has also been obtained from the reaction of methoxymethyldiphenylphosphine with HBr.[11] [c] Registry no., 10294-34-5. [d] Registry no., 109-63-7. [e] Registry no., 10294-33-4. [f] Registry no., 1707-03-5. [g] Of tertiary phosphine.

One possible explanation of this reaction is that a quasi-phosphonium salt is formed which subsequently undergoes a basic hydrolysis similar to that of quaternary phosphonium compounds. However, when the reaction mixture is worked up with deoxygenated water, diphenylphosphine oxide is isolated, indicating that cleavage under acidic conditions can indeed occur.

Experimental Section

All reactions were carried out in a dry nitrogen atmosphere. Infrared spectra were made on a Perkin-Elmer Model 337 infrared spectrophotometer, nmr spectra were made on a Jeolco Model C-60H1 spectrophotometer, and all melting points are reported uncorrected.

Synthesis of Starting Compounds. All starting compounds except triphenylphosphine (Aldrich) and 2-aminoethyldiphenylphosphine were prepared by standard literature methods. The compounds were characterized by ir spectra, pmr spectra, and comparison of their physical properties with those reported in the literature.

2-Aminoethyldiphenylphosphine. Triphenylphosphine (26.2 g, 0.1 mol) was stirred with excess lithium (cut in small pieces) in tetrahydrofuran at room temperature for 3 hr, resulting in a dark red solution. 2-Bromoethylamine hydrobromide (18.5 g, 0.9 mol) was added to the solution with vigorous stirring. A mildly exothermic reaction ensued and the reaction mixture became colorless at the end of the addition. The solvent was removed at reduced pressure and the residue was vacuum distilled, yielding 11.0 g (53%) of 2-aminoethyldiphenylphosphine, bp 135–138° (0.04 mm) [lit.[12] bp 220° (9 mm)].

The pmr spectrum of a deuteriochloroform solution of this compound gave a singlet (NH) at δ 1.6 ppm, a multiplet (PCH_2-) at 2.2 ppm, a multiplet (NCH_2-) at 2.8 ppm, and a complex (aromatic protons) at 7.5 ppm in the ratio 2:2:2:5, respectively.

Reaction with Boron Trichloride. Method A. The starting phosphine was added slowly with stirring to excess liquid boron trichloride (Matheson) at 0°. The reaction mixture was allowed to warm to room temperature with the evaporation of the boron trichloride, and basic 3% hydrogen peroxide was added to the residue. The resulting aqueous mixture was extracted with $CHCl_3$ and any unreacted starting compound was isolated from the $CHCl_3$ phase as the corresponding phosphine oxide. Acidification of the aqueous phase with HCl resulted in the precipitation of diphenylphosphinic acid, mp 188–190° (lit.[13] mp 190–192°). The ir spectrum of this compound was identical with that of a sample of diphenylphosphinic acid prepared by treating chlorodiphenylphosphine with basic hydrogen peroxide.

Reaction with Boron Trichloride. Method B. Methoxymethyldiphenylphosphine (7.0 g, 0.03 mol) was added with stirring to excess liquid boron trichloride at 0°. The reaction mixture was allowed to warm to room temperature with the evaporation of the excess boron trichloride. Deoxygenated water was added to the residue and the aqueous mixture was extracted with chloroform. The chloroform extract was dried and stripped of the solvent, and the residue was vacuum distilled, yielding 2.0 g (33%) of diphenylphosphine oxide, bp 135–138° (0.4 mm), which crystalized upon standing (lit.[14] mp 53–56°). The ir spectrum of this compound showed strong absorbtion at 2275 (PH) and 1175 cm^{-1} (P=O).

Reaction with Boron Trifluoride Etherate. The phosphines were added to excess boron trifluoride etherate and the mixture was heated mildly (below reflux) for 2 hr. Basic 3% hydrogen peroxide was then added and the resulting mixture was extracted with $CHCl_3$. Unreacted starting material was isolated as the corresponding oxide from the $CHCl_3$ phase. Acidification of the aqueous phase resulted in the precipitation of diphenylphosphinic acid, whose structure was verified by comparison of its melting point and ir with those of an authentic sample.

Reaction of Boron Tribromide with Methoxymethyldiphenylphosphine. Methoxymethyldiphenylphosphine (4.4 g, 0.02 mol) was added slowly over a period of 0.5 hr to excess boron tribromide at 0°. A very exothermic reaction occurred. The reaction mixture was allowed to warm to room temperature, then cooled with an ice bath, and basic 3% hydrogen peroxide was added slowly. A very exothermic reaction occurred. The aqueous mixture was extracted with $CHCl_3$ and the aqueous phase was acidified, yielding 0.8 g (20%) of diphenylphosphinic acid.

Acknowledgment. We are indebted to the Robert A. Welch Foundation, Houston, Texas, for support of this work through Grant V-314.

Registry No. 2-Bromoethylamine hydrobromide, 2576-47-8.

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The Reformatsky Reaction in a Continuous Flow System. An Improved Procedure for Preparation of β-Hydroxy Esters

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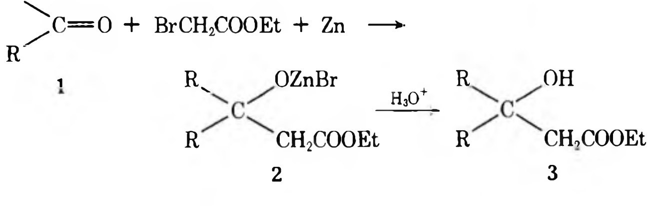
The Reformatsky synthesis of β-hydroxy esters[2] is unfortunately subject to a number of competing side reactions, including self-condensation of the α-bromo ester and carbonyl components, as well as elimination or retrograde aldol condensation of the intermediate β-alkoxyzinc ester,[3] which cause yields in this process to be highly variable. Much of the difficulty associated with the Reformatsky reaction may be traced to the fact that, although heat is generally required to initiate it, once started it becomes vigorously exothermic, often requiring careful moderation. This problem and attendant side reactions become particularly severe on a large scale, and have prompted us to search for a suitable modification of the conventional procedure.

Of the several published improvements for conducting the Reformatsky reaction,[4] that by Rathke and Lindert,[5] in which the reaction is carried out at room temperature in trimethyl borate–tetrahydrofuran (TMB–THF) solvent, appears to offer special promise. Our own approach to this problem, dictated in part by the need for large quantities of β-hydroxy esters, has been based upon the supposition that a continuous-flow system, having a minimum contact of starting materials and product in the reaction zone, would both enhance the yield and avoid the repetition of a batch procedure.

The procedure found to be most effective involved the dropwise addition of a 1:2 molar mixture of the carbonyl component (**1**) and ethyl bromoacetate in benzene to a benzene-presaturated column containing granular zinc. The apparatus for this purpose is shown in Figure 1. Sufficient heat was applied to the column to maintain a gentle benzene reflux at the head of the column. The resulting zinc alkoxide **2** is delivered by the column as a pale yellow benzene solution, and successive washings of this solution with 15% sulfuric acid, saturated sodium bicarbonate solution, and brine gave the hydroxy ester **3** in high yield.

The results are summarized in Table I. It can be seen that yields from the present procedure represent substantial improvements over those obtained by conventional methods and compare favorably with those of Rathke and Lindert.[5]



1 **2** **3**

It is also noteworthy that successive addition of different carbonyl components in admixture with ethyl bromoacetate to the same column resulted in no detectable cross-contamination of hydroxy esters. Reactions ranging in scale from 0.2 (1-butanal) to 1.6 M (cyclopentanone) were carried out without difficulty, the former requiring 0.6 hr and the latter 32 hr (optimum through-put was 60 ml of solution per hour). As the zinc becomes depleted the column can be simply recharged and the reaction resumed.

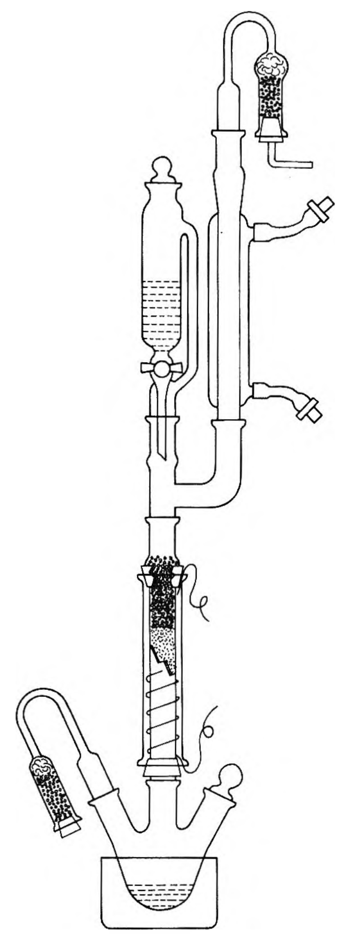


Figure 1. Apparatus for conducting continuous-flow Reformatsky reaction.

Product hydroxy esters from **4**–**11** were purified by short-path distillation and identified by ir, nmr, and mass spectral data. All showed a single peak upon glpc, but nmr evidence indicated that the products from compounds **8**–**11** were, in each case, a mixture of stereoisomers. No attempt was made to separate these isomers.

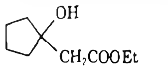
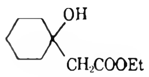
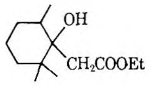
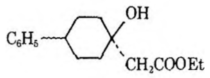
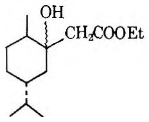
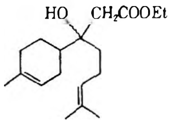
The continuous-flow Reformatsky reaction in a heated column of granular zinc offers several advantages over alternative modes, especially in regard to the extreme tractability of the reaction and the virtual absence of by-products. Hindered ketones such as 2,2,6-trimethylcyclohexanone, which give low yields of hydroxy ester in a conventional procedure, show only moderate improvement in the present variation.

Experimental Section

Materials. 1-Butanal, cyclopentanone, cyclohexanone, benzaldehyde, 2,2,6-trimethylcyclohexanone, and ethyl bromoacetate were obtained from commercial sources; they were distilled prior to use and checked for purity by glpc. 4-Phenylcyclohexanone was prepared by the method of Ungnade.[6] (−)-Carvomenthone was prepared from (+)-carvone following the procedure of Rothman and Day.[7] 1-Methyl-4-(5-methylhex-4-enoyl)cyclohexene was obtained by the route of Vig, *et al.*[8] Granular zinc (20 mesh) was activated prior to use by washing with 2% hydrochloric acid, water, 95% ethanol, acetone, and anhydrous ether; it was then dried *in vacuo* at 100° for 0.2 hr. Glc analysis was carried out on an Aerograph Autoprep 700 using a 5 ft × 0.25 in. column of 10% SE-30 on Chromosorb W.

Reactions Using Zinc Column. The following procedure for the conversion of cyclopentanone to ethyl (1-hydroxycyclopentyl)-acetate (**5**) is representative. The apparatus shown in Figure 1 was charged with 110 g (1.7 g-atoms) of zinc and sufficient glass helices to form a bed 4 cm deep above the zinc (total bed length was *ca.* 20 cm). The column was saturated with 15 ml of dry ben-

Table I
Reformatsky Reaction of Carbonyl Compounds with Zinc and Ethyl Bromoacetate

			Yield, %		
Carbonyl compd	Product	Bp, °C (mm)[a]	Zinc column[b]	Conventional method	TMB-THF method[c]
1-Butanal (**4**)	$CH_3(CH_2)_2CH(OH)CH_2COOEt$	45 (0.02)	89	69[d]	97
Cyclopentanone (**5**)		57 (0.03)	95	50[c]	93
Cyclohexanone (**6**)		66 (0.03)	93	56[e]	85
Benzaldehyde (**7**)	$C_6H_5CH(OH)CH_2COOEt$	95 (0.02)	94	61[e]	95
2,2,6-Trimethylcyclohexanone (**8**)		73 (0.02)	49	20[f]	
4-Phenylcyclohexanone (**9**)		70 (0.02)	96		
(−)-Carvomenthone (**10**)		126 (0.02)	83		
1-Methyl-4-(5-methylhex-4-enoyl)cyclohexene (**11**)		118 (0.02)	86		

[a] Analyzed sample. [b] Based upon glpc analysis using internal standards. [c] Data from ref 5. [d] Data from ref 4. [e] Data from ref 2. [f] This work.

zene and heated until refluxing benzene was just visible above the head of the column bed. A solution of 12.2 g (0.146 mol) of cyclopentanone and 48.6 (0.291 mol) of ethyl bromoacetate in 200 ml of dry benzene was added dropwise from the funnel at *ca.* 1 ml/min. The heat applied to the column was decreased by 25% soon after addition commenced to maintain a gentle reflux at the column head. After addition was complete, the column was flushed with 50 ml of benzene. The pale yellow solution which had collected was poured into 300 ml of ice-cold 15% sulfuric acid, and the mixture was shaken until the colorless precipitate had dissolved. The organic layer was separated and washed successively with saturated sodium bicarbonate solution and saturated sodium chloride solution. The benzene extract was dried ($MgSO_4$), the solvent was removed *in vacuo*, and the residue was distilled to give 23.6 g (95%) of **5**, bp 53-57° (0.03 mm).

Acknowledgments. We are grateful to Drs. Michael J. Dimsdale and John A. Katzenellenbogen and Miss L. Kathleen Green for the preparation of compounds **9**, **10**, and **11**. Financial support was provided by the National Science Foundation.

Registry No. **4**, 2305-25-1; **5**, 3197-76-0; **6**, 5326-50-1; **7**, 5764-85-2; **8**, 42908-40-7; 1-butanal, 123-72-8; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; benzaldehyde, 100-52-7; 2,2,6-trimethylcyclohexanone, 2408-37-9; zinc, 7440-66-6; ethyl bromoacetate, 105-36-2.

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Synthesis of Menthyl- and Neomenthyldiphenylphosphine. Epimeric, Chiral, Tertiary Phosphine Ligands for Asymmetric Synthesis

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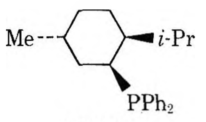
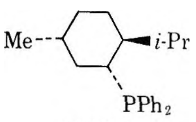
During the past several years the hydrogenation of unsaturated organic substrates using soluble transition-metal complexes as catalysts has been extensively studied. Numerous publications testify to the intrinsic interest and utility of homogeneous reducing systems.[1] Such systems are ideally suited for the introduction of chiral ligands which convey upon the transition metal complex the potential for diastereomeric interactions with unsaturated organic substrates, thus making asymmetric synthesis possible.[2] The realization of asymmetric synthesis in homogeneous hydrogenations,[3] hydrosilylations,[4] and hydroformylations[5] has been the subject of several recent papers.

In this paper we report details of the synthetic procedures for neomenthyldiphenylphosphine (NMDPP) and menthyldiphenylphosphine (MDPP), chiral tertiary phos-



NMDPP



MDPP

phine ligands that can be prepared in quantity from (−)-menthol *via* (−)-menthyl and (+)-neomenthyl chloride, respectively. Our initial syntheses of these ligands involved the reaction of lithium diphenylphosphide with neomenthyl or menthyl chloride in tetrahydrofuran solvent. Subsequently we have obtained much better results with sodium diphenylphosphide.[6]

Experimental Section

Diphenylphosphine.[7] Chlorodiphenylphosphine (908 g, 4.12 mol) was added to a stirred, ice-cold suspension of lithium aluminum hydride (47.1 g, 1.24 mol) in dry ether (2 l.) over a period of 1.5 hr. under nitrogen. The reaction mixture was allowed to stand overnight under nitrogen. It was then heated at reflux for 1 hr before water (110 ml) was added dropwise and reflux continued for an additional 3 hr. The ether layer was filtered through Celite (caution: after filtration the Celite cake may be pyrophoric) and the precipitate was washed well with ether. The combined ether solutions were concentrated under reduced pressure and distilled to give 565 g (74%) of diphenylphosphine, bp 99–100° (1 mm). Another 30 g of diphenylphosphine containing a trace of diphenylphosphine oxide was collected at a slightly higher temperature.

(+)-Neomenthyl chloride was prepared from (−)-menthol using the procedure of Horner, *et al.*[8]

(−)-Methyl chloride was prepared from (−)-menthol using the procedure of Smith and Wright.[9]

(+)-Neomenthyldiphenylphosphine. Sodium metal (34.5 g, 1.5 mol) was added in small pieces to 1.5 l. of anhydrous ammonia under a nitrogen atmosphere. Over a 1-hr period Ph_2PH (279 g, 1.5 mol), diluted to 600 ml with dry THF, was added to the sodium in ammonia solution (hydrogen evolution). The resulting red solution of sodium diphenylphosphide was allowed to warm to room temperature to expel the ammonia. A solution of (−)-menthyl chloride [262 g, 1.5 mol, $[\alpha]^{22}\text{D}$ −49.1° (c 2.15, heptane), diluted to 800 ml with dry THF] was added in one portion. The reaction mixture was heated at reflux for 54 hr. The resulting light orange solution was treated with 250 ml of water. The organic layer was separated, washed with water, concentrated, and vacuum distilled until crystal formation was observed in the distillation condenser [about 160° (1 mm)]. The forerun was saved for recovery of diphenylphosphine.[10] The pot residue (260 g) was carefully recrystallized from 95% ethanol (degassed with N_2[11]) using 16 ml of solvent/g of crude phosphine and very slow cooling. The first crop of crystals (130.5 g) contained 85% NMDPP (glpc, 3% SE-30 on Varaport 30, 80–100 mesh, 235° 50 ml/min He flow rate) and 15% NMDPP oxide. The mother liquors were cooled further and yielded 46 g of crystals (94–95% NMDPP), $[\alpha]^{23}\text{D}$ +94.4 (c 1.26, CH_2Cl_2), mp 96–99°.[12]

The mother liquor from the second crop of crystals was concentrated and cooled to give an additional 11 g of crystals [75% NMDPP, 10% NMDPP oxide, 15% $Ph_2P(O)H$]. The total conversion of menthyl chloride to NMDPP was about 34%, not counting the amount of NMDPP oxide produced. Careful recrystallization can provide high-purity NMDPP (95%), but the oxide is a tenacious impurity. Oxide does not interfere in the conversion of NMDPP to Rh(I) complexes of the Wilkinson type by displacement on μ-alkene Rh(I) precursors.[3g]

(+)-Neomenthyldiphenylphosphine Oxide. The mother liquor from the last crystallization of NMDPP described above was evaporated to dryness, and the residue was dissolved in chloroform and oxidized with bromine water to give crude NMDPP oxide, 21 g from xylene, mp 215–217°.

In another preparation, 5.0 g of impure NMDPP was treated with 10 ml of 30% H_2O_2 in a suspension containing 50 ml of benzene and 40 ml of 10% NaOH solution. After 18 hr the benzene layer was separated, washed with water, dried, and concentrated to give 3.3 g of crude NMDPP oxide. The crude material was crystallized from 30 ml of xylene to give crystals of NMDPP oxide, mp 216–217°, $[\alpha]^{29}\text{D}$ +54.5° (c 1.40, absolute ethanol).

(−)-Menthyldiphenylphosphine. Sodium metal (23.0 g, 1.0 mol) was added in small pieces to 1 l. of anhydrous ammonia under a nitrogen atmosphere. When the sodium was dissolved, a solution of Ph_2PH (186 g, 1.0 mol), diluted to 400 ml with anhydrous THF, was added dropwise. An additional 400 ml of THF was added after addition of the Ph_2PH solution was complete. The red solution was then allowed to warm to room temperature. The resulting solution was warmed slightly to expel all the ammonia, and was then cooled in an ice bath. A solution of (+)-neomenthyl chloride [159 g, 0.91 mol, $[\alpha]^{22}\text{D}$ +47.3° (*c* 3.08, heptane), diluted to 400 ml with anhydrous THF] was added over a 1-hr period. The reaction mixture was allowed to warm to room temperature slowly, stirred at room temperature for 3 hr, and then heated at reflux for 2 hr.

At the end of the reflux period, 200 ml of water was added to the light yellow reaction mixture. The organic layer was separated, washed with water, dried (Na_2SO_4), concentrated, and vacuum distilled (1 mm) until crystal formation was observed in the distillation condenser. The forerun was saved for recovery of diphenylphosphine. The pot residue weighed 95.0 g and was shown by glpc to be mainly menthyldiphenylphosphine. The total conversion of neomenthyl chloride to MDPP was about 25–30%.[13] The crude phosphine was recrystallized from 475 ml of degassed ethanol to give white crystals (27.8 g) which were isolated by vacuum filtration and dried under vacuum over P_2O_5. These crystals were shown by glpc to be 98% menthyldiphenylphosphine, $[\alpha]^{22}\text{D}$ −93.9° (c 1.67, CH_2Cl_2),[14] mp 57.5–58.5°. On further cooling the mother liquor yielded an additional 25.5 g of crystals, 96% MDPP by glpc.

(−)-Menthyldiphenylphosphine Oxide. The ethanol filtrate from the above crystallizations was concentrated and the residue was dissolved in 200 ml of $CHCl_3$ and treated with bromine water until an orange color persisted. The organic phase was separated, washed twice with 100 ml of 5% NaOH and twice with 100 ml of water, dried ($NaSO_4$), and concentrated to give crude MDPP oxide (27.5 g). Crystallization from toluene gave MDPP oxide, mp 183.5–185°, $[\alpha]^{25}\text{D}$ −87.4° (c 1.74, absolute ethanol).

Acknowledgments. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We also acknowledge support from Biomedical Grant NIH FR07108-02 and the Central University Research Fund of the University of New Hampshire.

Registry No. (+)-NMDPP, 43077-29-8; (+)-NMDPP oxide, 43077-30-1; (−)-MDPP, 43077-31-2; (−)-MDPP oxide, 43077-32-3; sodium diphenylphosphide, 4376-01-6; (−)-menthyl chloride, 16052-42-9; diphenylphosphine, 829-85-6; (+)-neomenthyl chloride, 13371-12-5.

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(6) For example, in ref 3g we reported that we had used a lithium diphenylphosphide procedure for the synthesis of NMDPP, but experimental details were not provided. Subsequently, a systematic comparison of $LiPPh_2$, $NaPPh_2$, and $KPPh_2$ revealed that $NaPPh_2$ was the most effective reagent, giving a higher yield and fewer side reactions.

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(10) The foreruns from the work-up of NMDPP and MDPP syntheses were redistilled to recover diphenylphosphine. The fraction boiling at 99–100° (1.0 mm) was collected.

(11) Precautions should be taken during all stages of the work-up of NMDPP and MDPP to limit contact with air as much as possible, and thus reduce the amount of oxide formed as a by-product.

(12) Melting points of NMDPP and MDPP samples vary slightly from preparation to preparation depending on the amount of oxide present.

(13) Methenes and diphenylphosphine are by-products in the sodium diphenylphosphide reactions. These products apparently result from elimination reactions in which the phosphide anion functions as a base rather than as a nucleophile. The elimination side reactions are the primary reason for the relatively low yields of the desired tertiary phosphines. Elimination is, as expected, a more serious competitive process in the case of neomenthyl chloride. The diphenylphosphine, which results from the elimination reaction and hydrolysis of unreacted sodium diphenylphosphide, can be recovered.[10]

(14) There is a recent literature report,[4b] without experimental details, that gives $[\alpha]^{20}{}_{D}$ −95.7° (c, 1.07, CH_2Cl_2).

The 1,3,5-Trinitrobenzene-N-Methylanilide σ Complex

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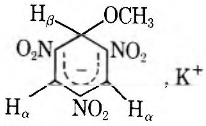
While σ complex formation between polynitroaromatic compounds and aliphatic amines has been well established,[1,2] only one instance of a σ complex involving an aromatic amine has been reported.[3] In the previous communication[3] we presented spectral evidence (nmr and uv-visible) which strongly suggested that the product of the reaction between the methoxide ion–1,3,5-trinitrobenzene (TNB) σ complex **1** and aniline in dimethyl sulfoxide (DMSO) solution was the anilide σ complex **2**.

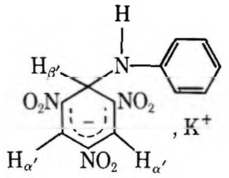
In an effort to confirm our earlier conclusions, we have extended the study to include the reaction of **1** with N-methylaniline. It was envisaged that use of this amine would result in an unambiguously interpretable nmr spectrum, since the NH–H$_{\beta'}$ coupling which was evident in **2** will have been removed in the anticipated σ complex **3**. Our previous findings of a relatively sharp AB quartet with a large coupling constant for the σ complex **2** was unexpected, as the observation of sharp doublets for NH protons coupled to CH is a relatively rare occurrence.[4,5] In view of the fact that we are concerned with structural identification of a novel complex, it was desirable to have at least one case where this feature would be absent from the nmr spectrum. In practice it turned out that the choice of N-methylaniline was only partially successful, as a result of interference from the aromatic protons of the amine; however, use of N-methylaniline-*2,4,6-d*$_3$ led to the desired simplification in the nmr spectrum and has thus allowed complete structural identification of the aryl amine σ complex.

After **1** was mixed with N-methylaniline in DMSO solution the following nmr spectral changes were observed. A spectrum taken 45 min after mixing exhibited the H$_\alpha$, H$_\beta$, and OCH_3 absorptions typical for **1** at 8.48 (doublet, J = 1.2 Hz), 6.16 (unresolved triplet), and 3.20 ppm (singlet), respectively; and for N-methylaniline typical multiplets in the aromatic proton region due to the ring protons, a broad singlet at 5.4 ppm for the amino proton, and a doublet (J = 5 Hz) centered at 2.63 ppm attributed to the N-methyl group. In addition there were present a small signal 0.05 ppm downfield from H$_\alpha$ and assigned to H$_{\alpha'}$ of **3**, and a singlet at 2.30 ppm which corresponds to the methyl protons in the N-methylaniline moiety of **3**. With time further development was evident for the peaks attributed to **3** and those due to methanol (quartet, J = 5 Hz at 4.0 ppm; doublet, J = 5 Hz at 3.1 ppm), while those belonging to **1** and N-methylaniline steadily decreased. The changes were observed to be complete within 1 day.

The signal expected for H$_{\beta'}$ in **3** was not observed, implying that it is "buried," likely under the aromatic proton multiplets which are centered at *ca.* 6.8 ppm. In order to locate the position of the H$_{\beta'}$ absorption, N-methylaniline-*2,4,6-d*$_3$ was treated with **1**. In DMSO solutions the 3 and 5 protons in the N-methylaniline-*2,4,6-d*$_3$ give rise to a single peak at 7.03 ppm. On reaction of this amine with **1**, two new features are discernible from the nmr spectra. Firstly, a peak at 7.13 ppm increases at the expense of the signal at 7.03 ppm and is assignable to the ring protons in the partially deuterated N-methylaniline moiety of the complex **3**. Secondly, the growth in a peak at 6.63 ppm corresponds to the decrease in intensity of the H$_\beta$ signal and is assigned to H$_{\beta'}$. Thus the nmr parameters for the σ complex can be assigned: H$_{\alpha'}$ 8.53 ppm, H$_{\beta'}$ 6.63 ppm, NCH_3 2.30 ppm.



1



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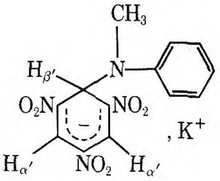

3

The reaction between N-methylaniline and **1** in DMSO was also followed by means of visible spectroscopy. Using solutions of comparable concentrations to those used in the nmr experiments, visible spectra were recorded periodically, following a 100-fold dilution with DMSO. The reaction was observed to be accompanied by a decrease in the 427- and 509-nm absorptions due to **1** and the development of absorption maxima at 436 and 516 nm due to product formation. Interconversion of the two absorbing species was characterized by reasonably tight isosbestic points. The double absorptions with the higher energy maximum being more intense are of course typical of σ complexes of TNB.[6-9]

The nmr and visible absorption spectral data presented above are fully consistent with the formation of the σ complex **3**. It may be concluded that the reaction of the TNB–methoxide ion complex **1** with primary or secondary aromatic amines in DMSO solution, leading to formation of TNB–aryl amine σ complexes, appears to be a general type of reaction.

Further examination of the nmr parameters for the complex **3** reveals additional information with probable structural significance. It will be noted that the nmr peaks of protons in the aromatic amine are shifted to low field on complex formation. This may be ascribed to the electron-withdrawing ability of the 2,4,6-trinitrocyclohexadienate moiety relative to an amino proton. Contrasting to the low-field shift of the aromatic protons of the amine moiety is the observed shift to high field of the N-methyl proton resonance on formation of **3**. This observation suggests that the methyl group protons experience an anisotropic effect due to preferential orientation above the 2,4,6-trinitrocyclohexadienate ring. It would appear that nmr should be of value in providing structural elucidation of aromatic amine–TNB σ complexes.

Experimental Section

Materials. 1,3,5-Trinitrobenzene was recrystallized from ethanol and dried *in vacuo,* mp 123–123.5°. DMSO (Fisher Certified Reagent) was distilled from barium oxide under nitrogen at reduced pressure and the middle fraction boiling at 44° was collected and stored in the dark.[2] *N*-Methylaniline was distilled from zinc dust under reduced pressure.

***N*-Methylaniline-*2,4,6-d*$_3$.** *N*-Methylaniline (6 ml) was added to a solution of D_2O (30 ml), ethanol-*O-d* (10 ml), and concentrated D_2SO_4 (6 ml) and the mixture was heated under reflux overnight. The reaction solution was then neutralized with saturated bicarbonate and extracted with ether; the extracts were dried and the ether was removed. Distillation *in vacuo* yielded *N*-methylaniline-*2,4,6-d*$_3$, which was shown by nmr to contain *ca.* 6% of the undeuterated material.

Potassium 1-Methoxy-2,4,6-trinitrohexadienate (1). The σ complex 1 was prepared from methanolic potassium methoxide and TNB, under nitrogen, followed by precipitation with dry benzene.[10] Filtration, washing with dry ether, and drying *in vacuo* yielded 1 as an orange-red solid.

Spectral Characterization of σ Complex 3. The nmr spectra were obtained with a Varian 60-MHz instrument at 35° on the DMSO-d_6 reaction solutions containing the σ complex 1 (0.40 *M*) and the aromatic amine (0.44 *M*). The spectrum was scanned periodically from the time of mixing. Tetramethylsilane was used as an external standard.

The visible spectra were obtained on a Unicam SP800 spectrophotometer following a 100-fold dilution with DMSO. The spectra were taken in a 0.1-mm cell.

Acknowledgment. We wish to thank the National Research Council of Canada for financial support.

Registry No. 1, 1270-21-9; **3,** 43190-53-0; *N*-methylaniline, 100-61-8.

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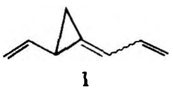
Communications

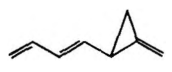
Synthesis and Thermolysis of 1-Allylidene-2-vinylcyclopropane and 1-(1-Buta-1,3-dienyl)-2-methylenecyclopropane

Summary: The syn and anti isomers of 1-allylidene-2-vinylcyclopropane (1) undergo thermal isomerization to 3-methylene-1,4-cycloheptadiene (5) and 4-vinyl-3-methylenecyclopentene (6). 1-(1-Buta-1,3-dienyl)-2-methylenecyclopropane (2) rearranges to 5-vinyl-3-methylenecyclopentene (7).

Sir: Current interest in the thermally induced vinylmethylenecyclopropane → 3-methylenecyclopentene rearrangement[1] prompts us to report on the synthesis and thermolysis of the interestingly related hydrocarbons, 1-allylidene-2-vinylcyclopropane (1) and 1-(1-buta-1,3-dienyl)-2-methylenecyclopropane (2).

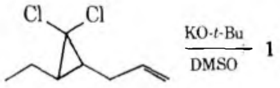


1

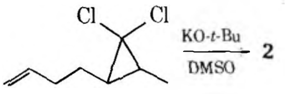


2

Addition of 1-allyl-2,2-dichloro-3-ethylcyclopropane (3)[2] to a solution of KO-*t*-Bu (2.1 equiv) in dimethyl sulfoxide at ~18° gives 1 (~40% yield) as a mixture of syn and anti isomers (eq 1). The mixture is separable by gas chromatography (10% UCON 50 HB on Chromosorb P column operated at 30°), but structural assignments have not been made.[3] Similarly, compound 2[4] is prepared in 30% yield from 1-(1-but-1-ene)-2,2-dichloro-3-methylcyclopropane (4)[5] (eq 2).

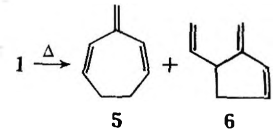


3 (1)



4 (2)

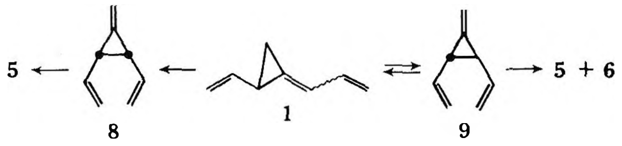
Thermolysis studies of 1 were carried out on the pure syn and anti isomers. Both isomers disappear in cyclohexane solution by a first-order rate law to give 3-methylene-1,4-cycloheptadiene (5)[6] and 4-vinyl-3-methylenecyclopentene (6).[7] One isomer (1a)[3] rearranged more readily and gave 80% 5 and 20% 6 (73% conversion). The slower isomer (1b)[3] gave 86% 5 and 13% 6 (eq 3).



5 6 (3)

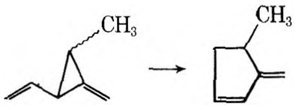
Some preliminary kinetic results on the rearrangements of 1a and 1b are shown in Table I. The activation parameters do not allow an unequivocal choice of mechanism, although the results are satisfactorily explained by invoking a series of consecutive reactions whereby 1a and 1b are converted into 8 and 9 by a methylenecyclopropane rearrangement[8] (Scheme I). This is consistent with the high positional selectivity imparted by the vinyl group in the degenerate methylenecyclopropane rearrangement observed for vinylmethylenecyclopropane.[1g] A Cope rearrangement of 8 would give 5, whereas 9 might be expected to give both 5 and 6. Attempts to detect 9 during rearrangement of 1a (the fast isomer) have been unsuccessful.

Scheme I



8 1 9

A regiospecific conversion ([3,5]-sigmatropic process) of *syn*-1 → 5 seems unreasonable since both *syn*- and *anti*-1 give mainly 5. Similarly, a concerted [3,3]-sigmatropic process involving the conversion 1 → 6 or 9 → 6 seems unlikely in view of recent studies involving related systems.[1e,g] More likely, 6 results from a concerted [1,3]-sigmatropic process or its structural equivalent in the form of a biradical. Kende and Riecke[1e] and Gilbert and Higley[2g] have proposed the intervention of orthogonal biradicals for similar rearrangements, although more recent studies favor a concerted [1,3]-sigmatropic process for the conversion 10 → 11 (eq 4).[9] At this time we are not able to differentiate between these mechanisms for the system under study here, although efforts directed toward the synthesis of 9 are underway.



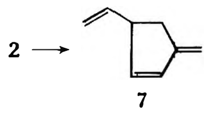
10 11 (4)

Hydrocarbon 2 rearranges cleanly by a first-order process (Table I) to give 7 (eq 5). Again, this conversion is probably best described mechanistically as involving a concerted [1,3]-sigmatropic shift or its structural equivalent in the form of a biradical.

Table I
Kinetic Data[a] and Activation Parameters for 1a and 1b

Reactant	T, °C	$k \times 10^5$, sec^{-1}	E_a, kcal/mol	Log A
1a	47.0	11.3 ± 1.3	22.8 ± 1.1	11.3 ± 0.70
	54.2	25.1 ± 1.1		
	61.5	52.2 ± 2.0		
	64.2	67.5 ± 0.90		
1b	42.0	2.54 ± 0.01	25.1 ± 0.70	12.4 ± 0.46
	49.5	6.43 ± 0.31		
	59.5	24.0 ± 1.8		
	66.5	47.3 ± 0.91		
	74.0	103 ± 3.5		
2	30.0	4.38 ± 0.31	19.4 ± 1.05	9.6 ± 0.70
	34.5	6.41 ± 2.05		
	49.0	29.1 ± 1.4		
	56.5	58.2 ± 5.1		

[a] Kinetic runs were carried out in sealed capillary tubes using cyclohexane solvent with gas chromatographic analysis.



(5)

Comparison of the activation energy reported for the vinylmethylenecyclopropane → 3-methylenecyclopentene rearrangement (25.8 kcal)[9] with that found for **2** → **7** is interesting. If rupture of the cyclopropane bond is the rate-determining step in both cases, then the difference in activation energies (~8.4 kcal) may reflect the difference in stabilization energies of the pentadienyl and allyl radicals, only slightly lower than the value of 9 kcal for another system involving cleavage of a cyclopropane bond.[10]

Acknowledgment. We gratefully acknowledge the Robert A. Welch Foundation (Grant C-490) and The Research Corporation for support of this work.

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(2) Prepared from 1,4-heptadiene and dichlorocarbene ($CHCl_3$, KO-*t*-Bu) in *n*-pentane at 0°.

(3) The isomer with the shorter retention time (**1a**) showed the following spectral properties: nmr (CCl_4) δ 1.07 (m, 1 H), 1.53 (m, 1 H), 2.11 (m, 1 H), 4.7–5.6 (m, 5 H), 6.42 (m, 2 H); ir (neat) 755 (m), 895 (s), 995 (s), 1614 (s), 1634 (s) cm^{-1}; uv λ_{max} (C_6H_{12}) 230 nm (ϵ 25,000). The remaining isomer (**1b**) showed nmr (CCl_4) δ 1.07 (m, 1 H), 1.52 (m, 1 H), 2.18 (m), 1 H), 4.7–5.7 (m, 5 H), 6.42 (m, 2 H); ir (neat) 897 (s), 995 (s), 1614 (s), 1634 (s) cm^{-1}; uv λ_{max} (C_6H_{12}) 232 nm (ϵ 19,000).

(4) Spectral properties: nmr (CCl_4) δ 1.01 (m, 1 H), 1.45 (m, 1 H), 2.17 (m, 1 HO), 4.60–5.48 (m, 5 H), 5.98 (m, 2 H); ir (neat) 882 (s), 990 (s), 1200 (m), 1428 (m), 1640 (s), 2960 (s) cm^{-1}; uv λ_{max} (C_6H_{12}) 237 nm (ϵ 38,000).

(5) Prepared from 1,5-heptadiene and dichlorocarbene ($CHCl_3$, KO-*t*-Bu) in *n*-pentane at 0°.

(6) Spectral properties: nmr (CCl_4) δ 2.32 (t, J = 2.5 Hz, 4 H), 5.1 (s, 2 H), 5.50–6.20 (m, 4 H) (irradiation at δ 2.32 reduces the δ 5.50–6.20 multiplet to an AB quartet with $J_{AB} \simeq$ 11 Hz); ir (neat) 785 (s), 880 (s), 1435 (m), 1445 (m), 1570 (m), 1786 (s), cm^{-1}; uv λ_{max} (C_6H_{12}) 246 mm (ϵ 15,000), 255 (13,000). The spectral data reported here for **5** differ substantially from those reported by earlier workers. See D. S. Matteson, J. J. Drysdale and W. H. Sharkey, *J. Amer. Chem. Soc.*, **82**, 2853 (1960); W. von E. Doering and D. W. Wiley, Tetrahedron, **11**, 183 (1960).

(7) Spectral properties: nmr (CCl_4) δ 1.98–2.87 (m, 2 H), 3.0–3.6 (m, 1 H), 4.60–5.90 (m, 5 H), 5.90–6.40 (m, 2 H); ir (neat) 760 (s), 864 (m), 908 (m) 988 (m), 1071 (m), 1432 (m), 1732 (s) cm^{-1}; uv λ_{max} (C_6H_{12}) 235 nm (ϵ 14,000).

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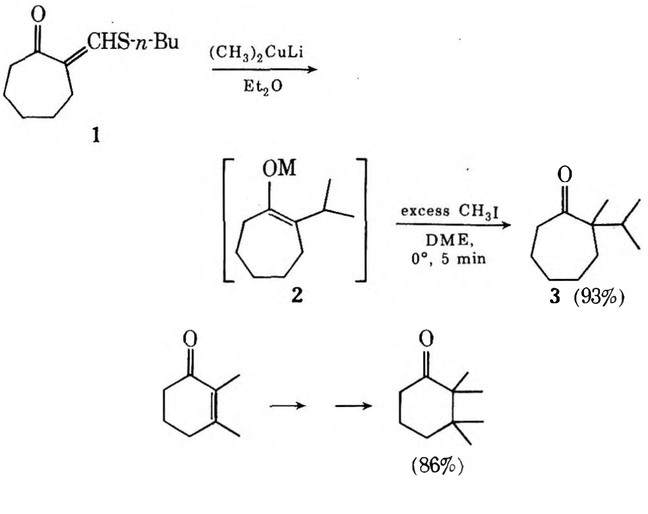
Conjugate-Addition Alkylation of α,β-Unsaturated Ketones

Summary: The copper–lithium enolates formed in the conjugate addition of organocopper lithium reagents to α,β-unsaturated ketones may be alkylated with generally high regioselectivity and efficiency in 1,2-dimethoxyethane as solvent.

Sir: The combination of dissolving metal reduction of α,β-unsaturated ketones (and analogous functions) with direct alkylation of the enolate anion so formed provides a simple and efficient method for regioselective alkylation.[1] Although it would clearly be a useful extension of this method to couple similarly the conjugate addition of organocopper reagents to α,β-unsaturated ketones[2] with alkylation,[3] attempts to alkylate the copper–lithium enolate intermediates have been either unsuccessful[4] or unsatisfactorily slow.[5,6] The ostensible unreactivity of these enolates was presumed to be the consequence of increased covalency of the copper–oxygen, as opposed to the lithium–oxygen, bond.[4]

We have discovered that the copper–lithium enolates formed in the conjugate addition of organo- (methyl- and vinyl-) copper lithium reagents to α,β-unsaturated ketones, while quite unreactive in ether (normally the solvent of choice for maximum yield of 1,4 addition),[2,7] become receptive to alkylation in 1,2-dimethoxyethane (DME). Thus, the half-life for methylation of the enolate produced in the double conjugate addition[4] to 2-*n*-butylthiomethylene ketone **1** is reduced from ~5 hr at room temperature in ether to ≪30 sec at 0° in DME, a reactivity difference of ~10^5.[8,9]



It is interesting that neither DME or tetramethylethylenediamine[10] in ether in stoichiometric proportions (3 equiv/1 equiv of Cu) nor 1:1 DME–ether was nearly so effective as pure DME in enhancing the rate of methylation of **2**, although all reactions were considerably faster than in pure ether. Accordingly, it seems to be necessary to remove essentially all of the ether prior to the addition of DME. Both tetrahydrofuran and hexamethylphosphoramide had a rate-accelerating effect comparable to, but apparently slightly less than, DME. The results of a survey upon the scope of this procedure for conjugate-addition alkylation are collected in Table I.

Some enolate ⇄ ketone equilibration is obviously occurring in certain cases (particularly the slower alkylation reactions) with concomitant formation of unalkylated, isomeric, and dialkylated products. However, we judge the yields of the desired conjugate-addition alkylation product to be comparable to those expected in the alkylation of the corresponding pure lithium enolate, considering the relatively hindered environment of the reaction site.[1b] It is noteworthy that the methylation of the lithium enolate **2**

Table I
Conjugate-Addition Alkylation of α,β-Unsaturated Ketones[a]

Substrate	Alkyln reagent[b]	Alkyln conditions Time, min (hr)	Alkyln conditions Temp, deg	Addn alkyln, % yield[c]	Other products (% yield)[c,d]
2-*n*-Butylthiomethylenecycloheptanone	CH_3I	5	0	93[e]	
	$(CH_3)_2CHCH_2I$	(18)	25	64	2-Isopropyl (15) 2,7-Dialkyl-2-isopropyl (8)
	$CH_2{=}CHCH_2CH_2Br$	(50)	25	53	2-Isopropyl (31) 2-Isopropyl-7-alkyl (3) Alkyl enol ether (5)
	$(CH_3)_2CHI$	(50)	25	19	2-Isopropyl (20) 2,7-Diisopropyl (10) Alkyl enol ether (40)
2-*n*-Butylthiomethylenecyclohexanone	CH_3I	5	0	86[e]	
2-Cyclohexenone	CH_3I	10	0	64[f]	3-Methyl (4) Trimethyl (10)
	$CH_2{=}CHCH_2Br$	10	0	74[g]	3-Methyl (10) 2,2- and 2,6-diallyl-3-methyl (6)
2-Cyclohexenone[h]	CH_3I	10	0	48[i]	3-Vinyl (2) Dimethyl-3-vinyl (11)
2,3-Dimethylcyclohexenone	CH_3I	10	0	86	2,3,3-Trimethyl (4)
2-Methyl-5-isopropenyl-2-cyclohexenone (carvone)	CH_3I	5	0	86[j]	
	CH_3CH_2I	(4)	25	63[k]	2,3-Dimethyl-5-isopropenyl (22) Diethyl-2,3-dimethyl-5-isopropenyl (16)
3-Penten-2-one	CH_3I	5	0	46	4-Methyl (2) 4,5-Dimethyl-3-hexanone (3)
3-Methyl-3-pentene-2-one	CH_3I	10	0	64	3,4-Dimethyl (2) 4,4,5-Trimethyl-3-hexanone (4)
4-Methyl-3-pentene-2-one	CH_3I	10	0	54	4,4-Dimethyl (11) 4,5,5-Trimethyl-3-hexanone (5)

[a] *Ketone in ether was added to* ~0.25 *M* *ethereal* $(CH_3)_2CuLi$ (3 equiv for *n*-butylthiomethylene ketones, 1.5 equiv for other substrates) at 0° and allowed to react for 30–45 min. The ether was evaporated and DME (~2.5–5 ml/mmol of ketone) was added. [b] Tenfold excess. [c] Yield by glc unless indicated otherwise. All nine previously unknown addition alkylation products gave satisfactory elemental analysis (eight by combustion, one by high resolution mass spectrometry). All products gave ir and nmr spectra consistent with the indicated structures. [d] Parent name for ketone by-products from enones, if not indicated, is the saturated ketone. [e] Isolated yield after distillation. [f] Trans–cis, 4:1, separated by preparative glc and identified by nmr spectral data comparison,[11] $NaOCH_3$–CH_3OH equilibration [cis–trans, 84:16 → 15:85 (lit.[12] 12:88)], and conversion of the trans isomer to its semicarbazone [mp 202° (lit.[13] mp 202°)]. [g] 8:1 mixture of two isomers, major isomer presumably trans. [h] $(CH_2{=}CH)_2CuLi$ in place of $(CH_3)_2CuLi$. [i] ~3:1 mixture of two isomers, major isomer presumably trans. [j] Only one isomer detected, presumably trans. [k] Only one isomer detected, presumably having secondary methyl and ethyl groups trans.

(M = Li), generated by cleavage of the corresponding enol acetate with methyllithium, proceeded with $t_{1/2} \sim 5$ hr in ether at room temperature, *i.e.*, at essentially the same rate as the copper–lithium enolate produced by conjugate addition (see above).

A typical procedure is as follows. 2-*n*-butylthiomethylenecycloheptanone (**1**, 13.4 g, 63.2 mmol) prepared in the usual manner[14] from the hydroxymethylene precursor,[15,16] in 60 ml of ether was added dropwise with stirring to ethereal dimethylcopper lithium (189 mmol, 0.25 *M*)[17] over 15 min at 0° under a nitrogen atmosphere. After 30 min at 0°, the solvent was removed by gentle heating under reduced pressure. (CAUTION—Since isolation of RCu compounds in the absence of zinc or magnesium salts is reported to give "a colored, explosive solid,"[2] the residue was never allowed to become dry. In this work, no special sensitivity or instability of the intermediate mixture was observed.) The remaining moist, yellow precipitate (under nitrogen) dissolved exothermically upon addition of DME (150 ml) giving a green-black mixture which was cooled to 0°. Methyl iodide (40 ml, 640 mmol) was added quickly and the reaction terminated after 5 min at 0° by pouring the mixture into saturated sodium bicarbonate (~500 ml). After addition of sufficient aqueous ammonia (~100 ml) to solubilize the precipitated copper salts, the product was extracted into pentane (three portions) and the pentane solution was washed with dilute ammonium hydroxide and water, dried ($MgSO_4$), and evaporated. Distillation of the resulting oil afforded 9.8 g (93%) of the known[18] 2-isopropyl-2-methylcycloheptanone (**3**) as a colorless liquid [bp 111° (17 mm)].

Acknowledgment. We thank the National Science Foundation for financial support and the National Institutes of Health for funds used in the purchase of the high resolution mass spectrometer.

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(9) The reactivity difference is not simply due to solubility differences as the copper–lithium enolate **2** was demonstrated to be soluble in ether.

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The Removal and Displacement of the Thiazolidine Ring in Penicillin.[1] IV. Formation of a Biologically Active Cephem System

Summary: The thiazolidine ring of penicillin V (1) has been removed and replaced by a cephem system.

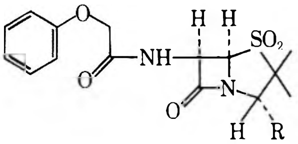
Sir: The thiazolidine ring of penicillins has been displaced for the case of 6-[2-methyl-2-(*o*-nitrophenoxy)propionamido]penicillanic acid[2] and phthalimidopenicillanic acid.[1] We now wish to report the extension of this displacement reaction to 6-phenoxyacetylaminopenicillanic acid (penicillin V, 1).

Penicillin V (1) was oxidized to the sulfone 2[3] using neutral aqueous permanganate: mp 149-151°; 94%; ir (KBr) 3450, 1800, 1735, 1675, 1600, 1530, 1325, 1240 cm^{-1}; nmr (acetone-d_6) δ 8.0 (d, 1, NH), 7.1 (m, 5, phenyl), 6.1 (dd, 1, $J_1 = 5$, $J_2 = 11$ Hz, H-6), 5.1 (d, 1, $J = 5$ Hz, H-5), 4.55 (s, 2, CH_2), 4.4 (s, 1, CH), 1.5, 1.3 (s, 6, CH_3). The sulfone 2 was converted to the isocyanate 3 *via* the mixed anhydride using ethyl chloroformate and pyridine, followed by treatment with sodium azide and thermal rearrangement. The use of triethylamine with the penicillin V side chain resulted in reduced yields of the isocyanate owing to loss of the β-lactam. Hydrolysis of the isocyanate afforded the "aldehyde" 4: 47%; mp 118-119°; $[\alpha]^{25}{}_D$ 72.7° (*c* 0.5, $CHCl_3$); ir (KBr) 3400, 1805, 1675, 1600, 1530, 1315, 1245 cm^{-1}; nmr ($CDCl_3$) δ 8.6 (d, 1, NH), m at 7.1 (aromatic and benzene solvate), 6.05 (dd, 1, $J_1 = 5$, $J_2 = 11$ Hz, H-6), 5.3 (s, 1, H-3), 4.85 (d, 1, $J = 5$ Hz, H-5), 4.5 (s, 2, CH_2), 1.4, 1.45 (s, 6, CH_3). This compound seems to exist entirely in the ring-closed form since no aldehyde absorption is detectable by nmr.[1,2,4]

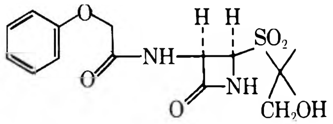
"Aldehyde" 4 was reduced to alcohol 5 with sodium borohydride: 56%; mp 142-144°; $[\alpha]^{25}{}_D$ 28.6 (*c* 1, $CHCl_3$); mass spectrum (70 eV) *m/e* 219 [$M^+ - SO_2C(CH_3)_2CH_2OH$]; ir (KBr) 3300-3500, 1780, 1660, 1600, 1530, 1300, 1250 cm^{-1}; nmr ($CDCl_3$) δ 8.2 (d, 1, NH), 7.8 (s, 1, NH), m at 7.2 (5, phenyl), 5.95 (dd, 1, $J_1 = 5$, $J_2 = 10$ Hz, H-6), 5.25 (d, 1, $J = 5$ Hz, H-5), 4.55 (s, 2, CH_2), 3.75, 3.95 (overlapping s, 3, CH_2,OH), 1.4, 1.3 (s, 6, CH_3).

In a model reaction, compound 4 reacted with thiophenol in the presence of triethylamine to give a mixture of cis and trans (1:1) 3-(phenoxyacetamido)-4-phenylthio-2-azetidinone (6): 80%; ir (KBr) 3380, 1763, 1655, 1600, 1540; nmr (acetone-d_6) δ 8.1 (br s, 1, NH), m at 7.2 (11, aromatic and solvate), 5.65 (dd, ½, $J_1 = 5$, $J_2 = 10$ Hz, H-3 cis), 5.4 (d, ½, $J = 5$ Hz, H-4 cis), 5.2 (d, ½, $J = 2$ Hz, H-4 trans), 4.8 (m, ½, H-3 trans), 4.6 (2s, 2, CH_2).

Azetidinones in which the nitrogen is substituted (7) do not react with mercaptans under these conditions. Also, if the mercaptan is sterically bulky the reaction is slow and the competing epimerization of H-4 becomes the dominant reaction route. Compound 5 reacted with isobutylmercaptan only very slowly (4 days) to give 3-(phenoxyacetamido)-4-*trans*-isobutylthio-2-azetidinone. *tert*-Butylmercaptan did not give the desired product at all; instead *trans*-5 was isolated.

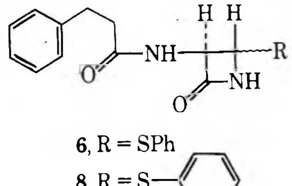


2, R = CO_2H
3, R = NCO
4, R = ~OH
7, R = $CO_2CH_2CH(CH_3)_2$

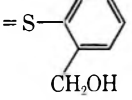


5

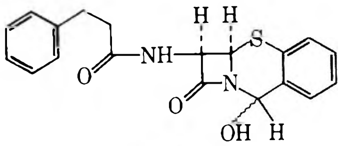
5 →



6, R = SPh
8, R = S—



8 →



9

Reaction of 5 with *o*-mercaptobenzyl alcohol in the presence of triethylamine gave cis and trans (1:1) 3-(phenoxyacetamido)-4-(2-hydroxymethylphenylthio)-2-azetidinone (8): 78%; ir (CH_2Cl_2) 3300, 1755, 1690, 1540, 1500 cm^{-1}; nmr (acetone-d_6) δ 8.7-6.9 (m, NH and aromatic, 11), 5.75 (dd, ½, $J_1 = 5$, $J_2 = 8$ Hz, H-3 cis), 5.4 (d, ½, $J = 5$, H-4 cis), 5.2 (d, ½, $J = 2$, H_4 trans), 4.9 (2s, 2, CH_2), 4.7 (2s, 2, CH_2), 4.4 (dd, ½, $J_1 = 2$, $J_2 = 7$ Hz, H_3 trans), 3.7 (s, 1, OH); mp 140-142°; mass spectrum (70 eV) *m/e* 358 (M^+).

Oxidation of 8 with dimethyl sulfoxide and dicyclohexylcarbodiimide[5] gave, after column chromatography, compound 9: 20%; mp 148-150°; ir ($CHCl_3$) 3400, 1775, 1690, 1600, 1495 cm^{-1}; nmr ($CDCl_3$, cephem numbering) δ 8.0-6.9 (m, aromatic and NH), 6.0 (s, 1, H-4), 5.7 (dd, 1, $J_1 = 5$, $J_2 = 8.5$ Hz, H-7), 5.25 (d, 1, $J = 5$ Hz, H-6), 5.05 (s, 1, OH), 4.5 (s, 2, CH_2).

Compound 9 was tested for biological activity[6] and was shown to be active against *Diplococcus pneumoniae,* 0.4;

Streptococcus pyogenes, 1.6; and *Staphylococcus aureus*, 6.3 (minimum inhibitory concentration in μg/ml).

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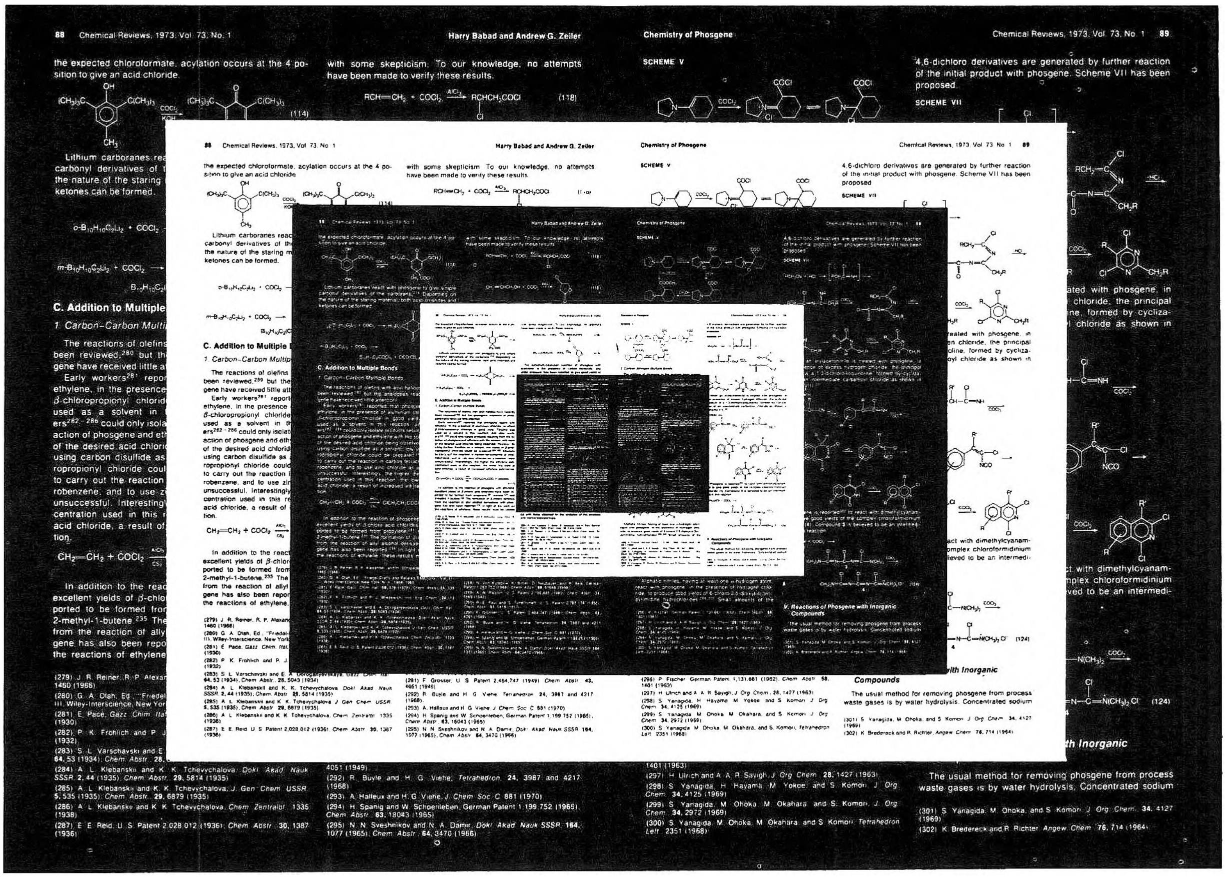

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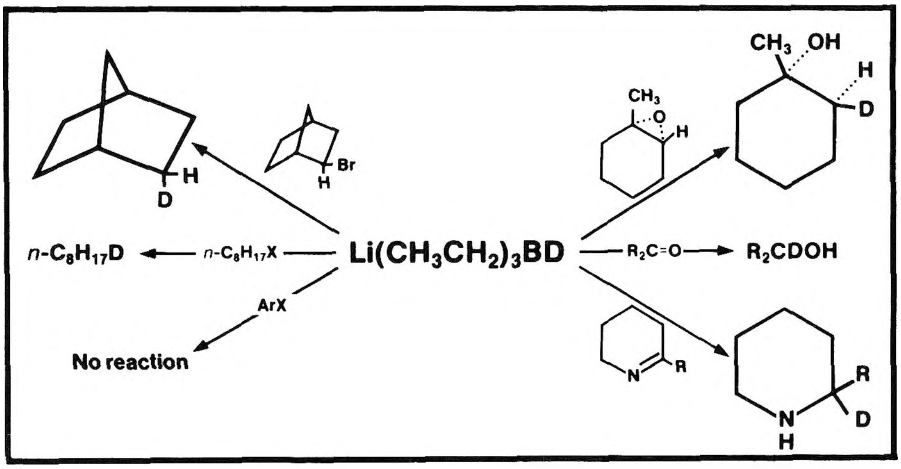

n-C8H17D
n-C8H17X
Li(CH3CH2)3BD
R2C=O
R2CDOH
ArX
No reaction
H
D
Br
H
CH3
O
H
CH3 OH
H
D
N
R
R
N
H
D