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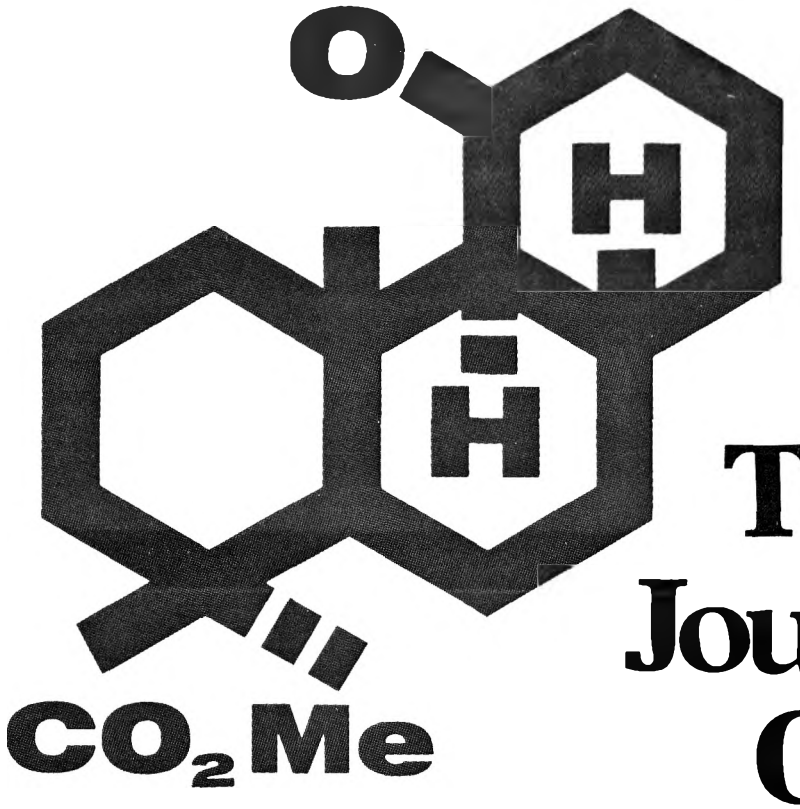

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New Photoisomerization Paths for Epoxy-2,4-cyclohexadienones and a General Mechanistic Scheme for the Photoisomerization of α,β-Unsaturated γ,δ-Epoxy Ketones

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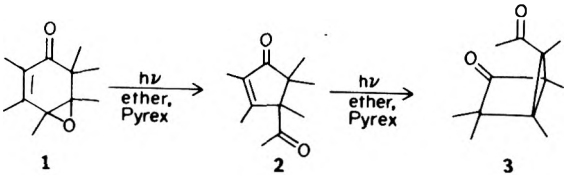
Received April 12, 1977

Two new reaction paths not previously observed in the irradiation of 2,4-cyclohexadienone 4,5-epoxides are described. Irradiation of 6,6-dimethyl-2,4-cyclohexadienone 4,5-epoxide (**5**) through Pyrex gave mainly the enol lactone **6**. The proposed mechanism, supported by isotopic labeling, involves as an intermediate the cyclopropanone aldehyde G (also implicated as the precursor of **6** in the singlet oxygen oxidation of dimethylfulvene). The photoisomerization of **5** to **6** involves a triplet excited state ($E_T \simeq 50$–60 kcal/mol). Irradiation of 2,3,4,6,6-pentamethyl-2,4-cyclohexadienone 4,5-epoxide (**19**) through Pyrex gave, among other products, the Δ^2-butenolide **22** (27%), a product best accounted for if the first bond-breaking step is cleavage of the C(1)–C(6) bond in **19**. This is the first example of α-cleavage in the irradiation of epoxy enones of this type. A general mechanism is proposed for the photoisomerization of 2,4-cyclohexadienone 4,5-epoxides. The first step following excitation is either α-cleavage (rare) or cleavage of the C(4)–O bond of the epoxide ring (common) to give diradical D, which may isomerize in one or more of four different ways depending on methyl substitution. Experimental examples of each path are given. A general mechanistic scheme is proposed which summarizes to date the observed photoisomerizations of α,β-unsaturated γ,δ-epoxy ketones.

We recently reported that the epoxy ketone **1** is converted by irradiation to **2** and then **3**.[1] In this paper, we will describe

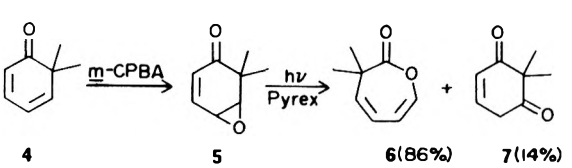


1 **2** **3**

the photochemistry of analogues of **1** containing fewer methyl substituents. These studies disclosed novel photoisomerization paths not previously observed with such epoxy ketones, for one of which we propose a cyclopropanone intermediate.[2] Following a description of these new reactions and evidence for their mechanisms, we will present a general mechanistic scheme which summarizes the known photochemistry of α,β-unsaturated γ,δ-epoxy ketones to date, and which places the new reactions in perspective.

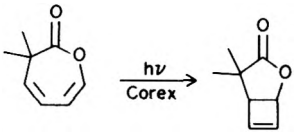
Results and Discussion

Photochemistry of 6,6-Dimethyl-2,4-cyclohexadienone 4,5-Epoxide (5). The epoxy ketone **5** was obtained in high yield by oxidizing the corresponding dienone **4**[3] with *m*-chloroperbenzoic acid (*m*-CPBA).



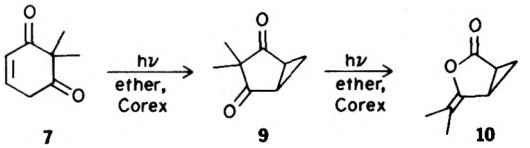
4 **5** **6**(86%) **7**(14%)

Irradiation of **5** (0.01 M in ether, Pyrex) gave two photoisomers in quantitative yield. The major product (86%) was the enol lactone **6**, a compound which has recently been obtained[4] as the major product from the reaction of singlet oxygen with 6,6-dimethylfulvene (Scheme II). Irradiation of **6** through Corex converted it to the isomeric lactone **8**.[5]



6 **8**

The minor product (14%) was assigned the unsaturated β-diketone structure **7** on the basis of its spectra and further transformations. In particular, irradiation of **7** through Corex gave in succession the known β-diketone **9**[6b] and unsaturated lactone **10**.[6b] The first of these photoisomerizations is an oxa-di-π-methane rearrangement,[7] and the second involves the typical α-cleavage of a cyclic nonenolizable β-diketone.[6]

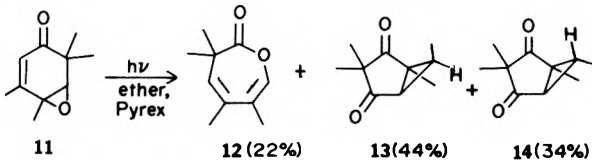


7 **9** **10**

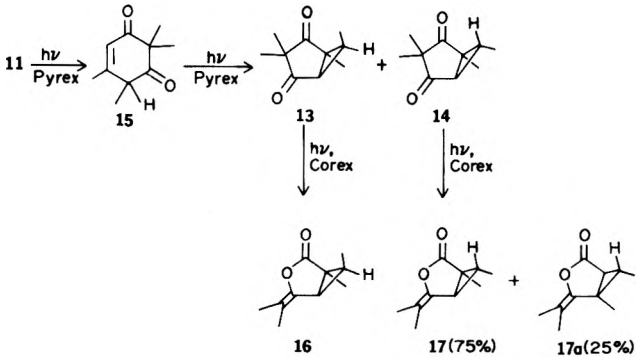
It is clear from the product structures that the methyl

substituents play an important part in determining the photoisomerization paths of 1 and 5. Before discussing the mechanism by which 6 and 7 are formed from 5, and before trying to rationalize the different photoisomerization paths of 1 and 5, it will be helpful to summarize the results obtained by irradiating dienone epoxides with an intermediate number of methyl substituents.

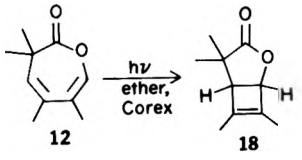
Photochemistry of Other 2,4-Cyclohexadienone Epoxides. The epoxy ketones 11, 19, and 24 were prepared from the corresponding dienones by oxidation with *m*-CPBA. Ir-



radiation of 11 (0.06 M in ether, Pyrex) gave the enol lactone 12 and the epimeric β-diketones 13 and 14. The latter two compounds are secondary products derived from the primary photoproduct 15 (analogous to the formation of 9 from 7). The methyl substituents must enhance this reaction, thus preventing us from observing 15.[8] The structures of 13 and 14 were confirmed by their conversion to the lactones 16–17 on irradiation through a Corex filter.[9]

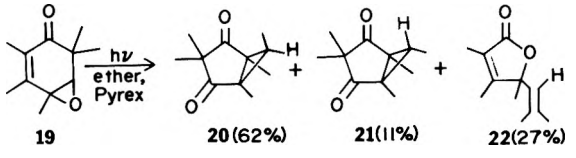


The structure of the enol lactone 12 was established as follows. Its IR and UV spectra were similar to those of 6. The NMR spectrum showed a sharp singlet for the *gem*-dimethyl group, two vinyl protons (not coupled to each other) and two vinyl methyl groups. The exact location of the methyl groups was established by further irradiation of 12 through a Corex filter. The resulting 18 had no vinyl protons, but two mutually



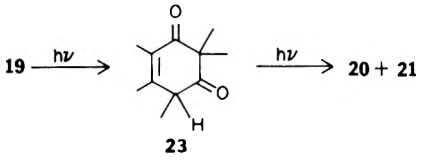
coupled aliphatic protons at δ 2.82 and 4.67 (J = 4 Hz), the latter being the proton adjacent to the oxygen. This result required that the vinyl protons in 12 be at the termini of the diene moiety. The remainder of the NMR spectrum of 18 was consistent with this assignment.

Except for quantitative aspects, the photochemistry of 5 and 11 appears to be identical, the primary products being an enol lactone (6 and 12, respectively) and an α,β-unsaturated



β-diketone (7 and 15, respectively). Differences appeared when one more methyl substituent was added.

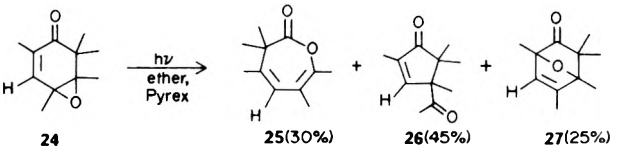
Irradiation of 19 (0.01 M in ether, Pyrex) gave the epimeric β-diketones 20 and 21 and the butenolide 22. The first two compounds are again secondary products, derived from the further photoisomerization of the unsaturated β-diketone 23.



As with the formation of 15 (vide supra), it was not possible to detect the primary product 23. However, we were able to obtain 23 through the treatment of 19 with trifluoroacetic acid.[10] Irradiation of 23 under the same conditions used with 19 gave a quantitative yield of 20 and 21, in the same ratio as they were formed by irradiating 19.

The structure of the butenolide 22 is based on its spectra. Its IR and UV spectra were nearly identical with those of the known analogue in which the vinyl hydrogen is replaced by a methyl group.[11] The NMR spectrum of 22 showed one aliphatic methyl singlet (δ 1.23), four vinyl methyls in the region δ 1.74–1.80 and one vinyl proton as a multiplet at δ 5.40. Decoupling by irradiation in the vinyl methyl region sharpened the vinyl proton signal to a singlet. Europium-shift data (see Experimental Section) and deuterium labeling experiments further support the structure. We consider 22 and 23 to be the direct photoproducts of 19.[12]

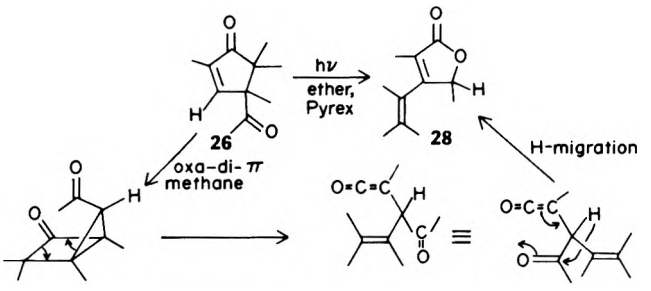
The third epoxy ketone whose photochemistry we will describe in this section is 24.[13] Irradiation of 24 (0.01 M in ether,



Pyrex) gave the enol lactone 25, the acetyl cyclopentenone 26, and the bicyclic ketone 27.

The gross structure of 25 was clear from the similarity of its IR, UV, and NMR spectra to those of 6 and 12. Since the vinyl proton in 24 occupies a position corresponding to a methyl group in 11 (and therefore in 12) the proton in 25 must be located on one of the two central carbons of the butadiene moiety. Of the two alternative structures, only 25 was consistent with the europium and chemical-shift data, and with the results of labeling experiments (vide infra).[14]

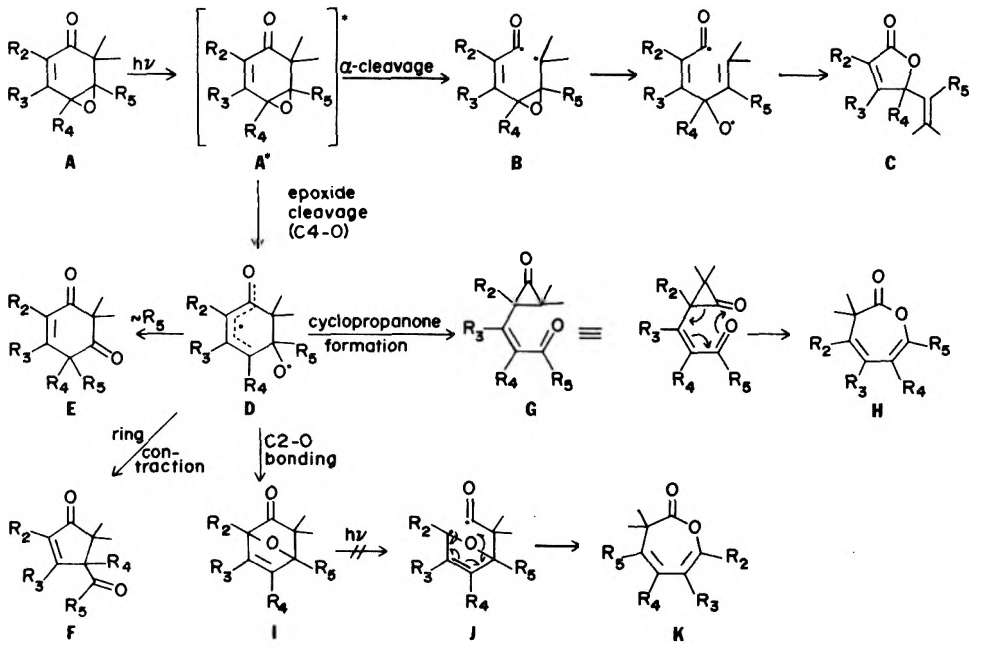
Compound 26 was analogous to 2; their IR, UV, and NMR spectra (except for the vinyl proton) were nearly identical. Although 26 was an initial photoproduct of 24, prolonged ir-



radiation converted it quantitatively to an isomer, the butenolide 28. This conversion has a direct analogy[1,15] and undoubtedly proceeds via the bicyclic and ketene intermediates shown.

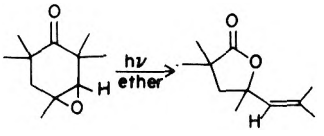
The third photolysis product of 24 had a carbonyl band at 1740 cm^{-1} typical of a five-membered-ring ketone, and the UV spectrum showed only end absorption. The NMR spectrum of 27 showed one vinyl proton (δ 5.56), coupled with an adjacent vinyl methyl (δ 1.72, J = 2 Hz), and four aliphatic

Scheme I



methyls, two gem (δ 1.12, 1.14) and two bridgehead (δ 1.30, 1.32), requiring a bicycle structure such as that shown. The remainder of the structural assignment (i.e., relative positions of the groups on the 2-carbon bridges) is based on mechanistic grounds and labeling results (vide infra).

Mechanisms for the Photoisomerization of 2,4-Cyclohexadienone 4,5-Epoxides. Scheme I summarizes the mechanisms we considered to rationalize our results. Following excitation to A* there are two options, α-cleavage to give B, or epoxide cleavage to give D. α-Cleavage has not been observed in any previous photochemical studies on α,β-unsaturated γ,δ-epoxy ketones, but we include the path A* → B → C to rationalize the formation of **22** from **19**. This minor reaction pathway has some precedent. Compound **29**, a close saturated analogue of **19**, gave the lactone **30** as the sole photoisomerization product.[16]



29 **30**

The predominant pathway following excitation to A* is epoxide cleavage at the C(4)–O bond to give the diradical D. Four options for this diradical are shown in Scheme I. 1,2-Migration of R_5 will give the unsaturated β-diketone E, a path which is particularly important when R_5 = H (as in the formation of **7** from **5**, **15** from **11**, and **23** from **19**). Type E products may not be observable, however, since they contain nearly the same chromophore as the starting epoxy ketone A. Consequently E may compete effectively with A for the light and rearrange further. This was true of **15** and **23**, which were detectable only as their oxa-di-π-methane rearrangement products (**13** and **14** from **15**; **20** and **21** from **23**).

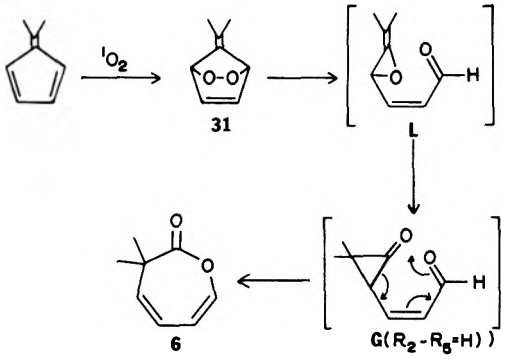
If R_5 is not hydrogen but methyl, then ring contraction is favored over R_5 migration, to give the cyclopentenone F. For example, this was the principal path in the photoisomerization of **1** (to **2**) and of **24** (to **26**). Once again the chromophore in this type of product (F) is similar to that of the starting epoxy ketone A, and further photoisomerizations may occur. In the examples studied, an oxa-di-π-methane rearrangement occurs (**3** from **2**, and **28** from **26**); however, this reaction usually is slow enough so that the initial photoproducts of type F can be isolated.

A third option open to biradical D is formation of cyclopropanone G. This reaction can be regarded as analogous to the ring contraction to F, except that a 1,4 instead of a 1,2 shift occurs. The reaction could be stepwise or concerted. The cyclopropanone G must be formed with cis geometry at the C(3)–C(4) double bond; consequently, a rapid subsequent six-electron electrocyclic reaction to form the seven-membered ring enol lactone H is possible.

A cyclopropanone intermediate of this type was proposed[4] to rationalize the formation of **6** from the reaction of singlet oxygen with dimethylfulvene (Scheme II). Cleavage of the O–O bond in the initial adduct **31** and rebonding was postulated to give the allene-oxide **L**, a precursor and valence tautomer of the cyclopropanone aldehyde G (R_2–R_5 = H).[17]

A plausible alternate route to the seven-membered ring enol lactones is also shown in Scheme I. The first step involves collapse of the diradical D to the bicyclic ether ketone I. In-

Scheme II



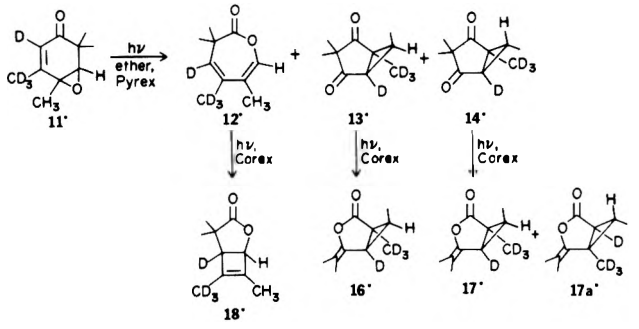
deed, a product of this type (**27**) was formed in the irradiation of **24**. Subsequent irradiation of I could cause α-cleavage to J, which on bond reorganization as shown in the scheme could lead to the enol lactone K.

This route to the enol lactones can be safely discarded on two grounds. First, irradiation of **27** (0.014 M in ether, Pyrex) under the same conditions which led to the enol lactone **25** from **24** gave no enol lactone whatever, only recovered starting material. Second, it will be noted that enol lactone derived from the cyclopropanone route (H) has the substituents R_2–R_5 arranged in the reverse order from enol lactone (K) derived from the two-photon route. The following deuterium-labeling

Table I. Substitution Pattern and Mechanistic Paths

Registry no.	Epoxy ketone	R_2	R_3	R_4	R_5	% R_5 migration	% ring contraction	% cyclopropanone formation	% C(2)–O bonding	% α-cleavage
63449-05-8	**5**	H	H	H	H	14	0	86	0	0
52898-22-3	**11**	H	CH_3	CH_3	H	78	0	22	0	0
63449-06-9	**19**	CH_3	CH_3	CH_3	H	73	0	0	0	27
50506-42-8	**1**	CH_3	CH_3	CH_3	CH_3	0	100	0	0	0
63449-07-0	**24**	CH_3	H	CH_3	CH_3	0	45	30	25	0

experiment was carried out to distinguish between these alternatives.



Irradiation of 11* (A, R_2 = D, R_3 = CD_3, R_4 = CH_3, R_5 = H) gave 12*. The NMR spectrum of unlabeled **12** has vinyl proton signals at δ 5.13 and 6.13 and a six-proton vinyl methyl signal at δ 1.80. In 12* the signal at δ 5.13 was absent and the peak at δ 1.80 was reduced in area to three protons. If the lower field vinyl proton in **12** is adjacent to the oxygen, the label can be assigned as shown in 12*. To confirm this assignment, 12* was irradiated in Corex to give 18*. The methine protons in unlabeled **18** appear at δ 2.82 and 4.67, the lower field proton clearly being the one adjacent to the oxygen. In 18*, the methine signal at δ 2.82 was absent, establishing the label pattern as shown on the structures. This result shows that the correct structural relationship between the epoxy ketone A and the enol lactone is as shown in H, not K (Scheme I), and supports the mechanism which involves the cyclopropanone intermediate G. Another labeling experiment, using deuterated **24**, verified this conclusion (see Experimental Section). The labeling pattern in the other products (for example **13*** and **14***) was also consistent with the mechanisms proposed in Scheme I.

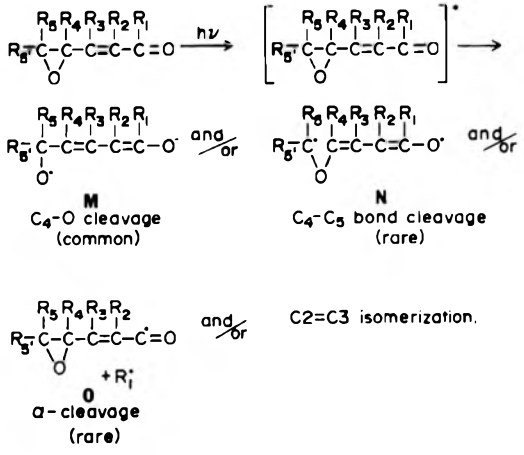
Table I summarizes the mechanistic paths in Scheme I that are followed by the simple cyclohexadienone epoxides studied thus far. Different products derived from the same path were summed (for example, **13** + **14**, **20** + **21**) to get the values in the table. Examination of the results in this way permits us to draw a few conclusions regarding the way in which methyl vis-a-vis hydrogen substituents influence the reaction course. Only when R_5 is hydrogen do we see the R_5-migration path; only when R_5 is methyl do we see ring contraction. The comparison between **19** and **1**, where this is the only structural change, is most striking. The sequence hydrogen migration > ring contraction > methyl migration is characteristic for the photorearrangement of α,β-epoxy ketones and α,β-epoxyalkenes.[18] Cyclopropanone formation appears to be dimished by substitution of methyl for hydrogen at R_2 (compare **11** and **19**) or at R_3 (compare **24** and **1**, or **5** and **11**). α-Cleavage was only observed when R_2 = CH_3, R_5 = H (**19**; see also **29**).

Since the highest yield of enol lactone was obtained from the unsubstituted epoxy ketone **5**, we studied its photochemistry in somewhat greater detail. The photoisomerization of **5** could be sensitized with either acetophenone or benzophenone. Although the reaction could not be quenched with piperylene, it was efficiently quenched by *trans*-1,3,5-hexatriene (E_T = 47 kcal/mol[19]). These results suggest that the photoisomerization of **5** occurs via a triplet excited state with an energy of about 50–60 kcal/mol.[20]

We tried to detect or trap the cyclopropanone intermediate G [R_2–R_5 = H]. After a 4-h irradiation of **5** in acetone-d_6 at −78 °C, a fairly strong multiplet was observed at δ 9.7 (aldehyde proton), which slowly disappeared on warming. This peak may have been due to G [R_2–R_5 = H],[21] though we were unable to definitely connect its disappearance with the appearance of peaks due to **6**. Infrared studies were similarly indicative but not conclusive. Irradiation of **5** in THF at −105 °C caused a weak band to appear at 1815 cm^{-1} which could be attributed to the cyclopropanone intermediate.[22] Its intensity decreased when irradiation was stopped, but its decay could not be associated directly with the appearance of bands due to **6**. Irradiation of **5** in CD_3OD at −78 °C, with the hope of trapping the cyclopropanone as a ketal, gave only **6** and **7** in the same ratio as in ether. Consequently, the aldehyde cyclopropanone intermediate G remains a plausible but not proven intermediate in the photoisomerization of A to H (Scheme I).[23]

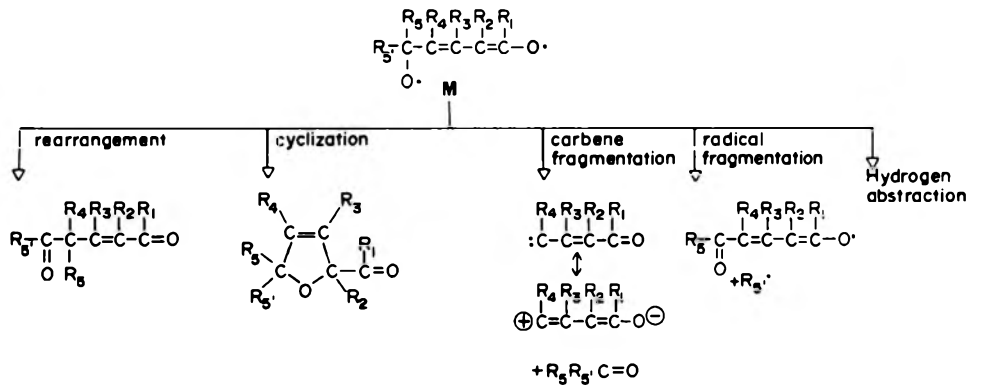
A General Mechanistic Scheme for the Photoisomerization of α-Unsaturated γ,δ-Epoxy Ketones. The cyclohexadienone epoxides whose photochemistry we have described here and summarized in Scheme I belong to the more general class of compounds, α,β-unsaturated γ,δ-epoxy ketones, many of which have been irradiated in recent years by Jeger, Schaffner, and co-workers.[24] We think it useful to summarize in one scheme the many types of reactions which have been observed to date following excitation of this interesting class of compounds (Schemes III and IV, no stereochemistry implied). The various alternatives are illustrated below with specific examples.

Scheme III

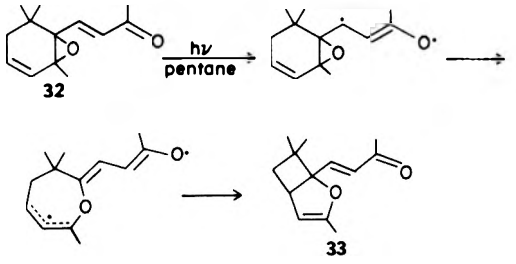


Following initial excitation (the reactive state is usually a triplet) one of three-bond-cleavage processes usually occurs. Carbon–carbon cleavage of the epoxide ring (to give N) has been observed[24e,h] when the groups at C(5) can stabilize the resulting radical (in **32**, R_5 = vinylic, R_5 = methyl).[25,26] The only example of α-cleavage (to give O) reported thus far is the formation of **22** from **19** reported in this paper (vide supra). In acyclic systems, $E \rightleftharpoons Z$ isomerism at the C(2)–C(3) double bond of the enone moiety is also known.[24d,g,h]

Scheme IV

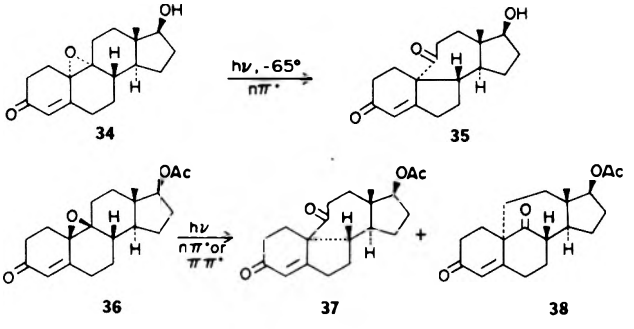


By far the most common reaction observed in these systems is cleavage of the epoxide ring at the C(4)–O bond.[1,24a–d,f–h] Scheme IV summarizes the types of subsequent reactions

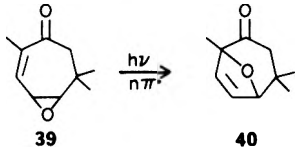


which have been observed for the resulting diradical M. Rearrangement of a group R_5 from C(5) to C(4) occurs frequently, and the group which migrates may be a hydrogen,[24a,f] methyl,[24h] or other carbon fragment.[1,24a–c] Although the precursor to these rearrangements has been written in Scheme IV as a diradical, the migration may in fact be stereospecific,[24b,c] as in Scheme V.

Scheme V

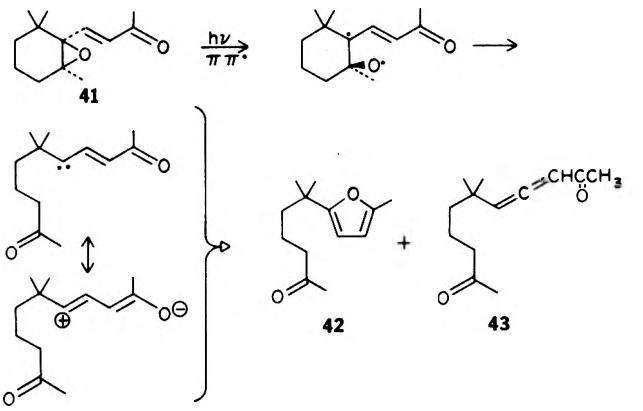


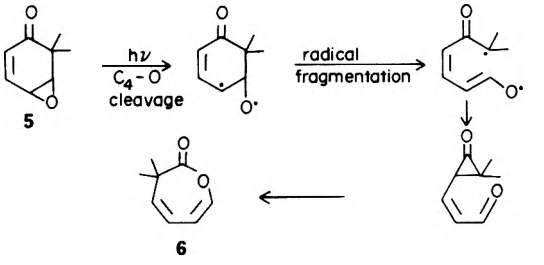
Cyclization to form a dihydrofuran by bond formation between the epoxide oxygen and C(2), as exemplified in this paper by the formation of **27** from **24** (vide supra), has precedent,[24d,f,h] the best example being eucarvone epoxide **39**.[24f]



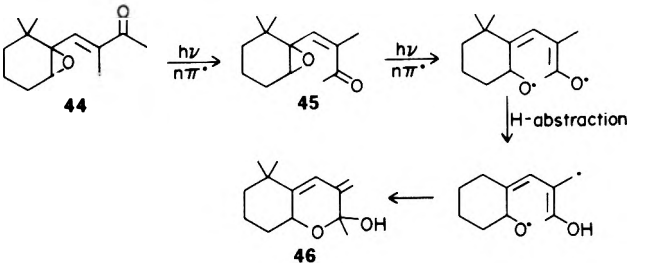
The diradical M may fragment by cleavage of the C(4)–C(5) bond to give a carbonyl compound and a carbene (or dipolar ion), as illustrated by the formation of **42** and **43** on irradiation of *trans*-β-ionone epoxide **41**.[24d,h,27,28]

The formation of the cyclopropanone G (Scheme I), and ultimately the enol lactone H reported in this paper (vide supra) can be visualized as a radical fragmentation of the diradical M (Scheme IV). This is shown specifically for the formation of **6** from **5**. This type of diradical fragmentation has not been observed previously in the photoisomerization of α,β-unsaturated γ,δ-epoxy ketones.[1,24,29]





Finally, the diradical intermediates M and N (Scheme III) may abstract hydrogen atoms, particularly from favorably located intramolecular positions.[24g,h] A good example is the predominant formation of the bicyclic alcohol **46** on nπ* excitation of **44**.



The reactions shown in Scheme I for cyclohexadienone epoxides constitute a subgroup of the more general Schemes III and IV. Certain reactions in Scheme III (C(4)–C(5) bond cleavage and *E*–*Z* isomerization) have not been observed or are precluded by the cyclic structure of this type of epoxy enone. One path in Scheme III (α-cleavage) is thus far unique to cyclohexadienone epoxides. Of the five alternatives open to the diradical M which results from C(4)–O bond cleavage (Scheme IV), three (rearrangement, cyclization, radical

fragmentation) are known with cyclohexadienone epoxides, the last of these being so far unique to this class of epoxy enones. Schemes III and IV provide a framework for studying structural effects on the photochemistry of epoxy enones; most of the various possible reaction paths have probably now been delineated, and further progress may rest on more quantitative studies.

Experimental Section

General Procedures. Analytical gas chromatography (VPC) was carried out on a Varian Aerograph Model 1400 (flame-ionization detector) and preparative VPC was performed with a Varian Aerograph Auto Model 700 instrument (thermal-conductivity detector).

NMR spectra were measured in $CDCl_3$ or CCl_4 solutions on a Varian Associates T-60 or HA-100 spectrometer using Me_4Si as an internal standard. Low-temperature NMR spectra were obtained on an A56-60 spectrometer. Spectra are reported in δ units. Numbers adjacent to protons in structures refer to chemical shifts of these protons. Numbers in brackets beside the chemical shifts are "europium-shift numbers" obtained by adding small increments of $Eu(fod)_3$. Shift numbers are the ratios obtained by dividing the shift of each signal in the spectrum by the shift of the least-shifted signal.

IR spectra were recorded on a Unicam SP-200 spectrometer except for the low-temperature study, in which a Perkin-Elmer 237 grating spectrophotometer was used. They were calibrated against a polystyrene film. UV spectra were recorded on a Unicam-800 spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6 operated at 70 eV; we are indebted to Mrs. Ralph Guile for this service. Melting points were determined with a Thomas-Hoover melting-point apparatus and are uncorrected. Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich., and by Clark Microanalytical Laboratories, Urbana, Ill.

Analytical chromatographic columns used in this work are as follows: column A: 5 ft × 0.125 in., 20% SE-30 on chromosorb W, AW-DMCS 80/100; column B: same, 10% Carbowax 20 M; column C: same, 10% FFAP; column D: same, 5% SE-30; column E: same, 20% FFAP. Preparative chromatographic columns used in this work are as follows: column F: 10 ft × 0.25 in., 20% SE-30 on chromosorb W, AW-DMCS 80/100; column G: 6 ft × 0.25 in., 10% FFAP on chromosorb W, AW-DMCS 80/100; column H: same as G, but 5 ft × 0.25 in.; column I: same as F but 20% FFAP; column J: same as I, but 5 ft × 0.25 in.

General Photolysis Procedures. Solutions of compounds to be irradiated were placed in septum-capped Pyrex tubes or NMR tubes and purged of oxygen by bubbling dry, oxygen-free nitrogen through them for 30 min prior to photolysis. Irradiations were carried out with a 450-W Hanovia Type L medium-pressure mercury vapor lamp with the appropriate filter. The tubes were fastened to an immersion well which was immersed in water at ambient temperature. Alternatively, a Rayonet photochemical chamber reactor or Type RS preparative photochemical reactor was used. Photolyses were monitored by withdrawing small (<1 μL) aliquots and injecting them into the analytical gas chromatograph.

6,6-Dimethyl-2,4-cyclohexadienone 4,5-Epoxide (5). To a solution of 2.5 g (0.02 mol) of 6,6-dimethyl-2,4-cyclohexadienone 4[3] in 20 mL of methylene chloride was added at 0 °C a solution of 3.54 g (0.02 mol) of *m*-chloroperbenzoic acid in 20 mL of methylene chloride. The mixture was stirred at room temperature for 8 h, precipitated *m*-chlorobenzoic acid was removed by filtration, and the solvent was removed by rotary evaporation. Petroleum ether (bp 30–60 °C) was added, the filtrate was washed with aqueous sodium bicarbonate and saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to give 2.37 g of a light yellow oil (86%). The crude product was chromatographed on Florisil (60–200 mesh) using ether–hexane (1:10) as eluent, to give **5**. Analytical VPC (column A, 130 °C, 30 mL of N_2/min) gave a retention time of 3 min; preparative VPC (column F, 100 °C, 60 mL of He/min, retention time 22 min) gave pure **5**: IR (neat) 3000 (s), 1680 (s), 1480 (m), 1385 (m), 1380 (w), 1295 (m), 1250 (m), 1225 (w), 1180 (m), 1118 (s), 1065 (m), 940 (m), 860 (m), 830 (s) cm^{-1}; UV (MeOH) λ_{max} 235 nm (ϵ 35 370) 280 (4080); NMR (CCl_4) see footnote 30; mass spectrum *m/e* (rel intensity) 138 (7), 123 (10), 122 (29), 109 (45), 95 (44), 82 (100), 79 (60), 77 (30), 70 (20), 67 (20), 55 (40), 54 (25).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.54; H, 7.26.

Irradiation of 5. A degassed solution of VPC collected 5 (100 mg, 0.73 mmol) in 50 mL of anhydrous ether was irradiated through Pyrex with a 450-W Hanovia lamp at room temperature. The photolysis, followed by VPC and NMR, was complete in 7 h. Analytical VPC (column B, 109 °C, 30 mL of N_2/min) showed two components, **6** (86%, retention time 17 min) and **7** (14%, 24 min). Preparative VPC (column G, 105 °C, 60 mL of He/min) gave pure **6** and **7**.

For **6** (3,3-dimethyl-2(3*H*)oxepinone): IR (neat) 1740 cm^{-1} ($\nu_{C=O}$), 1640 and 1603 cm^{-1} ($\nu_{C=C}$); UV (EtOH) λ_{max} 243 nm (ϵ 6460); NMR (CCl_4, 60 MHz) δ 1.30 (s, 6 H) and multiplets (4 H) between δ 5.47 and 6.39. The NMR spectrum (CCl_4, 100 MHz) showed four sets of vinyl protons at δ 5.47, 5.63, 6.02 and 6.39 ($J_{1,2}$ = 6.7 Hz, $J_{2,3}$ = 6.2 Hz, $J_{3,4}$ = 10.2 Hz); mass spectrum *m/e* (rel intensity) 138 (12) 109 (2), 95 (100), 81 (5), 79 (6), 77 (4), 68 (2), 67 (19), 66 (1), 65 (5), 55 (3), 52 (1), 50 (2), 43 (2), 42 (2), 40 (45), 39 (30), 38 (3). All spectral data were identical to the literature reports.[4]

For **7** (6,6-dimethyl-2-cyclohexene-1,5-dione): IR (neat) 2990 (m), 1720 (s), 1675 (s), 1640 (w), 1530 (m), 1385 (m), 1340 (w), 1300 (m), 1170 (2), 830 (m) cm^{-1}; UV (MeOH) λ_{max} 228 nm (ϵ 7000); NMR (CCl_4) δ 1.23 (s, 6 H, *gem*-dimethyl), 3.17 (br, 2 H, methylene), 5.80–6.20 [d, 1 H, J = 9 Hz, C(2) vinyl], and 6.57–7.03 [m, 1 H, C(3) vinyl]; mass spectrum *m/e* (rel intensity) 138 (42), 123 (1), 110 (12), 95 (22), 77 (4), 70 (100), 68 (55).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.60; H, 7.39.

Identical results were obtained as when carbon tetrachloride, benzene, methanol, *tert*-butyl alcohol, or acetone was used as the solvent for irradiation of **5** through Pyrex. Irradiation of **5** through a uranyl glass filter gave an almost quantitative yield of **6**; no **7** was isolated.

Irradiation of 6. A degassed solution containing 60 mg of **6** in 15 mL of anhydrous ether was irradiated through Corex with a 450-W Hanovia lamp. The photolysis was followed by analytical VPC (column B, 100 °C, 30 mL of N_2/min). As the reaction proceeded, the peak with a retention time of 12 min (corresponding to **6**) decreased in intensity and a peak with a retention time of 15 min due to **8** appeared. After a 20-h irradiation, preparative VPC (column G, 105 °C, 60 mL of He/min) allowed collection of the single photoproduct, 4,4-dimethyl-2-oxabicyclo[3.2.0]hept-6-en-3-one (**8**)[5]: IR (neat) 2980 (m), 2940 (2), 1770 (s), 1540 (m), 1390 (w), 1360 (m), 1350 (w), 1300 (w), 1270 (m), 1170 (m), 1140 (s), 1095 (s), 1015 (s), 970 (m), 930 (w), 910 (w), 860 (m), 800 (s) cm^{-1}; UV (MeOH) λ_{max} 220 nm (ϵ 235); NMR (CCl_4) δ 1.16 (s, 6 H; europium shift reagent showed that the two methyl groups are not identical), 3.13 [m, 1 H, C(5) methine], 4.98 [m, 1 H, C(1) methine], 6.30 (m, 2 H, vinyl protons); mass spectrum *m/e* (rel intensity) 138 (1.5), 123 (2), 110 (15), 109 (36), 95 (100), 93 (10), 91 (11), 83 (12), 81 (33), 79 (66), 77 (35), 67 (28), 53 (22), 51 (11).

Irradiation of 7. A degassed solution containing 40 mg of **7** in 10 mL of anhydrous ether was irradiated through Corex with a 450-W Hanovia lamp. The photolysis was followed by analytical VPC (column B, 100 °C, 30 mL of N_2/min). As the reaction proceeded, the peak with a retention time of 29 min corresponding to **7** decreased in intensity and the peak due to the product **9** appeared at 39 min. After complete reaction (2 h), preparative VPC (column H, 125 °C, 60 mL of He/min) allowed collection of the single photoproduct **9**[6] in 95% yield: IR (neat) 3001 (w), 1750 (w), 1710 (s), 1480 (m), 1400 (w), 1307 (w), 1290 (m), 1241 (w), 1190 (m), 1160 (w), 1010 (m), 900 (m) cm^{-1}; UV (ethanol) λ_{max} 215 nm (ϵ 550), 280 (190); NMR (CCl_4) see footnote 31; mass spectrum *m/e* (rel intensity) 138 (47), 123 (9), 110 (21), 109 (16), 97 (17), 95 (70), 93 (6), 91 (7), 83 (6), 82 (10), 81 (15), 79 (24), 77 (8), 70 (100), 69 (19), 68 (69), 67 (55).

Irradiation of 9. A degassed solution containing 35 mg of compound **9** in 10 mL of anhydrous ether was irradiated through Corex, or 30 mg of compound **9** in 10 mL benzene was irradiated through Pyrex with a 450-W Hanovia lamp. The photolysis was followed by NMR (benzene-d_6) and analytical VPC (column B, 153 °C, 30 mL of N_2/min). The reaction was complete within 30–45 min in Corex and within 2 h with the Pyrex filter. As the reaction proceeded, the peak with a retention time of 18 min corresponding to **9** decreased in intensity and the peak due to the product **10** appeared with a retention time 23 min. Preparative VPC (column G, 105 °C, 60 mL of He/min) allowed collection of the single photoproduct **10**[6] in 90% yield: IR (neat) 3100 (m), 1795 (s), 1720 (s), 1680 (w), 1480 (w), 1380 (w), 1238 (w), 1210 (m), 1150 (m), 1100 (m) cm^{-1}; UV (methanol) showed end absorption; NMR (CCl_4) see footnote 32; mass spectrum *m/e* (rel intensity) 138 (50), 123 (18), 110 (15), 109 (20), 96 (18), 95 (80), 79 (35), 77 (25), 70 (100), 68 (80), 67 (62).

Irradiation of 5 with 254-nm Light. Irradiation of an 0.01 M ether solution of **5** at 254 nm (Rayonet MGR-100) or with a Hanovia 450-W lamp and Corex filter gave **6** and **7** in a ratio 7:1 after 2 h. Further irradiation for 7 h followed by VPC (column C, 125 °C, 30 mL of N_2/

min) gave the following products (%, retention time in min): **6** (38, 6), **7** (46, 9.5), **9** (12, 17), and **10** (4, 30).

Irradiation of 5 at Low Temperatures. A degassed solution of **5** (25 mg) in 0.5 mL of acetone-d_6 was irradiated in a Pyrex NMR tube with a 450-W Hanovia lamp at −78 °C. The photolysis was followed by NMR and by VPC. After a 4-h irradiation, besides the strong product signals of **6** and **7**, an aldehyde proton peak at δ 9.7 was observed. When the solution stood at the same temperature for 3 h, the intensity of the aldehyde proton signal gradually decreased. Following a similar separate irradiation, the solution was warmed slowly (8 h) to room temperature, and the signal due to the aldehyde disappeared. Replacement of the acetone by methanol-d_4 gave identical results.

A solution of 20 mg of **5** in 0.1 mL of tetrahydrofuran was placed in a sodium chloride cavity cell (0.2-mm path length) held in a lead block and cooled to −105 °C. A beam from a 1000-W Hanovia mercury lamp was filtered through Pyrex and diverted into the cavity cell. Examination of the IR spectrum after irradiation for 10 min indicated a decrease in the intensity of the carbonyl absorption at 1680 cm^{-1} due to **5** and the appearance of a sharp intense absorption at 1740 and 1720 cm^{-1}, attributed to photoproducts. A weak peak also appeared at 1815 cm^{-1}. When the solution was warmed to room temperature, the band at 1815 cm^{-1} gradually disappeared.

Sensitization and Quenching Studies with 5. Analytical grade benzene was purified by stirring with concentrated sulfuric acid for several days, washing (10% sodium hydroxide, water, sodium chloride), drying (calcium hydride), and distilling (from potassium, middle cut). Methanol and acetophenone was purified by distillation, and benzophenone and hexamethylbenzene were purified by recrystallization from ethanol. *trans*-1,3,5-Hexatriene and piperylene were used as purchased from Aldrich Chemical Co.

In benzene: 110 mg of **5** and 64 mg of hexamethylbenzene (to serve as a VPC reference) were dissolved in 40 mL of benzene to give an 0.02 M standard solution of **5**. For sensitization, a 3 M solution of acetophenone was prepared by dissolving 3.6 g of acetophenone in 10 mL of the standard solution. For quenching, a 2.6 M solution of *trans*-1,3,5-hexatriene was prepared by dissolving 1 g of the triene in 5 mL of the standard solution.

Aliquots (2.8 mL) of each solution were sealed in Pyrex tubes after five freeze-thaw cycles (<0.005 Torr). Samples were irradiated in a merry-go-round apparatus with a 450-W Hanovia lamp and Pyrex filter. After varying times (to 7 h), samples were removed and analyzed by VPC (column B, 155 °C, 30 mL of N_2/min). At 7 h, the blank showed a single peak at 8.5 min due to **6**; the acetophenone solution gave the same result, but the triene solution showed only 10% **6** and 90% **5** (10.5).

In methanol: the standard solution of **5** was prepared as in benzene (vide supra). The sensitization solution was 2 M in benzophenone (3.5 g in 10 mL of standard solution). The quenching solution was 5 M in piperylene (3.4 g in 10 mL of standard solution). Irradiation as described for the benzene solutions and VPC analysis (column D, 131 °C) showed after 7 h only one peak due to **6** (2 min) in all three solutions.

3,4,6,6-Tetramethyl-2,4-cyclohexadienone-4,5-epoxide (11). To a solution containing 5.0 g (0.033 mol) of 3,4,6,6-tetramethyl-2,4-cyclohexadienone[33] in 25 mL of methylene chloride was added at 0 °C a solution of *m*-chloroperbenzoic acid (5.9 g, 0.034 mol) in 50 mL of the same solvent. The reaction, which was followed by NMR, was complete in about 1 h, during which time *m*-chlorobenzoic acid precipitated from solution. The precipitate was removed by filtration, the solvent was removed by rotary evaporation, and the residue, which consisted mainly of the desired epoxy ketone **11** contaminated with a trace of *m*-chlorobenzoic acid (NMR), was chromatographed on a short column of Florisil (80–100 mesh) using ethyl ether as eluent. The yield of **11**, which was identified by comparing its IR and NMR spectra[30] with those of an authentic sample,[34] was nearly quantitative.

2-Deuterio-3-trideuteriomethyl-4,6,6-trimethyl-2,4-cyclohexadienone 4,5-Epoxide (11*). To a solution of **11** (500 mg, 3.01 mmol) in dimethyl-d_6 sulfoxide (15 mL) was added with stirring and under N_2 370 mg (3.30 mmol) of potassium *tert*-butoxide. The mixture was stirred at room temperature for 3 h and then quenched with ice–water and extracted with ether. The combined organic layers were dried (Na_2SO_4) and the solution was evaporated to give a nearly quantitative yield of **11***. The NMR spectrum was identical to that of **11**,[30] except that the peaks at δ 2.08 (3 H) and 5.72 (1 H) were absent.

Irradiation of 11. A degassed solution containing 300 mg (1.81 mmol) of **11** in 30 mL of anhydrous ether was irradiated through Pyrex with a 450-W Hanovia lamp. The photolysis was followed by analytical VPC (column C, 140 °C, 30 mL of N_2/min). The reaction was complete in about 8 h. VPC showed that there were three products, **13** (44%, retention time 8.5 min), **14** (34%, 12.5 min), and **12** (22%, 16.5 min). The products were isolated by preparative VPC (column H, 150 °C). A similar irradiation in methanol gave the same result.

For **12** (4,5,7,7-tetramethyl-2-oxacyclohepta-3,5-dien-1-one): IR (CCl_4) 1745 (s), 1145 (w), 1085 (w) cm^{-1}; UV (MeOH) λ_{max} 240 nm (ϵ 3225); NMR (CCl_4) δ 1.25 (s, 6 H, *gem*-dimethyl), 1.80 (m, 6 H, separates to two doublets, J = 1 Hz, with Eu shift reagent), 5.13 [br, 1 H, C(6) vinyl], 6.13 [br, 1 H, C(3) vinyl]; mass spectrum *m/e* (rel intensity) 167 (5), 166 (40), 138 (78), 124 (35), 123 (100), 109 (22), 96 (10), 95 (37), 91 (15), 77 (22), 67 (57), 55 (35), 53 (28), 51 (13).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.25; H, 8.37.

For **13** (*endo*-6-methyl-1,3,3-trimethylbicyclo[3.1.0]hexane-2,4-dione): IR (CCl_4) 3000 (m), 1745 (w), 1710 (s), 1465 (w), 1385 (w), 1300 (w), 1140 (w) cm^{-1}; UV (MeOH) λ_{max} 215 nm (ϵ 2590); NMR (CCl_4) see footnote 31; mass spectrum *m/e* (rel intensity) 167 (9), 166 (77), 151 (29), 138 (14), 124 (15), 123 (55), 107 (20), 105 (10), 96 (100), 95 (27), 91 (17), 81 (19), 70 (23), 68 (64), 67 (65), 53 (38).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.28; H, 8.49.

For **14** (*exo*-6-methyl-1,2,3-trimethylbicyclo[3.1.0]hexane-2,4-dione): IR (CCl_4) 3000 (m), 1740 (m), 1705 (s), 1465 (w), 1390 (w), 1280 (m), 1130 (w), 1095 (m) cm^{-1}; UV (MeOH) λ_{max} 225 nm (ϵ 1240); NMR (CCl_4) see footnote 31; mass spectrum (70 eV) *m/e* (rel intensity) 167 (9), 166 (58), 151 (19), 149 (16), 138 (18), 124 (20), 123 (59), 107 (28), 105 (15), 97 (10), 96 (100), 95 (35), 91 (20), 81 (20), 78 (17), 76 (11), 70 (20), 68 (78), 67 (83), 55 (21), 53 (58), 51 (15).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.32; H, 8.55.

Irradiation of 11*. The conditions and workup procedure were as described for **11** (ether). The NMR spectrum of the resulting **13*** was identical with that of **13**,[31] except that the signals at δ 1.40 and 2.22 were absent. The NMR spectrum of the resulting **14*** was identical with that of **14**,[31] except that the signals at δ 1.33 and 1.70 were absent. The NMR spectrum of the resulting **12*** was identical with that of **12**, except that the signal at δ 5.13 was absent and the area of the peak at δ 1.80 was reduced to 3 H and simplified to a doublet.

Irradiation of 12. A degassed solution containing 100 mg (0.60 mmol) of **12** in 10 mL of anhydrous ether was irradiated through Corex with a 450-W Hanovia lamp. The photolysis was followed by analytical VPC (column C, 135 °C, 30 mL of N_2/min). As the reaction proceeded, the peak with a retention time of 12.5 min (corresponding to **12**) decreased in area and a product peak appeared at 6 min. After 2 h, the reaction was complete and the product, 2,2,6,7-tetramethyl-4-oxabicyclo[3.2.0]hept-6-en-3-one (**18**), was collected by preparative VPC (column H, 180 °C): IR (CCl_4) 2960 (m), 2920 (w), 1780 (s), 1385 (w), 1330 (w), 1250 (w), 1160 (m), 1100 (s), 1060 (m), 1050 (m), 875 (s) cm^{-1}; UV (MeOH) λ_{max} 210 nm (ϵ 830); NMR (CCl_4) δ 1.10 [s, 3 H, C(2) methyl], 1.17 [s, 3 H, C(2) methyl], 1.68 [s, 6 H, C(6) and C(7) methyls, separate with Eu shift reagent], 2.82 [m, 1 H, C(1) methine], 4.67 [d, 1 H, J = 4 Hz, C(5) methine]; mass spectrum *m/e* (rel intensity) 166 (4), 148 (40), 123 (100), 109 (18), 107 (32), 91 (28), 79 (22), 77 (13), 67 (22), 55 (19), 53 (16). Since the mass spectrum showed that **18** was an isomer of **12**, it was not subjected to elemental analysis.

Irradiation of 12*. The conditions and workup procedure were as described for **12**. The resulting **18*** had an NMR spectrum identical with that of **18**, except that the signal at δ 2.82 was absent and the peak at δ 1.68 was reduced in area to 3 H.

Irradiation of 2,3,6,6-tetramethyl-2-cyclohexene-1,5-dione (15a). A degassed solution containing 200 mg of **15a**[8] in 15 mL of anhydrous ether was irradiated through Pyrex with a 450-W Hanovia lamp. The photolysis was followed by analytical VPC (column C, 160 °C, 30 mL of N_2/min). As the reaction proceeded, the peak with a retention time of 7.0 min (corresponding to **15a**) decreased in area and a product peak appeared at 2.0 min. After 3 h, the reaction was complete and the product, 1,3,3,5-tetramethylbicyclo[3.1.0]hexane-2,4-dione (**13a**), was collected by preparative VPC (column H, 170 °C): IR (CCl_4) 3000 (m), 1750 (m), 1710 (s), 1470 (w), 1390 (w), 1290 (m), 1070 (m) cm^{-1}; UV (MeOH) λ_{max} 225 nm (ϵ 1190); NMR (CCl_4) see footnote 31; mass spectrum *m/e* (rel intensity) 167 (4), 166 (38), 151 (10), 124 (20), 123 (53), 97 (7), 96 (100), 95 (14), 68 (38), 67 (35), 53 (15).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.23, H, 8.57.

Irradiation of **15a** labeled with a CD_3 group at C(3) under the same conditions gave labeled **13a** whose NMR spectrum had the peak at δ 1.33 reduced in area to 3 H.

Irradiation of 13a. A degassed solution containing 100 mg (0.60 mmol) of **13a** in 10 mL of anhydrous ether was irradiated through

Corex with a 450-W Hanovia lamp. The photolysis was followed by analytical VPC (column C, 160 °C, 30 mL of N_2/min). As the reaction proceeded, the peak with a retention time of 7.0 min (corresponding to **13a**) decreased in area and a product peak appeared at 16 min. After 1 h, the reaction was complete and the product, 1,5-dimethyl-4-isopropylidene-3-oxabicyclo[3.1.0]hexan-2-one (**10a**), was collected by preparative VPC (column H, 170 °C): IR (CCl_4) 3000 (m), 1780 (s), 1700 (m), 1350 (w), 1300 (w), 1150 (w), 1135 (w), 1070 (m), 1030 (m) cm^{-1}; UV (MeOH) λ_{max} 235 nm (ϵ 3780); NMR (CCl_4) see footnote 32; mass spectrum *m/e* (rel intensity) 167 (4), 166 (34), 151 (10), 124 (21), 123 (58), 97 (7), 96 (100), 95 (16), 69 (10), 68 (35), 67 (33), 53 (15).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.04; H, 8.34.

Irradiation of **13a** labeled at C(1) [C(5)] with a CD_3 group under the same conditions gave labeled **10a** whose NMR spectrum differed from that of **10a** in that the areas of the peaks at δ 1.28 and 1.45 were each reduced by 50%.

Irradiation of 13. A degassed solution containing 100 mg (0.60 mmol) of **13** in 10 mL of anhydrous ether was irradiated through Corex with a 450-W Hanovia lamp. The photolysis was followed by analytical VPC (column C, 140 °C, 30 mL of N_2/min). As the reaction proceeded, the peak with a retention time of 8.5 min (corresponding to **13**) decreased in area and a product peak appeared at 10.5 min. After 1.5 h, the reaction was complete and the product, *endo*-6-methyl-1-methyl-4-isopropylidene-3-oxabicyclo[3.1.0]hexan-2-one (**16**), was collected by preparative VPC (column H, 170 °C): IR (CCl_4) 3000 (m), 1780 (s), 1710 (m), 1450 (w), 1305 (w), 1140 (w), 1100 (m), 1050 (m), 970 (w), 870 (m) cm^{-1}; UV (MeOH) λ_{max} 230 nm (ϵ 3320); NMR (CCl_4) see footnote 32; mass spectrum *m/e* (rel intensity) 167 (5), 166 (46), 151 (29), 148 (31), 138 (19), 124 (22), 123 (76), 107 (20), 105 (15), 96 (100), 95 (29), 91 (21), 68 (41), 66 (50), 55 (22), 53 (21). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.27; H, 8.46.

Irradiation of 13*. The conditions and workup procedure were as described for **13**. The NMR spectrum of the resulting **16*** was identical with that of **16**,[32] except that the signals at δ 1.37 and 2.38 were absent.

Irradiation of 14. A degassed solution containing 100 mg (0.60 mmol) of **14** in 10 mL of anhydrous ether was irradiated through Corex with a 450-W Hanovia lamp. The photolysis was followed by analytical VPC (column C, 140 °C, 30 mL of N_2/min). As the reaction proceeded, the peak with a retention time of 12.5 min (corresponding to **14**) decreased in area, and two product peaks appeared with retention times of 17.0 and 28.5 min in the ratio of 3:1. After 1.5 h the reaction was complete. Preparative VPC (column H, 170 °C) gave a major component, *exo*-6-methyl-1-methyl-4-isopropylidene-3-oxabicyclo-[3.1.0]hexan-2-one (**17**): IR (CCl_4) 3000 (m), 1780 (s), 1715 (m), 1450 (w), 1290 (w), 1140 (w), 1060 (m) cm^{-1}; UV (MeOH) λ_{max} 235 nm (ϵ 2400); NMR (CCl_4) see footnote 32; mass spectrum *m/e* (rel intensity) 167 (5), 166 (39), 151 (20), 138 (14), 124 (22), 123 (68), 107 (25), 96 (100), 95 (30), 91 (26), 79 (20), 68 (52), 67 (71), 55 (31), 53 (55).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.24; H, 8.57.

The minor component was *exo*-6-methyl-5-methyl-4-isopropylidene-3-oxabicyclo[3.1.0]hexan-2-one (**17a**): IR (CCl_4) 2980 (w), 2940 (w), 1785 (s), 1700 (m), 1460 (w), 1280 (m), 1250 (w), 1180 (m), 1140 (w), 1080 (w), 975 (w), 890 (w) cm^{-1}; UV (MeOH) λ_{max} 235 nm (ϵ 6150); NMR (CCl_4) see footnote 32; mass spectrum *m/e* (rel intensity) 167 (12), 166 (100), 151 (40), 138 (13), 124 (15), 123 (49), 107 (27), 97 (14), 96 (52), 95 (27), 91 (27), 81 (16), 79 (19), 70 (30), 69 (20), 68 (48), 67 (45), 55 (16), 53 (27), 51 (8). Since the mass spectra showed that **17** and **17a** were isomers, **17a** was not subjected to elemental analysis.

Irradiation of 14*. The conditions and workup procedure were as for **14**. The resulting **17*** had an NMR spectrum identical with that of **17**,[32] except that the peaks at δ 1.33 and 1.93 were absent. Insufficient **17a*** was isolated for an NMR spectrum.

2,3,4,6,6-Pentamethyl-2,4-cyclohexadienone 4,5-Epoxide (19). To a solution of 1.20 g (7.32 mmol) of 2,3,4,6,6-pentamethyl-2,4-cyclohexadienone[35] in 20 mL of methylene chloride was added, at 0 °C, a solution of 1.42 g (8.61 mmol) of *m*-chloroperbenzoic acid in 20 mL of methylene chloride. The mixture was stirred at room temperature for 3 h (NMR monitoring showed complete reaction at this time). *m*-Chlorobenzoic acid was removed by filtration, and the solvent was removed by rotary evaporation. Petroleum ether (bp 30–60 °C) was added, the filtrate was washed with aqueous sodium bicarbonate and saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to give 1.20 g (91%) of **19** as a light oil. The crude produce was chromatographed on Florisil (60–200 mesh) using ether–hexane (1:5) as eluent, to give pure epoxide **19**: IR (neat) 3000 (s), 1674 (s), 1616 (m), 1480 (m), 1390 (m), 1320 (m), 1260 (m), 1090 (m), 1050 (m), 918 (m); UV (MeOH) λ_{max} 210 nm (ϵ 2970), 255 (8460), 325 (270); NMR (CCl_4) see footnote 30; mass spectrum *m/e* (rel intensity) 180 (50), 165 (35), 164 (15), 151 (26), 137 (100), 135 (52), 123 (34), 121 (31), 119 (25), 112 (35), 110 (55), 95 (20), 91 (20), 83 (15), 81 (30), 69 (24), 67 (50), 55 (26), 53 (30).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.24; H, 8.92.

3-Trideuteriomethyl-2,4,6,6-tetramethyl-2,4-cyclohexadienone 4,5-Epoxide (19*). To a solution containing 500 mg (2.77 mmol) of **19** in 10 mL of dimethyl-d_6 sulfoxide was added with stirring and under N_2, 310 mg (2.77 mmol) of potassium *tert*-butoxide. The mixture was stirred at room temperature for 1 h and then quenched with ice-water and extracted with ether. Organic layers were dried ($MgSO_4$) and the solution was evaporated to give a nearly quantitative yield of **19***. The NMR spectrum was identical to that of the starting material, except that the signal at δ 1.95 had disappeared.

Irradiaion of 19. A degassed solution of 100 mg (0.55 mmol) of **19** in 30 mL of anhydrous ether was irradiated through Pyrex with a 450-W Hanovia lamp at room temperature for 2 h. The photolysis was followed by VPC. Analytical VPC (column C, 160 °C, 30 mL of N_2/min) showed three components: **20** (62%, retention time 2.5 min), **21** (11%, 5 min), and **22** (27%, 25 min). Preparative VPC (column I, 140 °C, 60 mL of He/min) gave pure **20** (retention time 18 min), **21** (31 min), and **22** (over 1 h). Further purification of **22** with VPC (5 ft × 0.25 in. column J, 180 °C, 60 mL of He/min) gave pure **22** (retention time 12 min).

For **20** (*endo*-1,3,3,5,6-pentamethylbicyclo[3.1.0]hexane-2,4-dione): IR (KBr) 3000 (m), 1700 (s), 1462 (m), 1380 (m), 1360 (w), 1300 (m), 1205 (m), 1110 (w), 1090 (w), 1040 (m), 845 (m) cm^{-1}; UV (MeOH) λ_{max} 215 nm (ϵ 2610); NMR (CCl_4) see footnote 31; decoupling at δ 1.06–1.27 caused the doublet at δ 1.04 to sharpen to a singlet; mass spectrum *m/e* (rel intensity) 180 (42), 165 (20), 163 (10), 137 (60), 120 (11), 110 (100), 109 (22), 105 (15), 95 (25), 82 (22), 79 (13), 67 (80).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.29; H, 8.97.

For **21** (*exo*-1,3,3,5,6-pentamethylbicyclo[3.1.0]hexane-2,4-dione): IR (neat) 3000 (m), 1742 (w), 1701 (s), 1470 (m), 1398 (m), 1295 (m), 1101 (w), 1080 (m), 1040 (w), 845 (w) cm^{-1}; UV (MeOH) λ_{max} 215 nm (ϵ 1870); NMR (CCl_4) see footnote 31; decoupling at δ 1.46 caused the methyl signal at δ 1.13 to sharpen to a singlet; mass spectrum *m/e* (rel intensity) 180 (53), 165 (20), 162 (9), 138 (20), 137 (60), 121 (13), 120 (25), 110 (100), 109 (27), 105 (10), 95 (25), 82 (25), 81 (15), 67 (88), 55 (7), 54 (7).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.11; H, 8.98.

For **22**: IR (neat) 2985 (m), 1741 (s), 1680 (m), 1448 (m), 1382 (m), 1325 (m), 1281 (m), 1180 (w), 1140 (w), 1100 (m), 1005 (m), 760 (m) cm^{-1}; UV (MeOH) λ_{max} 225 nm (ϵ 7150); NMR ($CDCl_3$) δ 1.23 [s, 3 H, C(4) methyl], 1.74 (br s, 3 H), 1.76 (s, 3 H), 1.79 [s, 3 H, C(3) methyl], 1.80 [s, 3 H, C(2) methyl], 5.40 (m, 1 H, vinyl); decoupling at δ 1.74–1.80 caused the vinyl proton at δ 5.40 to sharpen to a singlet; europium shift slopes, respectively, 3.00, 1.00, 1.30, 2.57, 5.80, 4.28; mass spectrum *m/e* (rel intensity) 180 (60), 165 (92), 137 (30), 135 (80), 125 (20), 119 (25), 112 (21), 110 (35), 105 (20), 97 (100), 91 (19), 69 (65), 68 (25), 55 (40), 54 (40), 53 (30).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.11; H, 9.02.

Irradiation of 3-Trideuteriomethyl-2,4,6,6-tetramethyl-2,4-cyclohexadienone 4,5-Epoxide (19*). The conditions and workup procedure were as described for the unlabeled material. From **19*** the resulting **20*** had an NMR spectrum identical with that of **20**, except that the signal at δ 1.32 (s, 6 H) was reduced to half its area (s, 3 H). The spectrum of the resulting **21*** was identical with that of **21**, except that the signal at δ 1.20 (s, 6 H) was reduced to half its area (s, 3 H). The spectrum of the resulting **22*** was identical with that of **22**, except that the signal at δ 1.79 was absent.

Irradiation of 23. A degassed solution of **23** (50 mg, 0.27 mmol) in 25 mL of anhydrous ether was irradiation through Pyrex with a 450-W Hanovia lamp. The photolysis, followed by VPC and NMR, was complete in about 1 h. Analytical VPC (column C, 160 °C, 30 mL of N_2/min) showed two components: **20** (85%, retention time 2.5 min) and **21** (15%, 5 min). Preparative VPC (column I, 140 °C, 60 mL of He/min) gave pure **20** and **21** in the same ratio.

Irradiation of **23** labeled at C(3) with a CD_3 group gave, under the same conditions, **21*** and **22*** in the same ratio as obtained from **19***.

2,4,5,6,6-Pentamethyl-2,4-cyclohexadienone 4,5-Epoxide (24). To a solution of 2.10 g (12.8 mmol) of 2,4,5,6,6-pentamethyl-2,4-cyclohexadienone[35] in 40 mL of methylene chloride was added, at 0

°C, a solution of 2.20 g (12.8 mmol) of *m*-chloroperbenzoic acid in 60 mL of methylene chloride. The mixture was stirred at room temperature for 2 h (NMR monitoring showed complete reaction). During this time a white precipitate formed; it was removed by filtration. The solvent was removed by rotary evaporation, petroleum ether (bp 30–60 °C) was added, the filtrate was washed three times with 15% aqueous sodium sulfite, water, and saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to give 2.24 g (97.4%) of a light yellow oil. The crude product was chromatographed on Florisil (60–200 mesh) using ether–hexane (1:10) as eluent, to give colorless epoxide **24**. When epoxide **24** was subjected to preparative VPC (column F, 180 °C, 60 mL of He/min, retention time 18 min), only 60% was recovered and 40% was converted to an isomeric alcohol due to thermal oxirane ring opening. For **24**: IR (neat) 3000 (s), 1680 (s), 1550 (w), 1480 (s), 1400 (s), 1380 (m), 1278 (m), 1200 (w), 1130 (m), 1100 (s), 1080 (m), 1060 (m), 1003 (m), 978 (m), 900 (s), 848 (m), 780 (w), 740 (m) cm^{-1}; UV (methanol) λ_{max} 208 nm (ϵ 3200), 250 (9560), 320 (500); NMR (CCl_4) see footnote 30; mass spectrum *m/e* (rel intensity) 180 (9), 165 (18), 137 (100), 112 (40), 110 (20), 109 (18), 97 (10), 69 (35), 67 (36).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.33; H, 9.02.

5-Trideuteriomethyl-2,4,6,6-tetramethyl-2,4-cyclohexadienone 4,5-Epoxide (24*). 2,4,5,6,6-Pentamethylcyclohexa-2,4-dienone[29] (1 g) was added to a solution of 0.30 g of potassium *tert*-butoxide in dimethyl-d_6 sulfoxide. The solution became deep red immediately and remained so. The mixture was stirred at room temperature for 5 h (NMR monitoring showed complete reaction). The red-brown solution was poured into 300 mL of methylene chloride and washed with ice–water (three 50-mL portions). After being dried, the solution was evaporated to an oil, which was distilled, and then further purified by VPC (column J, 148 °C, 60 mL of He/min, retention time 2 min). The NMR spectrum, which was consistent with deuteration at the C(5) methyl group, consisted of three signals at δ 1.12, 1.81, and 6.60 with relative 6:6:1, assigned respectively to the *gem*-dimethyls, the allylic methyls at C(2), C(4), and C(3) vinyl proton.

To a solution containing 120 mg (0.73 mmol) of the labeled cyclohexadienone in 2 mL of methylene chloride was added a solution of 148 mg (0.86 mmol) of *m*-chloroperbenzoic acid in 2 mL of methylene chloride. The mixture was stirred at room temperature for 2 h, and workup was as described for the preparation of **24**. The product **24*** had an NMR spectrum identical with that of **24**,[30] except that the signal at δ 1.40 was absent.

Irradiation at 24. A degassed solution of 100 mg (0.55 mmol) of **24** in 50 mL of anhydrous ether was irradiated through Pyrex with a 450-W Hanovia lamp. The photolysis was followed by VPC, and was complete in about 1 h. Analytical VPC (column E, 178 °C, 30 mL of N_2/min) showed three components: **27** (retention time 1 min), **26** (7 min), and **25** (9 min). Preparative VPC (column F, 120 °C, 60 mL of He/min) gave pure **27** (25%; retention time 8 min), **26** (45%; 25 min), and **25** (30%; 40 min).

For **25** [3,3,4,6,7-pentamethyl-2(3*H*)-oxepinone]: IR (neat) 3000 (s), 1750 (s), 1660 (m), 1460 (m), 1400 (m), 1340 (w), 1280 (w), 1260 (w), 1200 (m), 1150 (m), 1120 (w), 1100 (w), 1040 (w), 950 (w), 880 (w) cm^{-1}; UV (MeOH) λ_{max} 212 nm (ϵ 2700), 250 (10 570); NMR (100 MHz, CCl_4) δ 1.23 (s, 6 H, *gem*-dimethyl), 1.67 [br s, 3 H C(6) methyl], 1.83 [d, 3 H, J = 2 Hz, C(4) methyl], 1.89 (br s, 3 H, C(7) methyl], 5.60 (m, 1 H, vinyl); decoupling at δ 5.60 caused the doublet at δ 1.83 to become a singlet; europium shift slopes, respectively, are 3.76, 1.05, 2.03, 1.00, 1.92; mass spectrum *m/e* (rel intensity) 180 (61), 165 (7), 138 (30), 137 (98), 109 (100), 108 (71), 93 (75), 91 (32), 97 (34), 67 (50), 65 (20), 55 (15), 53 (20).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.21; H, 9.09.

For **26** (4-acetyl-2,4,5,5-tetramethyl-2-cyclopentenone): IR (CCl_4) 3000 (s), 1710 (s), 1660 (w), 1480 (w), 1460 (w), 1400 (w), 1373 (m), 1305 (w), 1300 (w), 1192 (w), 1160 (m), 1050 (m), 990 (m), 890 (m) cm^{-1}; UV (cyclohexane) λ_{max} 265 (ϵ 7000); NMR (CCl_4), δ 0.90 [s, 3 H, C(5) methyl], 1.03 [s, 3 H, C(5) methyl], 1.25 [s, 3 H, C(4) methyl], 1.75 [d, 3 H, J = 1.0 Hz, C(2) methyl], 1.95 (s, 3 H, acetyl methyl), 6.92 (q, 1 H, J = 1 Hz, vinyl); europium shift slopes, respectively, are 4.80, 3.40, 1.00, 3.00, 2.50, 2.80; mass spectrum *m/e* (rel intensity) 180 (6), 162 (5), 144 (5), 139 (26), 138 (100), 137 (35), 123 (62), 109 (43), 93 (7), 91 (7), 81 (8), 71 (10), 77 (9), 69 (8), 67 (60), 55 (15).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.14; H, 8.91.

For **27** (1,3,3,4,5-pentamethyl-7-oxabicyclo[2.2.1]hept-5-en-2-one): IR (neat) 3000 (s), 1740 (s), 1640 (w), 1470 (m), 1450 (m), 1392 (m), 1300 (w), 1220 (m), 1200 (m), 1180 (m), 1100 (s), 1020 (w), 1000 (s), 900 (w), 860 (w), 810 (s) cm^{-1}; UV (MeOH) λ_{max} 207 nm (ϵ 950) with a shoulder at 280 (ϵ 100); NMR (CCl_4) δ 1.12 [s, 3 H, C(3) methyl], 1.14 [s, 3 H, C(3) methyl], 1.30 [s, 3 H, C(4) methyl], 1.32 [s, 3 H, C(1) methyl], 1.72 [d, 3 H, J = 2 Hz, C(5) methyl], 5.56 (q, 1 H, J = 2 Hz, vinyl]; europium shift slopes are, respectively, 3.50, 3.37, 2.77, 2.98, 1.00, 1.93; mass spectrum *m/e* (rel intensity) 180 (14), 165 (5), 152 (5), 140 (100), 139 (42), 138 (35), 137 (75), 124 (20), 122 (76), 121 (83), 111 (11), 110 (84), 108 (15), 95 (40), 94 (62), 92 (15), 82 (64), 77 (77), 69 (12), 67 (25), 59 (60), 55 (20), 54 (68), 53 (31), 52 (10), 51 (15).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.34; H, 8.96.

Irradiation of 24*. The conditions and workup procedure were as for the unlabeled material. From **24*** the resulting **27*** had an NMR spectrum identical with that of **27**, except the signal at δ 1.30 was absent. The spectrum of the resulting **26*** was identical with that of **26**, except that the singlet at δ 1.95 was absent. The resulting **25*** was identical with that of **25**, except that the signal at δ 1.89 was absent and the peak at δ 1.67 sharpened to a singlet.

Irradiation of 26. A degassed solution of 50 mg (0.28 mmol) of **26** in 25 mL of anhydrous ether was irradiated through Pyrex with a 450-W Hanovia lamp at room temperature. The photolysis was followed by VPC and was complete in about 40 min. Analytical VPC (column C, 150 °C, 30 mL of N_2/min) showed two components with retention times of 3.5 and 19 min, respectively, in a ratio of 1:6. Preparative VPC (column I, 120 °C, 60 mL of He/min) allowed collection of the major product **28** with a retention time of 52.5 min. For **28**: IR (neat) 3000 (m), 1760 (s), 1662 (m), 1460 (m), 1396 (m), 1360 (w), 1330 (m), 1200 (w), 1120 (m), 1080 (m), 1040 (w), 940 (w) cm^{-1}; UV (MeOH) λ_{max} 222 (ϵ 7640), 263 (6250); NMR (CCl_4) δ 1.35 [d, 3 H, J = 6 Hz, C(4) methyl], 1.66 (s, 3 H, vinyl methyl), 1.68 [s, 3 H, C(2) methyl], 1.86 (homoallylic coupling, 6 H, terminal vinyl methyls), 4.85 [q, 1 H, J = 6 Hz, C(4) proton]; europium shift slopes are respectively 2.30, 1.00, 5.47, (1.50, 1.62), 4.37; mass spectrum *m/e* (rel intensity) 180 (60), 165 (4), 137 (100), 138 (30), 123 (10), 110 (17), 109 (85), 108 (50), 93 (50), 91 (20), 77 (20), 67 (40), 55 (10), 53 (14).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.33; H, 8.86.

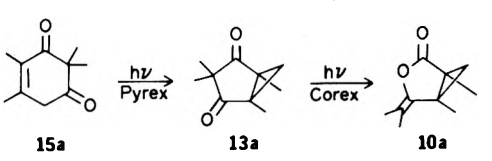
Irradiation of 27. A degassed solution of **27** (25 mg, 0.14 mmol) in 10 mL of anhydrous ether was irradiated through Pyrex with a 450-W Hanovia Type L lamp. The reaction was followed by NMR. After 1 h the NMR spectrum showed no change and **27** was recovered.

Acknowledgment. We are indebted to the National Institutes of Health (GM 15997) and the National Science Foundation (GP 43659X) for their support of this research.

Registry No.—**4**, 21428-63-7; **6**, 34786-27-1; **7**, 63449-15-0; **8**, 63449-16-1; **12**, 63449-17-2; **15a**, 63449-18-3; **18**, 63449-19-4; **22**, 63449-20-7; **23**, 63449-21-8; **25**, 63449-22-9; **25a**, 63449-23-0; **26**, 63449-24-1; **27**, 63449-25-2; **28**, 63449-26-3; 2,4,5,6,6-pentamethyl-2,4-cyclohexadienone, 16336-75-7; 3,4,66-tetramethyl-2,4-cyclohexadienone, 14069-95-5; 2,3,4,6,6-pentamethyl-2,4-cyclohexadienone, 16395-18-9.

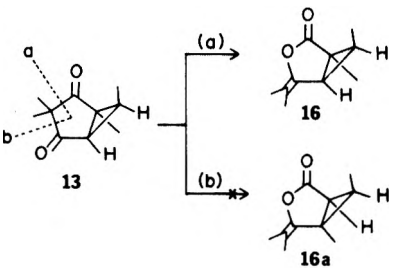
References and Notes

(1) H. Hart and E.-m. Shih, *J. Org. Chem.*, **41**, 3377 (1976).
(2) For a preliminary report, see H. Hart, C.-t. Peng and E.-m. Shih, *Tetrahedron Lett.*, in press (1977).
(3) K. Alder, F. H. Flock, and H. Lessenich, *Chem. Ber.*, **90**, 1709 (1957).
(4) (a) W. Skorianetz, K. H. Schulte-Elte and G. Ohloff, *Helv. Chim. Acta*, **54**, 1913 (1971); (b) N. Harada, S. Suzuki, H. Uda, and H. Ueno, *J. Am. Chem. Soc.*, **94**, 1777 (1972); (c) N. Harada, H. Uda, and H. Ueno, *Chem. Lett.*, 663 (1972); (d) N. Harada, S. Suzuki, H. Uda, and H. Ueno, *ibid.*, 803 (1972); (e) H. Uda, H. Ueno, and S. Utsumi, *ibid.*, 1173 (1973).
(5) This photoisomerization of **6** to **8** was recently described by K. Sato, H. Hagiwara, H. Uda, M. Sato, and N. Harada, *J. Am. Chem. Soc.*, **98**, 8281 (1976), who also observed that lactones analogous to **6** but with an aryl group in place of one of the methyls photoisomerize in a different manner, with aryl migration.
(6) (a) H. Nozaki, Z. Yamaguti, T. Okada, R. Noyori, and M. Kawanisi, *Tetrahedron*, **23**, 3993 (1967); (b) T. Okada, K. Kamogawa, M. Kawanisi, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **43**, 2908 (1970), and references cited therein.
(7) For reviews, see K. N. Houk, *Chem. Rev.*, **76**, 1 (1976); W. G. Dauben, G. Lodder, and J. Ipaktchi, *Fortschr. Chem. Forsch.*, **54**, 73 (1975).
(8) That such isomerizations do occur in Pyrex was established by irradiating **15a** (obtained from the acid-catalyzed rearrangement of **11**; details will



be described in a separate paper), which gave a quantitative yield of **13a**. Further irradiation through Corex gave **10a**.

(9) These rearrangements proceed through α-cleavage and rebonding at oxygen. There appears to be a strong preference for cleavage α to the carbonyl group that is adjacent to the methyl-bearing ring-juncture carbon. For example, with **13** cleavage occurs exclusively at a to give **16**; no **16a**



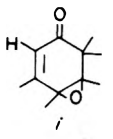
was formed. A similar (though not exclusive, but 3:1) preference was shown with **14**. We have no good explanation for this observation.

(10) Unpublished results, H. Hart and C.-t. Peng.

(11) Compound **10** in ref 1.

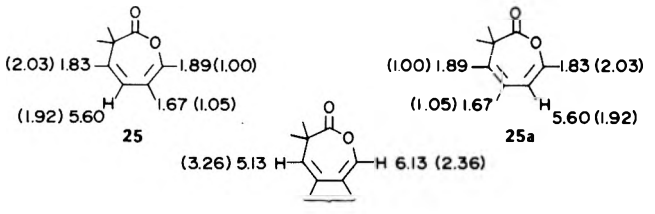
(12) Two Δ^1-butenolides and one Δ^2-butenolide were obtained[1] as a consequence of the thermal or photochemical isomerization of **3**, and it was conceivable that **19** photoisomerized to an aldehyde analogue of **3**, which could rearrange further to a butenolide. We therefore considered the butenolide structures that might have been obtained in this way, and were able to reject each structure as being inconsistent with the spectra of **22**.

(13) Compound **24** does not logically belong in this sequence and it would have perhaps been more instructive to study the photochemistry of i, the missing member of the series **13**, **19**, i, **1**. Unfortunately, the necessary dienone



precursor of i is not accessible. However, the precursor of **24** was readily available from the same reaction that gave the precursor of **19**.

(14) The NMR spectrum of **25** showed that the vinyl proton (δ 5.60) was coupled with an adjacent vinyl methyl at δ 1.83 (J = 2 Hz); decoupling by irradiation of the vinyl proton collapsed the methyl signal to a singlet. The other two vinyl methyls were homoallylically coupled, at δ 1.67 and 1.89. The low-field vinyl methyls were at the termini of the butadiene moiety, limiting the possibilities to **25** and **25a**. The figures in parentheses are the relative europium-shift slopes. In **12**, where the assignment is unequivocal, the proton adjacent to the ether oxygen is at lowest field and has the *lowest* Eu-shift slope (coordination apparently occurs at the carbonyl, not the ether oxygen). By analogy, the lowest field, lowest Eu-shift methyl (δ, 1.89, slope 1.00) should be adjacent to the ether oxygen, as in **25**, not **25a**. Deuterium labeling results and mechanistic arguments confirm this assignment.



(15) D. A. Plank and J. C. Floyd, *Tetrahedron Lett.*, 4811 (1971); T. Mutsuura and K. Ogura, *J. Am. Chem. Soc.*, **89**, 3850 (1967); G. F. Burkinshaw, B. R. David, and P. D. Woodgate, *J. Chem. Soc. C*, 1607 (1970).

(16) R. K. Murray, Jr., T. K. Morgan, Jr., J. A. S. Polley, C. A. Andruskiewicz, Jr., and D. L. Goff, *J. Am. Chem. Soc.*, **97**, 938 (1975).

(17) Whereas the allene oxide is a precursor of the cyclopropanone aldehyde G in the singlet oxygen oxidation of dimethylfulvene, it is *not* a necessary precursor of G in the photoisomerization of dienone epoxides (Scheme I). Indeed, when the fulvene oxidation is carried out in methanol a variety of products are formed[4] in place of the enol lactone. These products must arise from the reaction of methanol with **31** or L, since the epoxy ketone photoisomerization gives **6** and **7** whether carried out in ether or methanol. It seems safe to conclude that the conversion of L to G is irreversible, or at least that the conversion of G to 6 is much faster than its reversion to L.

(18) C. S. Markos and W. Reusch, *J. Am. Chem. Soc.*, **89**, 3363 (1967); D. R. Paulson, G. Korngold, and G. Jones, *Tetrahedron Lett.*, 1723 (1972); for reviews, see N. R. Bertoniere and G. W. Girffin, *Org. Photochem.*, **3**, 115 (1973); A. Padwa, *ibid.*, **1**, 91 (1967); O. Jeger, K. Schaffner, and H. Wehrli, *Pure Appl. Chem.*, **9**, 555 (1964).

(19) S. L. Murov, "Handbook of Photochemistry", Marcel Dekker, New York, N.Y., 1973, p 27.

(20) This value compares favorably with the 55 kcal/mol estimated for the triplet energy of a related steroidal epoxy enone.[24a]

(21) An aldehyde signal at δ 9.77 was observed in an NMR study of the thermal isomerization of **9** to **6** (Scheme II). However, this peak persisted at room temperature and could not be attributed to either the allene oxide I or the cyclopropanone E.[4e]

(22) N. J. Turro, *Acc. Chem. Res.*, **2**, 25 (1969).

(23) Matrix isolation studies are being undertaken in collaboration with Professor O. L. Chapman.

(24) (a) J. A. Saboz, T. Iizuka, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **51**, 1362 (1968); (b) M. Debono, R. M. Malloy, D. Bauer, T. Iizuka, K. Schaffner, and O. Jeger, *J. Am. Chem. Soc.*, **92**, 420 (1970); (c) D. Bauer, T. Iizuka, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **55**, 852 (1972); (d) B. R. von Wartburg, H. R. Wolf, and O. Jeger, *ibid.*, **56**, 1948 (1973); (e) J. Ehrenfreund, Y. Gaoni, and O. Jeger, *ibid.*, **57**, 2704 (1974); (f) A. B. Alder and H. R. Wolf, *ibid.*, **58**, 1048 (1975); (g) B. R. von Wartburg, H. R. Wolf, and O. Jeger, *ibid.*, **59**, 727 (1976); (h) E. Eichenberger, H. R. Wolf, and O. Jeger, *ibid.*, **59**, 1253 (1976).

(25) There is evidence[24h] that C(4)–C(5) and C(4)–O cleavage of the epoxide ring may be associated with different excited states ($\pi\pi^*$ vs. $n\pi^*$) of the epoxy ketone.

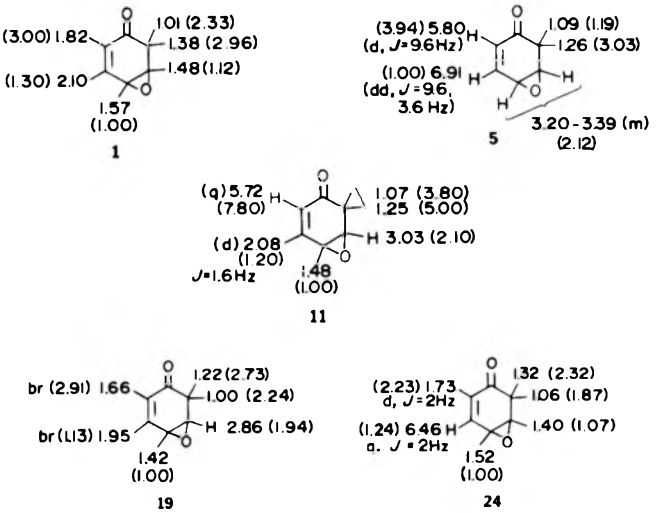
(26) There is ample precedent for carbon–carbon bond cleavage in epoxide photochemistry. For examples and leading references, see G. W. Griffin, K. Ishikawa, and I. J. Lev, *J. Am. Chem. Soc.*, **98**, 5697 (1976); V. Markowski and R. Huisgen, *Tetrahedron Lett.*, 4643 (1976).

(27) Since both the C(4)–O and C(4)–C(5) bonds are broken in the overall reaction, the carbene may be derived by fragmentation of the diradical M as shown in Scheme IV, or by fragmentation of N (Scheme III).

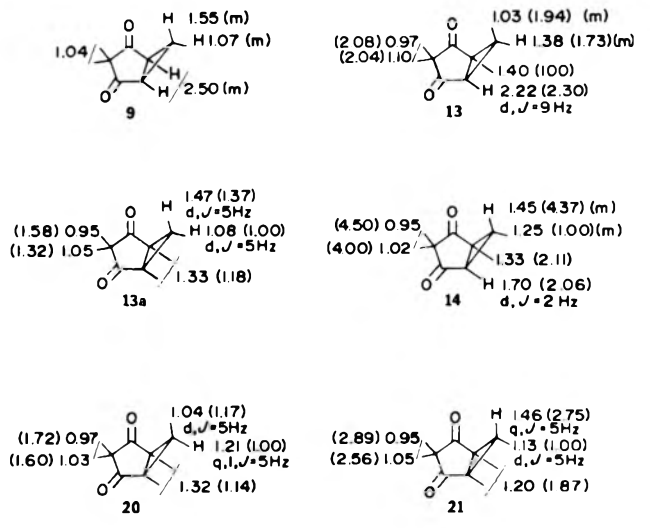
(28) For other examples of fragmentation to a carbene in epoxide photochemistry, see P. C. Petrellis, H. Dietrich, E. Meyer, and G. W. Griffin, *J. Am. Chem. Soc.*, **89**, 1967 (1967); A. M. Torzzolo, W. A. Yager, G. W. Griffin, K. Kristinnsson, and I. Sarkar, *ibid.*, **89**, 3357 (1967); J. K. Crandall and D. R. Paulson, *Tetrahedron Lett.*, 2751 (1969).

(29) This fragmentation is, of course, similar to what one could write as a stepwise path for the migration of a group R_5 from C(5) to C(4), and indeed similar migrations in the photoisomerization of α,β-epoxy ketones have been discussed in these terms [H. E. Zimmerman, B. R. Cowley, C.-Y. Tseng, and J. W. Wilson, *J. Am. Chem. Soc.*, **86**, 947 (1964)].

(30) Simple 4,5-epoxy-2,4-cyclohexadienones mentioned in this paper have the following NMR spectra (all peaks whose multiplicity is not indicated are singlets):

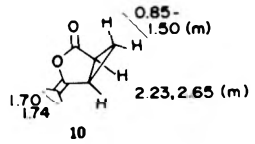


(31) The bicyclo[3.1.0]hexan-2,4-diones mentioned in this paper have the following NMR spectra (all peaks whose multiplicity is not indicated are singlets), where isomeric pairs (**13**, **14** and **20**, **21**) can be distinguished by the Eu-shift slopes and chemical shifts of the C(6) hydrogens and

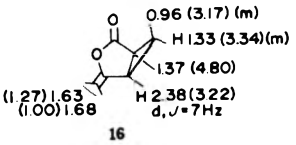


methyls. Registry no.: **9**, 15973-50-9; **13**, 63449-08-1; **14**, 63526-14-7; **20**, 63449-09-2; **21**, 63449-10-5; **13a**, 63449-11-6.

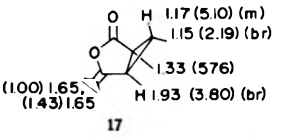
(32) The γ-lactones mentioned in this paper have the following NMR spectra (all peaks whose multiplicity is not indicated are singlets), where isomeric pair **16** and **17** can be distinguished by the Eu-shift slopes and chemical shifts of the C(6) hydrogens and methyls, and isomeric pair **17** and **17a** can be distinguished by similar examination of the C(1) and C(5) substituents. Registry no.: **10**, 29980-22-1; **16**, 63449-12-7; **17**, 63526-15-8; **17a**, 63449-13-8; **10a**, 63449-14-9.



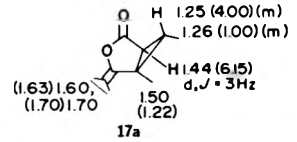
10



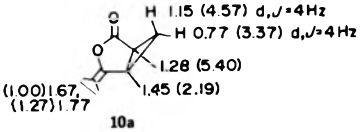
16



17



17a



10a

(33) H. Hart and R. M. Lange, *J. Org. Chem.*, **31**, 3776 (1966).
(34) H. Hart and P. Lavrik, *J. Org. Chem.*, **39**, 1793 (1974).
(35) H. Hart and P. M. Collins, *J. Chem. Soc. C*, 895 (1967).

Synthesis of 4aα-Phorbol 9-Myristate 9a-Acetate and Related Esters

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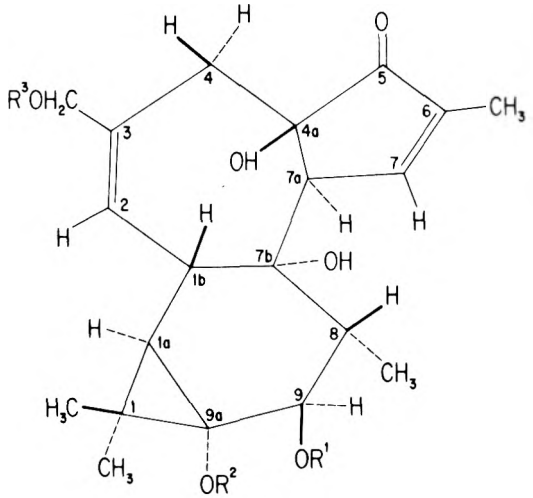
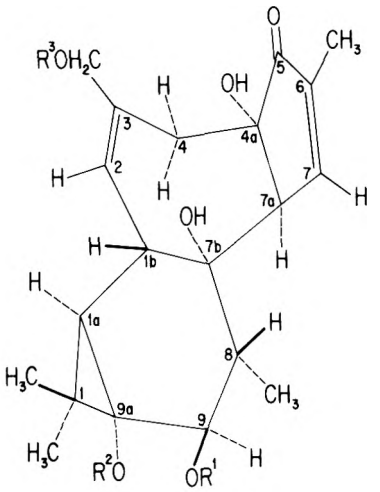
The stereoisomer of the most potent tumor-promoting agent phorbol 9-myristate 9a-acetate and its analogues have been synthesized and fully characterized. Phorbol isolated from croton oil was epimerized with 0.1 N sodium methoxide to 4aα-phorbol. Selective base-catalyzed esterification of 4aα-phorbol and selective acid-catalyzed hydrolysis of the resulting esters gave the desired compounds. They are: 4aα-phorbol 9-myristate 9a-acetate, 4aα-phorbol 9,9a-didecanoate, 3-decanoyl-4aα-phorbol 9,9a-didecanoate, 3-acetyl-4aα-phorbol 9,9a-diacetate, 3-acetyl-4aα-phorbol 9a-acetate, 4aα-phorbol 9a-acetate, 3-acetyl-4aα-phorbol 9-myristate 9a-acetate, 3-myristoyl-4aα-phorbol 9-myristate 9a-acetate, and 3-myristoyl-4aα-phorbol 9a-acetate.

Croton oil is a complex lipid mixture obtained by extraction or expression of the seeds of *Croton tiglium L.* This oil was first discovered to be a tumor promoter on mouse skin in two-stage carcinogenesis by Berenblum.[1] The subject of tumor promoters and cocarcinogens was recently reviewed.[2] The active principles of croton oil were isolated and characterized as the esters of the tetracyclic diterpene alcohol, phorbol[3,4] (**1a**). The structure and stereochemistry of **1a** was established from x-ray crystallographic studies.[5,6] Partial syntheses of phorbol esters have been reported.[7] We now wish to report the synthesis of 4aα-phorbol 9-myristate 9a-acetate (**2b**), which is the most important counterpart of the potent tumor promoter phorbol 9-myristate 9a-acetate[8] (**1b**), and the related



1a. $R^1=R^2=R^3=H$
b. $R^1=CO(CH_2)_{12}CH_3$; $R^2=COCH_3$; $R^3=H$
c. $R^1=R^2=CO(CH_2)_8CH_3$; $R^3=H$



2a. $R^1=R^2=R^3=H$
b. $R^1=CO(CH_2)_{12}CH_3$; $R^2=COCH_3$; $R^3=H$
c. $R^1=R^2=CO(CH_2)_8CH_3$; $R^3=H$
d. $R^1=R^2=R^3=CO(CH_2)_8CH_3$
e. $R^1=R^2=R^3=COCH_3$
f. $R^1=H$; $R^2=R^3=COCH_3$
g. $R^1=R^3=H$; $R^2=COCH_3$
h. $R^1=CO(CH_2)_{12}CH_3$; $R^2=R^3=COCH_3$
i. $R^1=R^3=CO(CH_2)_{12}CH_3$; $R^2=COCH_3$
j. $R^1=H$; $R^2=COCH_3$; $R^3=CO(CH_2)_{12}CH_3$

esters: 4aα-phorbol 9,9a-didecanoate (**2c**), 3-decanoyl-4aα-phorbol 9,9a-didecanoate (**2d**), 3-acetyl-4aα-phorbol 9,9a-diacetate (**2e**), 3-acetyl-4aα-phorbol 9a-acetate (**2f**), 4aα-phorbol 9a-acetate (**2g**), 3-acetyl-4aα-phorbol 9-myristate 9a-acetate (**2h**), 3-myristol-4aα-phorbol 9-myristate 9a-acetate (**2i**), and 3-myristol-4aα-phorbol 9a-acetate (**2j**). Com-

Table I. Selective NMR Data for Phorbol, 4aα-Phorbol, and Esters[a]

	Registry no.	1a	1b	2	3-CH_2	3-CH_2OR	4	7	9	9a
1a	17673-25-5	0.56 (1 H) d, J = 5	2.92 (1 H) m	5.50 (1 H) d, J = 6	3.80 (2 H) d, J = 5	4.70 (OH) t, J = 5	2.32 (2 H) s	7.58 (1 H) br s	4.06 (1 H) m; 4.30 (OH) d, J = 5	3.90 (OH) s
2a	26241-63-4	0.35 (1 H) d, J = 5	1.52–1.82 (1 H) m	5.12 (1 H) br s	3.55 (2 H) d, J = 5	4.66 (OH) br s	1.95 (1 H) d, J = 14; 3.23 (1 H) d, J = 14	7.30 (1 H) br s	4.06 (1 H) d, J = 7; 4.58 (OH) br s	4.02 (OH) s
2b	63597-44-4	0.80 (1 H) d, J = 5	1.50–2.00 (1 H) m	5.25 (1 H) br s	3.92 (2 H) s	2.85 (OH) s	2.31 (1 H) d, J = 14; 3.74 (1 H) d, J = 14	7.06 (1 H) br s	0.85 (3 H) t, J = 7; 1.28 (22 H) br s; 1.50–2.00 (2 H) m; 5.50 (1 H) d, J = 10	2.06 (3 H) s
2c	27536-56-7	0.81 (1 H) d, J = 5	1.50–2.00 (1 H) m	5.25 (1 H) br s	3.95 (2 H) s	2.33 (OH) s	2.30 (1 H) d, J = 14; 3.73 (1 H) d, J = 14	7.05 (1 H) br s	0.85 (3 H) t, J = 7; 1.26 (14 H) br s; 1.50–2.00 (2 H) m; 5.48 (1 H) d, J = 10	0.85 (3 H) t, J = 7; 1.26 (14 H) br s; 1.50–2.00 (2 H) m
2e	22338-57-4	0.86 (1 H) d, J = 5	1.60–2.00 (1 H) m	5.29 (1 H) br s	4.32 (2 H) s	2.12 (3 H) s	2.30 (1 H) d, J = 14; 3.70 (1 H) d, J = 14	7.05 (1 H) br s	2.04 (3 H) s; 5.43 (1 H) d, J = 10	2.08 (3 H) s
2f	63640-08-4	0.85 (1 H) d, J = 6	1.62–2.00 (1 H) m	5.30 (1 H) br s	4.32 (2 H) s	2.08 (3 H) s	2.26 (1 H) d, J = 14; 3.55 (1 H) d, J = 14	7.03 (1 H) br s	3.48 (OH) s; 4.03 (1 H) d, J = 10	2.06 (3 H) s
2g	63640-19-7	0.90 (1 H) d, J = 6	1.62–2.00 (1 H) m	5.30 (1 H) br s	3.93 (2 H) s	2.41 (OH) s	2.38 (1 H) d, J = 14; 3.65 (1 H) d, J = 14	7.13 (1 H) br s	3.55 (OH) s; 4.10 (1 H) d, J = 10	2.10 (3 H) s
2h	63588-55-6	0.81 (1 H) d, J = 6	1.50–2.00 (1 H) m	5.29 (1 H) br s	4.33 (2 H) s	2.12 (3 H) s	2.30 (1 H) d, J = 14; 3.72 (1 H) d, J = 14	7.03 (1 H) br s	0.85 (3 H) t, J = 7; 1.26 (22 H) br s; 1.50–2.00 (2 H) m; 5.38 (1 H) d, J = 10	2.08 (3 H) s
2i	63533-70-0	0.81 (1 H) d, J = 6	1.50–2.00 (1 H) m	5.29 (1 H) br s	4.35 (2 H) s	0.85 (3 H) t, J = 7; 1.26 (22 H) br s; 150–2.00 (2 H) m	2.30 (1 H) d, J = 14; 3.70 (1 H) d, J = 14	7.05 (1 H) br s	0.85 (3 H) t, J = 7; 1.26 (22 H) br s; 1.50–2.00 (2 H) m; 5.50 (1 H) d, J = 10	2.08 (3 H) s
2j	63533-71-1	0.82 (1 H) d, J = 6	1.50–2.00 (1 H) m	5.30 (1 H) br s	4.33 (2 H) s	0.85 (3 H) t, J = 7; 1.27 (22 H) br s; 1.50–2.00 (2 H) m	2.31 (1 H) d, J = 14; 3.72 (1 H) d, J = 14	7.04 (1 H) br s	2.40 (OH) s; 4.05 (1 H) d, J = 10	2.06 (3 H) s

[a] Spectra were run in $CDCl_3$ solutions (unless otherwise stated) at 60 MHz with Me_4Si as internal standard. Coupling constants are in hertz and chemical shifts values are in units of δ (ppm). Multiplicity: d, doublet; m, multiplet; s, singlet; br s, broadened singlet; t, triplet. [b] Spectra were taken in Me_2SO-d_6.

pounds **2c, 2d,** and **2e** have been reported in the literature,[9,10] but no synthesis or characterization was given for **2c** and **2d.** The availability of 4aα-phorbol esters described in this paper provides additional important molecules for studying the structure–activity relationships and the mechanisms of tumor promotion.

The starting compound **1a** was isolated and purified from croton oil according to the procedures previously described.[11-14] To achieve the epimerization at the 4a position, **1a** was treated with 0.1 N sodium methoxide in methanol at room temperature for 2 days. Pure **2a** was isolated in 72% yield after column chromatography and recrystallization. This compound is hygroscopic; therefore, crystallization was performed in a drybox. Elemental analysis and chemical ionization mass spectrometry, with isobutane as reagent gas, confirmed the molecular formula $C_{20}H_{28}O_6$. The IR spectrum and mass spectrometric fragmentation pattern were essentially identical with that of **1a.** However, in the UV spectrum the 234-nm peak of phorbol was shifted to 240 nm. Dreiding molecular models show that **1a** has a rigid structure. The cyclopentenoyl ring is trans connected with the unsaturated seven-membered ring. Because the latter is fixed in an envelope conformation with the fold between C-4a and C-1b, it imposes the strain on the former, and the cyclopentenoyl ring is not planar. In **2a,** where the 4a-hydroxyl group is in the α configuration, the cyclopentenoyl ring is cis connected to the seven-membered ring. The latter has more flexibility, with the fold through C-4 and C-7b. This allows the cyclopentenoyl ring to achieve the coplanarity. The NMR spectrum also showed some proton absorption peaks characteristic of this stereochemistry. The absorption peak of the methine proton at the C-1b position in **1a** was shifted downfield to δ 2.92 due to its steric interaction with the 4aβ-hydroxyl group; however, the same methine proton in **2a** is free of hydrogen bonding and showed the usual absorption peaks at δ 1.52–1.82 region. On the other hand, one of the C-4 methylene protons in **2a** is hydrogen bonded to the C-7b hydroxyl group; these two protons are not equivalent and showed two doublets at δ 1.95 and 3.23 with the typical geminal proton coupling constant of 14 Hz. In **1a,** these two protons are equivalent and free of hydrogen bonding, thus giving only a singlet peak at δ 2.32. The TLC also distinguished **1a** and **2a,** the R_f values were 0.6 and 0.5, respectively, in the solvent system of methanol–chloroform (1:3). On spraying the TLC plates with vanillin–sulfuric acid solution in ethanol and heating, **1a** showed a light green color while **2a** showed a dark green color. The stereoisomer of **1a** had been reported as 4α-phorbol by Hecker and his coworkers;[10,15] however, they could not obtain the crystalline form and this compound was isolated as the corresponding triacetate.[10,15] When **2a** was treated with acetic anhydride in dry pyridine under a nitrogen atmosphere, at room temperature, **2e** was isolated. Its melting point and IR, UV, and NMR spectra were identical with that of 4α-phorbol triacetate reported by Jacobi et al.[10] The NMR data of relevant compounds are given in Table I.

The difference in reactivity among five hydroxyl groups in **2a** provides the opportunity for selective esterification. There are three tertiary, one secondary, and one primary hydroxyl groups in the molecule. The tertiary hydroxyl group at C-9a is attached to a cyclopropane ring. It may be considered as a "homoenol" and should show the similar chemical reactivity compared with the ordinary enol.[16] In fact, when **2a** was treated with acetic anhydride in pyridine, **2f** was also isolated as the minor product. The difference in reactivity of the three hydroxyl groups of **2a** may be partially explained in terms of steric and conformational factors. The C-9 is probably more sterically hindered by the C-9 methyl group than is the C-9a hydroxyl group by either methyl group attached at C-1. Similarly, the primary hydroxyl group might be hydrogen bonded with the carbonyl at C-5. When milder conditions were used, in which the reaction was conducted in acetic anhydride and dimethylformamide in the presence of calcium carbonate, the diacetate **2f** and monoacetate **2g** were obtained, but **2e** was not isolated. This indicates that C-9a–OH of **2a** was acetylated even more rapidly than the hydroxyl group at the 3-methyl position. Similar results had been observed for **1a** by Szczepanski et al.[17] Under these weak basic and oxygen-free conditions, products due to the opening of the cyclopropane ring in **2a** were not isolated. Elemental analysis and chemical ionization mass spectrometry indicate molecular formulas $C_{24}H_{32}O_8$ and $C_{22}H_{30}O_7$ for **2f** and **2g,** respectively; moreover, mass spectrometric fragmentation patterns and NMR peak intensity for the methyl protons also confirmed the number of acetyl groups in these molecules. IR spectra of both acetates showed the characteristic ester carbonyl band at 1740 cm^{-1}. The UV spectra of both **2f** and **2g** were similar to that of the parent **2a.** In the NMR spectra, the downfield chemical shift (δ 4.32) of the C-3 methylene protons in **2f** indicated that one acetyl group was attached to the 3-hydroxymethyl position. By comparing the chemical shifts of the C-9 proton in **2e** (δ 5.45), **2f** (δ 4.03), and **2g** (δ 4.10), it can be concluded that C-9–OH was not acetylated and that the other acetyl group must be attached to the C-9a position in both **2f** and **2g.**

The next step in the synthesis of **2b** was then conducted by the esterification at the C-9 position. It was found that the esterification proceeded very slowly when **2f** or **2g** in pyridine was stirred with myristoyl chloride at room temperature. Much better results were obtained when the reactions were conducted in pyridine–toluene solutions and the mixtures heated to 90 °C. Under these conditions **2f** gave **2h,** and **2g** gave **2i** and **2j.** These three compounds were isolated by chromatography, and their structures were confirmed by UV, IR, NMR, and mass spectrometry. Finally, acid-catalyzed hydrolysis of both **2h** and **2i** with 60% perchloric acid[10] selectively removed the ester group at the C-3 hydroxymethyl position to yield **2b.** This selective hydrolysis is probably due to the accessibility and reactivity of the primary allylic hydroxyl, which may also be relevant to the acetylation reactions discussed above.

Our original attempts to obtain molecular weight information for **2b** and the other 4aα-phorbol esters by electron impact mass spectrometry were not successful; only the low mass fragmentation peaks were detected. By changing to the chemical ionization mode with isobutane as reagent gas, however, we were able to obtain not only molecular weights but also fragmentation peaks indicating the number and the kind of ester present in the molecules. In **2b,** the molecular weight (616) was clearly indicated by the protonated molecular ion peak (*m/e* 617 $(M + H)^+$). The fragmentation peaks at *m/e* 557 $(M + H - CH_3COOH)^+$ and 389 $[M + H - CH_3(CH_2)_{12}COOH]^+$ showed that **2b** contained one acetate group and one myristate group. Furthermore, the mass spectrum also showed three peaks (*m/e* 329, 311, and 293) characteristic of the phorbol molecule. Similar spectra were obtained for all the other 4aα-phorbol esters. A more detailed analysis of the chemical ionization mass spectra of 4aα-phorbol esters will be published elsewhere.[18] Elemental analysis confirmed that **2b** has the molecular formula $C_{36}H_{56}O_8$. Its IR spectrum was essentially identical with that of the pure **1b** isolated from croton oil in this laboratory.[19] However, the UV spectra of **1b** and **2b** (Figure 1) were significantly different; the longer wavelength band in **2b** was more pronounced than that in **1b** and this band was shifted to a yet longer wavelength, thus indicating that **2b** is a stereoisomer of **1b** with C-4a–OH oriented in the α configuration as discussed above. The NMR spectrum also showed proton absorption peaks characteristic of **2b,** the methylene protons

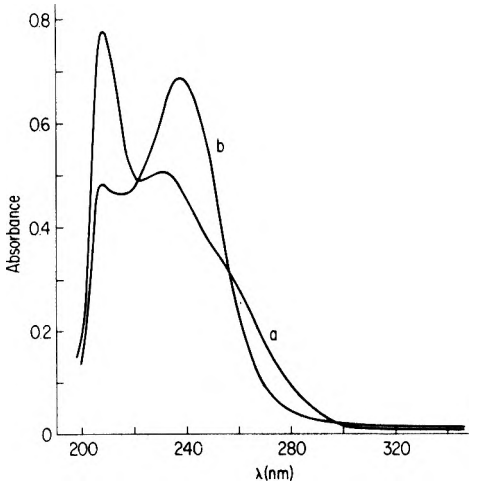


Figure 1. UV spectra of phorbol 9-myristate 9a-acetate (**1b**) (a) and 4aα-phorbol 9-myristate 9a-acetate (**2b**) (b) in ethanol, both at 1×10^{-4} M.

at the C-4 position showed two doublets at δ 2.30 and 3.65 (J = 14 Hz) due to one of the protons which was hydrogen bonded to C-7b–OH. The C-7b hydroxyl apparently exerts a deshielding effect on one C-4 proton because of close proximity. The TLC R_f value of **2b** (0.31) was lower than that of **1b** (0.44) using acetone–methylene chloride (1:6) as eluent. Compound **2b** was obtained as a viscous oil. The diester **2c** was prepared by the acid-catalyzed hydrolysis of **2d**, which in turn was synthesized from **2a** and decanoyl chloride in pyridine. For comparison, phorbol 9,9a-didecanoate (**1c**) was also synthesized from **1a** in the same manner. The structures of **2c** and **1c** were fully characterized.

Long-term in vivo two-stage carcinogenesis experiments with these 4aα-phorbol esters are currently underway in this laboratory in order to evaluate the effects of stereochemical configuration on tumor-promoting activity.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer 137 spectrophotometer; samples were run in potassium bromide pellets or in carbon tetrachloride solutions. UV spectra were recorded on a Beckman Model 25 spectrophotometer. NMR spectra were recorded on a Varian Associates Model T-60A spectrometer in deuteriochloroform and deuteriodimethyl sulfoxide using tetramethylsilane as an internal standard. For the convenience of the reader all NMR data are summarized in Table I. Mass spectra were recorded on a DuPont 21-492 computer-based double-focusing high-resolution mass spectrometer in the chemical ionization mode using isobutane as reagent gas.[18] Analytical TLC was run on EM Reagents precoated TLC plates silica gel 60F-254 with fluorescent indicator. Spots were detected by UV light (254 nm) and by spraying the plates with a vanillin (3 g)–sulfuric acid (0.5 mL) solution in ethanol (100 mL), followed by heating. Column chromatography was carried with EM Reagents silica gel 60 (70-230 mesh ASTM) and neutral Florisil[19] (60–100 mesh; Fisher Scientific Co., New York, N.Y.). Croton oil was purchased from Amend Drug Company, Hillside, N.J. Microanalysis were performed by Galbraith Laboratories, Knoxville, Tenn.

Isolation and Purification of Phorbol (1a). The procedures of Flaschenträger[11,12] and Kauffmann[13,14] were used to isolate **1a** from croton oil. Compound **1a** crystallized with 1 mol of ethanol; 5.97 g of this material was obtained from 450 g of croton oil after recrystallization from ethanol (yield, 1.3%): mp 248–250 °C dec (lit.[20] 249–250 °C dec); IR (KBr) 3400 (OH), 1710 (α,β-unsaturated C=O), 1640 cm^{-1} (C=C); TLC, R_f 0.60 (CH_3OH–$CHCl_3$, 1:3).

Anal. Calcd for $C_{20}H_{28}O_6 \cdot C_2H_5OH$: C, 64.35; H, 8.35. Found: C, 64.18; H, 8.48.

Compound **1a**·C_2H_5OH was unstable; upon standing at 5 °C for several days the TLC of this compound showed several other spots. **1a**·C_2H_5OH (5 g) was dissolved in 100 mL of water and allowed to stand for 15 min at 60 °C. Water was removed in a rotatory evaporator (temperature bath, 60 °C) until crystals began to separate. This preparation was kept in the cold room for 1 week, and the crystals formed were collected by suction and dried under vacuum (4.40 g): mp 230–231 °C dec.

Anal. Calcd for $C_{20}H_{28}O_6 \cdot H_2O$: C, 62.82; H, 7.85. Found: C, 62.78; H, 7.80.

Pure **1a** (4.35 g) was obtained by azeotropic distillation of the water with benzene and drying under high vacuum for 24 h at 100 °C: mp 250–251 °C dec (lit.[20] 250–251 °C dec); TLC, R_f 0.6 (CH_3OH–$CHCl_3$, 1:3); IR (KBr) 3501, 3350, 1710, 1640 cm^{-1}; UV (C_2H_5OH) λ_{max} 210 (ε 7343), 234 (5117), 332 nm (70); mass spectrum, m/e 365 $(M + H)^+$.

Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.93; H, 7.75. Found: C, 66.08; H, 7.66.

4aα-Phorbol (2a). To a solution of **1a** (1.0 g, 2.7 mmol) in 30 mL of methanol under a nitrogen atmosphere was added 30 mL of 0.2 N sodium methoxide in methanol. A pink color developed immediately, which turned yellow after 30 min. The solution was stirred at room temperature in the dark for 2 days and then evaporated to dryness in vacuo. Column chromatography (silica gel) using methanol–chloroform (1:9, 1:6, and 1:3) gave **2a** (0.72 g, 72%). This compound is hygroscopic; it was recrystallized from ethyl acetate in a drybox: mp 135–150 °C; TLC, R_f 0.5 (CH_3OH–$CHCl_3$, 1:3), dark green color with vanillin spray; IR (KBr) 3450, 1710 (α,β-unsaturated C=O), 1640 cm^{-1} (C=C); UV (C_2H_5OH) λ_{max} 204 (ε 4568), 240 (5327), 334 nm (85); mass spectrum, m/e 365 $(M + H)^+$.

Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.93; H, 7.75. Found: C, 66.11; H, 7.65.

3-Acetyl-4aα-phorbol 9,9a-Diacetate (2e). Acetic anhydride (0.1 mL) was added to a solution of **2a** (0.05 g, 0.14 mmol) in dry pyridine (2 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at room temperature for 24 h. To this mixture was added 10 mL of water and 10 mL of methylene chloride. The water layer was further extracted with methylene chloride (2 × 10 mL). The organic layer was acidified with 1 N HCl, neutralized with 5% $KHCO_3$, washed with saturated NaCl, and then dried over $MgSO_4$. Evaporation of the solvent afforded 0.065 g of crude solid product. TLC (acetone–methylene chloride, 1:3) showed two spots with R_f values 0.73 and 0.30. Column chromatography (silica gel) with acetone–methylene chloride (1:9) as eluent gave 0.050 g (73%) of **2e** (TLC, R_f (0.73)). This product was recrystallized from ether–petroleum ether: mp 171–173 °C (lit.[10] 172–175 °C); IR (KBr) 3550, 3400, 2900, 1740 (ester C=O), 1720, 1710, 1630 cm^{-1}; UV (C_2H_5OH) λ_{max} 205 (ε 5050), 240 (6784), 334 nm (110); mass spectrum, m/e 491 $(M + H)^+$.

Anal. Calcd for $C_{26}H_{34}O_9$: C, 63.67; H, 6.93. Found: C, 63.75; H, 6.81.

Another 0.010 g of a white solid (TLC, R_f 0.30) was obtained from column chromatography. This material was identified as **2f** as described below.

3-Acetyl-4aα-phorbol 9a-Acetate (2f) and 4aα-Phorbol 9a-Acetate (2g). Acetic anhydride (1.8 mL) and $CaCO_3$ (1.8 g) were added to a solution of **2a** (0.88 g, 2.4 mmol) in dry dimethylformamide (18 mL) with stirring at room temperature under a nitrogen atmosphere. The resulting suspension was stirred at room temperature for 24 h, at which time another 3.6 mL of acetic anhydride and 3.6 g of $CaCO_3$ were added. After 24 h the mixture was poured into 80 mL of water. The aqueous solution was then extracted with ethyl acetate (3 × 80 mL). The extracts were washed with 50 mL of 5% $KHCO_3$ and then with 50 mL of saturated NaCl. The ethyl acetate layer was dried over $MgSO_4$. Evaporation of this solution gave 0.87 g of crude solid product. TLC showed two major spots with R_f values of 0.30 and 0.10 using acetone–methylene chloride (1:3) as eluent. Column chromatography (silica gel) of the crude products with ether and ether–ethyl acetate (6:1) as eluents gave 0.45 g of **2f** (42%) and 0.30 g of the monoacetate **2g** (30%). Compound **2f** was recrystallized from ether: mp 182–184 °C; TLC, R_f 0.30 (acetone–methylene chloride, 1:3); IR (KBr) 3550, 3400, 2900, 1740 (ester C=O), 1720, 1710, 1630 cm^{-1}; UV (C_2H_5OH) λ_{max} 205 (ε 4552), 240 (6552), 334 nm (100); mass spectrum, m/e 449 $(M + H)^+$.

Anal. Calcd for $C_{24}H_{32}O_8$: C, 64.29; H, 7.74. Found: C, 64.13; H, 7.33.

Compound **2g** was recrystallized from ethyl acetate: mp 223–225 °C; TLC, R_f 0.10 (acetone–methylene chloride, 1:3); IR (KBr) 3550, 3400, 2950, 1740 (ester C=O), 1720, 1710, 1630 cm^{-1}; UV (C_2H_5OH) λ_{max} 204 (ε 4036), 240 (6330), 334 nm (91); mass spectrum, m/e 407 $(M + H)^+$.

Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.02, H, 7.39. Found: C, 65.32; H, 7.56.

3-Acetyl-4aα-phorbol 9-Myristate 9a-Acetate (2h). To a solution of **2f** (0.10 g, 0.2 mmol) in pyridine (5 mL) and toluene (10 mL)

was added 0.1 g of myristoyl chloride. The mixture was stirred at 90 °C for 30 h. Evaporation of the toluene–pyridine solution in vacuo yielded a semisolid. It was washed with 5% $NaHCO_3$ (20 mL) and extracted with methylene chloride (3 × 20 mL), and then dried (Na_2SO_4). Evaporation of solvent gave the crude product, which after purification by column chromatography on Florisil (petroleum ether–ether, 2:1) yielded **2h** as a colorless oil (0.10 g, 77%): TLC, R_f 0.57 (acetone–methylene chloride, 1:6); IR (CCl_4) 3450, 2950, 2860, 1740, 1720, 1640 cm^{-1}; UV (C_2H_5OH) λ_{max} 207 (ε 4750), 237 (6520), 334 nm (100); mass spectrum, *m/e* 659 $(M + H)^+$.

3-Myristoyl-4aα-phorbol 9-Myristate 9a-Acetate (2i) and 3-Myristoyl 4aα-phorbol 9a-Acetate (2j). Myristoyl chloride (0.3 g) was added to a solution of **2g** (0.15 g, 0.3 mmol) in dry pyridine (5 mL) and toluene (10 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred at 90 °C for 20 h. Then the pyridine–toluene solution was evaporated in vacuo to give a semisolid residue. This residue was washed with 5% $NaHCO_3$ (20 mL), extracted with methylene chloride (3 × 30 mL), and dried over Na_2SO_4. Evaporation of solvent yielded the crude product. The TLC contained two major spots. Column chromatography of this crude product on neutral Florisil with petroleum ether–ether (1:1) as eluent gave **2i** as a semisolid (0.16 g, 63%): TLC, R_f 0.89 (acetone–CH_2Cl_2, 1:6); IR (CCl_4) 3450, 2950, 2860, 1740, 1720, 1640 cm^{-1}; UV (C_2H_5OH) λ_{max} 207 (ε 7600), 234 (9090), 332 nm (450); mass spectrum, *m/e* 827 $(M + H)^+$.

Further column chromatography of the crude product with acetone–methylene chloride mixture (1:9) as eluent gave **2j** (0.05 g, 27%): TLC, R_f 0.39 (acetone–CH_2Cl_2, 1:6); IR (CCl_4) 3450, 2950, 2860, 1740, 1720, 1640 cm^{-1}; UV (C_2H_5OH) λ_{max} 207 (ε 4390), 237 (6300), 334 (140); mass spectrum, *m/e* 617 $(M + H)^+$.

1aα-Phorbol 9-Myristate 9a-Acetate (2b). Two procedures were used. (a) To a solution of **2h** (0.10 g, 0.15 mmol) in methanol (10 mL) under a nitrogen atmosphere was added 0.1 mL of 60% perchloric acid. The mixture was stirred at room temperature for 20 h; 0.10 g of $NaOAc·3H_2O$ was then added to the methanol solution with stirring. After 10 min the solution was evaporated to dryness. Water (15 mL) and methylene chloride (15 mL) were added to the residue. The water layer was extracted with methylene chloride (2 × 20 mL). The combined organic layers were washed with 5% $NaHCO_3$ (15 mL) and saturated NaCl (15 mL), and then dried over Na_2SO_4. Evaporation of the solvent gave crude **2b** as an oil (0.08 g, 87%). It was purified by column chromatography on Florisil with acetone–methylene chloride (1:9) as eluent: TLC, R_f 0.31 (acetone–CH_2Cl_2 1:6); IR (CCl_4) 3450, 2950, 2860, 1740, 1720, 1640 cm^{-1}; UV (C_2H_5OH) λ_{max} 207 (ε 4409), 237 (6236), 334 (140); mass spectrum, *m/e* 617 $(M + H)^+$.

Anal. Calcd for $C_{36}H_{56}O_8$: C, 70.13; H, 9.09. Found: C, 70.33; H, 9.00.

(b) To a solution of **2i** (0.10 g, 0.12 mmol) in methanol (10 mL) under a nitrogen atmosphere was added 0.1 mL of 60% perchloric acid. The mixture was stirred at room temperature for 24 h. Upon workup as described under (a) above, it gave the crude product, which, after purification by column chromatography, afforded pure **2b** (0.05 g, 68%). All spectral data were identical with that described under (a) above.

3-Decanoyl-4aα-phorbol 9,9a-Didecanoate (2d) and 4aα-Phorbol 9,9a-Didecanoate (2c). To a solution of **2a** (0.15 g, 0.41 mmol) in dry pyridine (5 mL) at 0 °C under a nitrogen atmosphere was added 0.55 g of decanoyl chloride. The mixture was stirred at room temperature for 3 days. To this mixture were added 30 mL of water and 30 mL of methylene chloride. The water layer was further extracted with methylene chloride (2 × 30 mL). The combined organic layers were acidified with 1 N HCl, neutralized with 5% $KHCO_3$, washed with saturated NaCl, and then dried over $MgSO_4$. Evaporation of the solvent gave a light yellow oil. Column chromatography (silica gel) with hexane–methylene chloride mixture (1:4) afforded pure **2d** as a colorless oil (0.23 g, 70%): TLC, R_f 0.90 (acetone–CH_2Cl_2, 1:6); IR (CCl_4) 3550, 3400, 2950, 2860, 1740, 1720, 1710, 1640 cm^{-1}; UV (C_2H_5OH) λ_{max} 207 (ε 4960), 238 (6740), 334 nm (120); mass spectrum, *m/e* 827 $(M + H)^+$. To a solution of **2d** (0.20 g, 0.24 mmol) in methanol (15 mL) was then added 0.15 mL of 60% perchloric acid. After the mixture was stirred at room temperature for 20 h, $NaOAc·3H_2O$ (0.2 g) was added, and the solution evaporated to dryness. Water (30 mL) and methylene chloride (30 mL) were added to the residue. The water layer was further extracted with methylene chloride. The organic layers were washed with 5% $KHCO_3$ and saturated NaCl, and dried over $MgSO_4$. Evaporation of the solvent gave a yellow oil. Column chromatography on Florisil with acetone–methylene chloride (1:9) as eluent afforded pure **2c** as a colorless oil (0.10 g, 63%): TLC, R_f 0.26 (acetone–CH_2Cl_2, 1:6); IR (CCl_4) 3450, 2950, 2860, 1740, 1720, 1710, 1640 cm^{-1}; UV (C_2H_5OH) λ_{max} 207 (ε 4390), 238 (6440), 334 nm (120); mass spectrum, *m/e* 673 $(M + H)^+$.

Phorbol 9,9a-Didecanoate (1c). This compound was prepared from **1a** by the procedures described above for **2c.** Pure **1c** had the following physical properties: TLC, R_f 0.36 (acetone–CH_2Cl_2, 1:6); IR (CCl_4) 3400, 2950, 2860, 1740, 1720, 1710, 1635 cm^{-1}; UV (C_2H_5OH) λ_{max} 210 (ε 8560), 234 (5230), 332 nm (75); mass spectrum, *m/e* 673 $(M + H)^+$.

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Registry No.—**1b,** 16561-29-8; **1c,** 24928-17-4; **2d,** 63597-45-5; myristoyl chloride, 112-64-1; decanoyl chloride, 112-13-0.

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Synthesis of Cyclopenin and Glycosminine from Phenylpyruvic Acid

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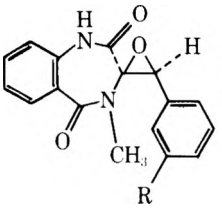
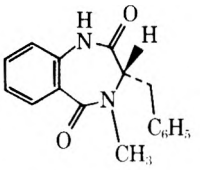
Condensation of ethyl phenylalaninate (**6**) with anthranilic acid gave **7**, which underwent cyclization to **8**. Condensation of anthranilamide (**11**) with phenylpyruvic acid, on the other hand, afforded quinazolinone **14**. The latter was converted to its methyl ester **15**, which gave **16** upon heating. Treatment of **15** with piperidine furnished **17** which, after heating in the presence of acetic acid, afforded glycosminine (**18**). Condensation of *o*-nitrobenzamide with phenylpyruvic acid yielded **20**, together with **21**. Ester **23** was converted to its *N*-methyl derivative **25**, bringing this pathway into convergence with a previous route to cyclopeptine (**4**) and cyclopenin (**1**).

Biosynthetic studies by Luckner have established that cyclopenin (**1**) and cyclopenol (**2**), metabolites of *Penicillium cyclopium* Westling, incorporate anthranilic acid and phenylalanine efficiently.[1] Supporting evidence[2] for a pathway which proceeds via the cyclic dipeptide **3** (cyclopeptine) and/or its 3,10-dehydro derivative **4** comes from (1) isolation of **3** from cultures of *P. cyclopium*,[3] and (2) the purification of a dehydrogenase which converts **3** reversibly to **4**.[4] Subsequent biological oxidation of **4** leads to **1**, which has been shown[5] to undergo an enzymatic meta hydroxylation to **2**.



1, R = H
2, R = OH



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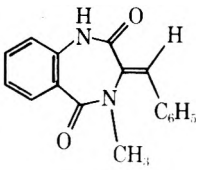

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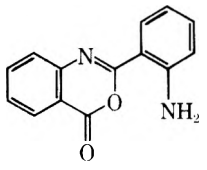
In previous syntheses of **1** and **2**,[6] **4** and its *m*-hydroxyphenyl analogue were prepared along nonbiogenetic lines and, upon epoxidation, afforded cyclopenin and cyclopenol, respectively. Intrigued by the possibility of simulating the biogenesis of **1** and related metabolites based on dehydrophenylalanine,[7] we have studied the condensation of anthranilic acid derivatives with phenylalanine and phenylpyruvic acid.

Attempts to bring about a reaction between anthranilic acid and phenylalanine in the presence of DCC in acetonitrile were unsuccessful. The sole product was the self-condensation product (**5**) of anthranilic acid.[8] However, when the ethyl ester



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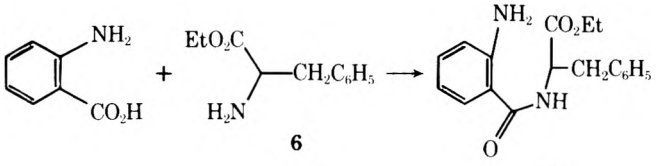
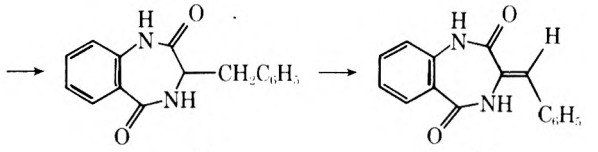
6 of phenylalanine was treated with anthranilic acid, a smooth cross-condensation led to hippuric ester **7**. Closure of **7** to the benzodiazepin **8** was effected by a mixture of piperidine and methanol at reflux. The formation of cyclic dipeptide **8** was readily apparent from the carbonyl bands in its infrared spectrum, which are typical of 1,4-benzodiazepin-2,5-diones of this type.[6,9] A further characteristic of the transformation of **7** to **8** is the upfield shift of the C-3 proton, apparently reflecting the preference of the hetero ring in **8** for a boat-like conformation (enhanced amide resonance) which places this proton on the periphery of the shielding zone of the benzo ring.

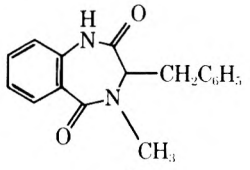
The precursor incorporation results of Luckner[2-5] imply



6 **7**



8 **10**



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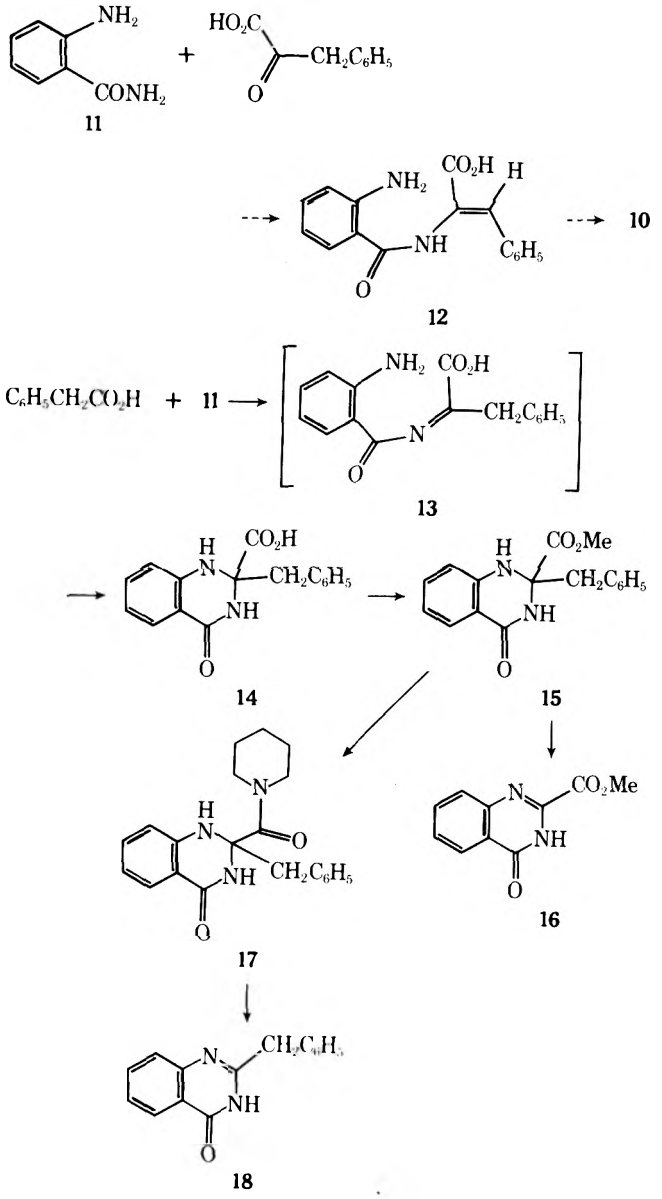
that the biosynthetic pathway to cyclopenin proceeds from **8** to the N(4)-methylated derivative (cyclopeptine) **9**. However, the 3*S* enantiomer of **8**, when treated with a purified enzyme preparation (cyclopeptine dehydrogenase) from *P. cyclopium*, was converted to nordehydrocyclopeptine (**10**) at 60% of the rate at which (3*S*)-**3** is transformed to natural cyclopeptine (**4**),[4] indicating only modest preference by the enzyme for the N-methylated substrate. Efforts directed toward N(4) methylation of **8** in the presence of base failed to yield **9** selectively, affording both O- and N-alkylated products. Furthermore, neither anthranilic acid nor its ester gave any condensation product with esters of *N*-methylphenylalanine. Significantly, it has been found that *N*-methylphenylalanine is not incorporated into cyclopenin.[2]

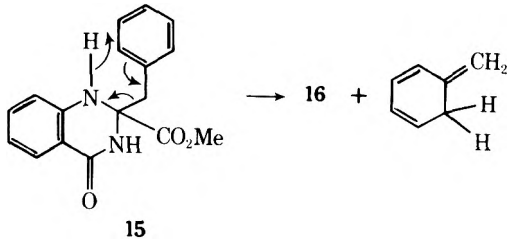
An alternative view of cyclopenin biosynthesis, which is not inconsistent with Luckner's results and which can be extended conceptually to other secondary metabolites derived formally from α,β-dehydroamino acids, involves transamination of an α-keto acid.[10] In the present case, phenylpyruvic acid could undergo *transamidation* with anthranilamide (**11**) to enamide **12**, which might then dehydrate to **10** (Scheme I).[11] Kirby and Narayanaswami[12] have recently shown that [3-^{3}H]phenylalanine is incorporated into cyclopenin with a loss of tritium label consistently in excess of 50%, and they suggested that conversion of phenylalanine to phenylpyruvic acid (and hence its enol) plays a significant role in the biosynthesis of **1**.

When an equimolar mixture of phenylpyruvic acid and anthranilamide (**11**) was heated in benzene, a crystalline condensation product was formed in 93% yield. Spectral data ruled out the expected structure **12** and, with the appearance of an infrared band corresponding to a *saturated* carboxylic acid, suggested the quinazolinone **14**. The latter can be readily

Scheme I



explained, either by assuming initial condensation to give acylimine **13**, which undergoes an internal, conjugate addition by the aromatic amino group, or by the alternate pathway involving a reaction between phenylpyruvic acid and the aromatic amino function of **11**, followed by addition of the amide nitrogen to the resulting imine. Esterification of **14** with diazomethane or with methanol containing sulfuric acid furnished **15**. This ester, upon exposure to refluxing xylene for 48 h, underwent a remarkably facile elimination of toluene to furnish the aromatic quinazolinone derivative **16** in good yield. A rationale for this elimination process is the retro-ene pathway depicted below.[13]



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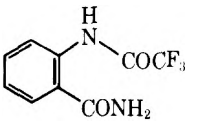
In contrast, the reaction between ester **15** and piperidine in methanol afforded the *N*-acyl derivative **17** which, upon treatment with refluxing acetic acid, yielded crystalline glycosminine (**18**). The latter is a minor alkaloid of the Indian medicinal plant *Glycosmis arborea* (Roxb.)[14] and, although its biogenesis has not been investigated, a plausible origin is the condensation of anthranilic acid or a derivative with phenylalanine (or phenylpyruvic acid), followed by oxidative decarboxylation.

Since the reaction of **11** with phenylpyruvic acid led to a quinazolinone rather than the anticipated benzodiazepine **10**, it was reasoned that modification of the aromatic amino group of **11** in a way that would suppress cyclization of **13** to **14** might permit a subsequent dehydration to the cyclic dipeptide **10**. *N*-Trifluoroacetylanthranilamide (**19**) was prepared,[15] but



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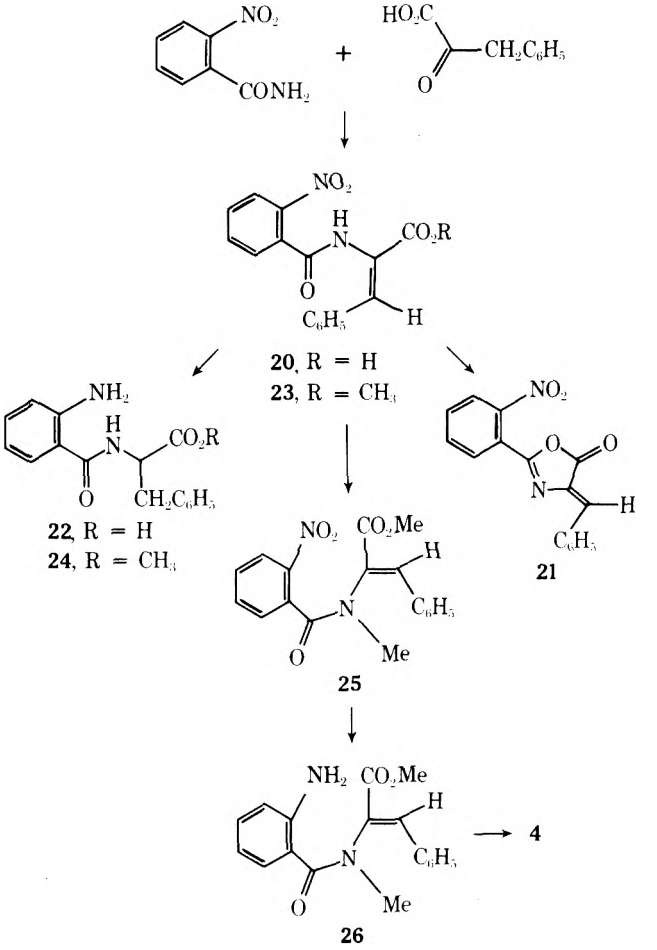
underwent intramolecular condensation to 2-trifluoromethyl-3,4-dihydro-4-quinazolinone in preference to reaction with phenylpyruvic acid. On the other hand, when a mixture of o-nitrobenzamide and phenylpyruvic acid in toluene containing *p*-toluenesulfonic acid was heated, a crystalline solid was precipitated which was readily identified as the desired benzylidenehippuric acid **20** by comparison with material prepared by an alternate route[6a] (Scheme II). Prolonged exposure of these reactants to heat in the presence of acid led to increasing amounts of the oxazolone **21**, derived from **20** by dehydration.

Scheme II



Attempts to selectively reduce the nitro group of **20** by catalytic hydrogenation were unsuccessful, and led uniformly to the saturated derivative **22**. A similar outcome prevailed in the catalytic hydrogenation of ester **23**, prepared from

20 and diazomethane, which gave **24.** Since it was known from earlier studies[6a] that the *N*-methyl derivative (**25**) of **23** underwent selective hydrogenation of the nitro function, the amide **23** was converted to its salt with sodium hydride in DMF and then treated with methyl iodide. The resulting nitro amide **25** was hydrogenated to the amine **26,** which underwent condensation in methanol–piperidine at reflux to dehydrocyclopeptine (**4**). The latter has been previously converted to cyclopenin (**1**) by epoxidation.[6] The diminished reactivity of the double bond in **25** toward hydrogen, as compared with **23,** is attributed to increased steric bulk in the *N*-methyl compound, which forces the cisoid benzamide and phenyl substitutents to rotate out of coplanarity with resulting obstruction of the π system.

In conclusion, synthesis of the benzo-1,4-diazepin-2,5-dione nucleus characteristic of cyclopenin (**1**) and related metabolites via transamidation of phenylpyruvic acid with a benzamide derivative is possible when an ortho amino group in the amide is masked. When this group is free, as in anthranilamide, condensation to give the 2-benzyl-3,4-dihydro-4-quinazolinone system, common to the alkaloids arborine[16] and glycosminine (**18**), takes place.

Experimental Section

Melting points were determined on a Buchi melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 727B spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained on Varian Associates EM-360 and HA-100 spectrometers. Peak positions are given in parts per million (δ) downfield from the internal standard Me_4Si. The abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. The coupling constant (J) is given in hertz. Mass spectra were determined by Dr. Susan Rottschaefer, Department of Chemistry, University of Oregon, using a CEC-103B spectrometer. The abbreviation M^+ refers to the molecular ion.

Ethyl 2-Benzyl-o-aminohippurate (7). A mixture of 1.00 g (6.06 mmol) of ethyl phenylalaninate, 0.83 g (6.06 mmol) of anthranilic acid, and 1.44 g (7.0 mmol) of *N,N'*-dicyclohexylcarbodiimide in 15 mL of acetonitrile was stirred for 4 h. A few drops of acetic acid was added and the precipitated dicyclohexylurea was filtered off. The filtrate was taken up in ethyl acetate and washed once with 1 N hydrochloric acid, twice with saturated potassium bicarbonate, and once with saturated brine. The organic phase was dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was chromatographed on 30 g of Merck silica gel, eluting with benzene, to give 1.52 g (80%) of **7** as an oil: IR (film) 3550, 3400, 1745, 1650, 1620, 1590, 1510 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (3 H, t, J = 7), 3.20 (2 H, d, J = 6), 4.19 (2 H, q, J = 7), 4.99 (1 H, q, J = 6), 5.43 (3 H, br, disappears on addition of D_2O), 6.60 (3 H, m), 7.02 (1 H, m), 7.36 (5 H, br s).

3-Benzyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (8). A mixture of 1.50 g (5.0 mmol) of **7** in 10 mL of methanol and 10 mL of piperidine was heated under reflux for 24 h. The solvent was evaporated in vacuo and the residue was crystallized from acetone to give 0.51 g (38.5%) of **8**: mp 270–272 °C; IR (Nujol) 3200 (br), 1675, 1655 cm^{-1}; NMR (CF_3CO_2D) δ 2.93 (2 H, d, J = 6), 4.00 (1 H, t, J = 6), 6.9–7.7 (11 H, br); m/e 266 (m^+). An analytical sample was prepared by sublimation at 200 °C (0.01 mm).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.18; H, 5.42; N, 10.52.

2-Benzyl-1,2,3,4-tetrahydro-4-oxoquinazoline-2-carboxylic Acid (14). A mixture of 2.00 g (12.2 mmol) of phenylpyruvic acid and 1.80 g (13.2 mmol) of anthranilamide in 100 mL of benzene was heated under reflux for 3 h. Water was collected from the reaction mixture in a Dean–Stark trap. During the reaction a colorless, crystalline deposit formed. After cooling the mixture, the crystalline mass was filtered to give 3.20 g (93%) of virtually pure **14**: mp 182–189 °C; IR (Nujol) 3340, 3295, 1720, 1637, 1612 cm^{-1}; NMR (CD_3SOCD_3) δ 3.2 (2 H, s), 6.4–7.7 (10 H, m), 8.25 (1 H, br s); m/e 282 (M^+).

Methyl 2-Benzyl-1,2,3,4-tetrahydro-4-oxoquinazoline-2-carboxylate (15). A solution of 0.19 g (0.68 mmol) of **14** in 25 mL of methanol containing 2 drops of concentrated sulfuric acid was heated under reflux for 4 h. The mixture was concentrated to a small volume in vacuo and was taken up into ethyl acetate. This solution was washed with saturated sodium bicarbonate and water, and dried ($MgSO_4$). Removal of the solvent in vacuo left a solid residue which was crystallized from acetone–petroleum ether to give 0.145 g (72%) of **15**: mp 182–183 °C; IR (Nujol) 3350, 3175, 1720, 1675, 1620 cm^{-1}; NMR (CD_3COCD_3) δ 3.28 (2 H, s), 3.64 (3 H, s), 6.60–7.78 (11 H, m); m/e 296 (M^+).

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.78; H, 5.47; N, 9.39.

Methyl Quinazolin-4(3*H*)-one-2-carboxylate (16). A solution of 0.068 g (0.23 mmol) of **15** in 5 mL of xylene was heated under reflux for 48 h. After cooling, the mixture was diluted with ether and the crystalline product was collected by filtration. Recrystallization from acetone–petroleum ether yielded 0.025 g (54%) of **16**: mp 209–210 °C (lit.[17] 203–204 °C); IR (Nujol) 3135–3125, 1730, 1655, 1605 cm^{-1}; NMR ($CDCl_3$) δ 4.12 (3 H, s), 7.56–8.46 (5 H, m); m/e 204 (M^+).

2-Benzyl-2-piperidinoxo-1,2,3,4-tetrahydroquinazolin-4-one (17). A solution of 0.40 g (1.35 mmol) of **15** and 5.16 g (60 mmol) of piperidine in 12 mL of dry methanol was heated under reflux for 24 h. The solvent was removed in vacuo and the residue was crystallized from acetone to give 0.39 g (83%) of **17**: mp 186–189 °C; IR (Nujol) 3225, 3160, 1650, 1615 cm^{-1}; NMR (CD_3SOCD_3) δ 1.58 (6 H, br s), 2.90 (2 H, s), 2.97 (4 H, br s), 6.4–7.5 (10 H).

Anal. Calcd for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found: C, 72.04; H, 6.77; N, 11.81.

2-Benzylquinazolin-4(3*H*)-one (Glycosminine, 18). A solution of 1.00 g (2.97 mmol) of **17** in 13 mL of glacial acetic acid was heated under reflux for 4 h. After the mixture had cooled, the crystalline precipitate was filtered and washed with water. Recrystallization from ethanol afforded 0.30 g (43%) of **18**: mp 250–253 °C (lit.[14] 249 °C); IR (Nujol) 1680, 1625 cm^{-1}; NMR (CD_3SOCD_3) δ 3.94 (2 H, s), 7.3–8.2 (10 H); m/e 236 (M^+).

***trans*-2-Benzylidene-*o*-nitrohippuric Acid (20).** A mixture of 6.43 g (39 mmol) of *o*-nitrobenzamide, 9.50 g (58 mmol) of phenylpyruvic acid, and 15.0 g (77 mmol) of *p*-toluenesulfonic acid in 300 mL of toluene was heated under reflux for 4 h. The solvent was concentrated to a small volume in vacuo, and the solid residue was triturated with ether, filtered, and washed with chloroform until colorless. Recrystallization of the collected solid from acetone–petroleum ether gave 5.59 g (47%) of **20**: mp 235–237 °C (lit.[6a] 235–237 °C). This material was identical with **20** prepared by a previously described method.[6a]

The filtrate, after removal of solvent in vacuo, deposited an orange-colored solid which was taken up into hot ethanol. Crystallization at 5 °C overnight gave 2.63 g (23%) of *trans*-2-(*o*-nitrophenyl)-4-benzylidene-3-oxazol-5-one (**21**): mp 147–148 °C (lit.[6a] 151–152 °C). This material possessed chromatographic and spectral (IR, NMR) properties identical with those of authentic material.[6a]

Methyl *trans*-2-Benzylidene-*o*-nitrohippurate (23). To a solution of 0.825 g (2.65 mmol) of **20** in 10 mL of anhydrous methanol was added an excess of diazomethane in ether. After 1 h diazomethane and the solvent were removed by a water aspirator to leave a yellow, crystalline residue. This was taken up into a small volume of acetone, decolorized with charcoal, and recrystallized by addition of petroleum ether to give 0.75 g (87%) of **23**: mp 135–137 °C (lit.[6a] 141.5–143 °C).

Methyl 2-Benzyl-o-aminohippurate (24). A mixture of 0.20 g (0.62 mmol) of **23** and 45 mg of 10% palladium on charcoal in 10 mL of ethyl acetate was hydrogenated at atmospheric pressure. The catalyst was removed by filtration and the filtrate was concentrated to a colorless oil. Thin-layer chromatography showed this to be pure **24**: yield 0.18 g (100%); IR (film) 3450–3345, 1730, 1640 cm^{-1}; NMR ($CDCl_3$) δ 3.23 (2 H, d, J = 6), 3.78 (3 H, s), 5.03 (1 H, q, J = 6); m/e 298 (M^+).

An analogous procedure was followed for hydrogenation of **20** and afforded **22** (100%) as a colorless oil: IR (Nujol) 3500 (br), 1715, 1670, 1630 cm^{-1}; NMR (CD_3SOCD_3) δ 3.10 (2 H, d, J = 6), 4.55 (1 H, q, J = 6).

Acknowledgments. We are grateful to Dr. Walter E. Haefliger for preliminary experiments and to the National Science Foundation for financial support.

Registry No.—**1**, 20007-87-8; **6**, 3081-24-1; **7**, 32771-73-6; **8**, 24919-39-9; **14**, 63569-80-2; **15**, 63569-81-3; **16**, 63569-82-4; **17**, 63569-83-5; **18**, 4765-56-4; **20**, 25673-46-5; **22**, 63569-84-6; **23**, 25673-45-4; **24**, 63569-85-7; phenylpyruvic acid, 156-06-9; anthranilic acid, 118-92-3; anthranilamide, 88-68-6; piperidine, 110-89-4; *o*-nitrobenzamide, 610-15-1.

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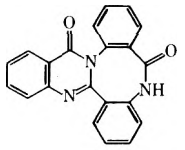

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Synthetic Approaches to Adriamycin. 2. Degradation of Daunorubicin to a Nonasymmetric Tetracyclic Ketone and Refunctionalization of the A Ring to Adriamycin

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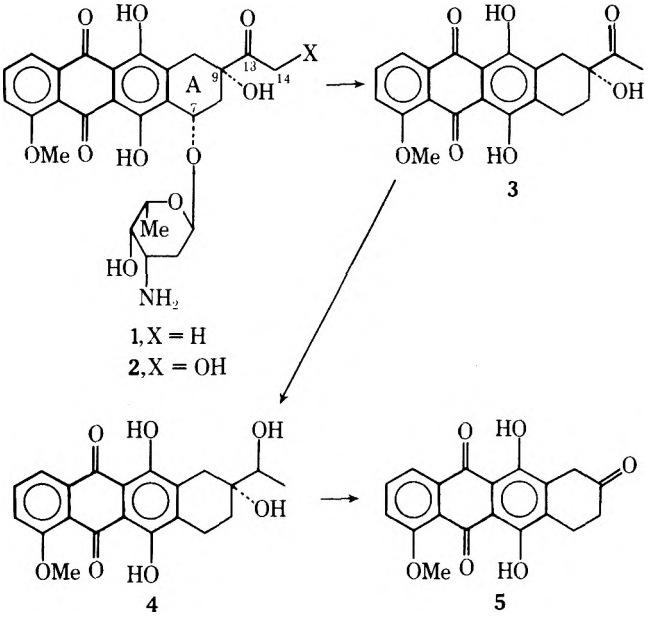
A synthesis of adriamycin (**2**) via elaboration of the functionalities at the 7 and 9 positions of the nonsymmetric tetracyclic ketone **5** is described. Daunorubicin (**1**) was degraded in high yield to **5** by a three-step procedure. Addition of HCN to **5** afforded the cyanohydrin **18**. The 9-OH was protected by conversion to the THP ether **19**, which afforded (±)-7-deoxydaunomycinone (**20**) upon reaction with excess MeMgI followed by acid workup. Model studies employing β-tetralones **6a** and **6b** as substrates showed this sequence to be superior to several other potential methods of side-chain elaboration. Stepwise stereo- and regiospecific hydroxylation of the 7 and 14 positions of 7-deoxydaunomycinone (**3**) afforded adriamycinone (**29**). By a minor modification of the 7-hydroxylation procedure, 7-epidaunomycinone (**27**) is obtained as the major product. The 14-OH was protected by conversion to the *p*-anisyldiphenylmethyl ether **30**. This was condensed with the protected 1-chlorodaunosamine derivative **36** under Koenigs–Knorr conditions to afford adriamycin (**2**) after deprotection.

The anthracycline antibiotics daunorubicin (**1**)[2] and adriamycin (**2**)[3] are clinically useful antineoplastic agents, with adriamycin having an especially broad spectrum of activity. However, chemotherapy employing these drugs is hampered by a number of undesirable side effects, the most serious being dose-related cardiotoxicity.[3b,4] As part of this laboratory's ongoing efforts to prepare anthracyclines having improved therapeutic properties, the possibility of developing a practical total synthesis of **2** was investigated. We now report the results of those studies.

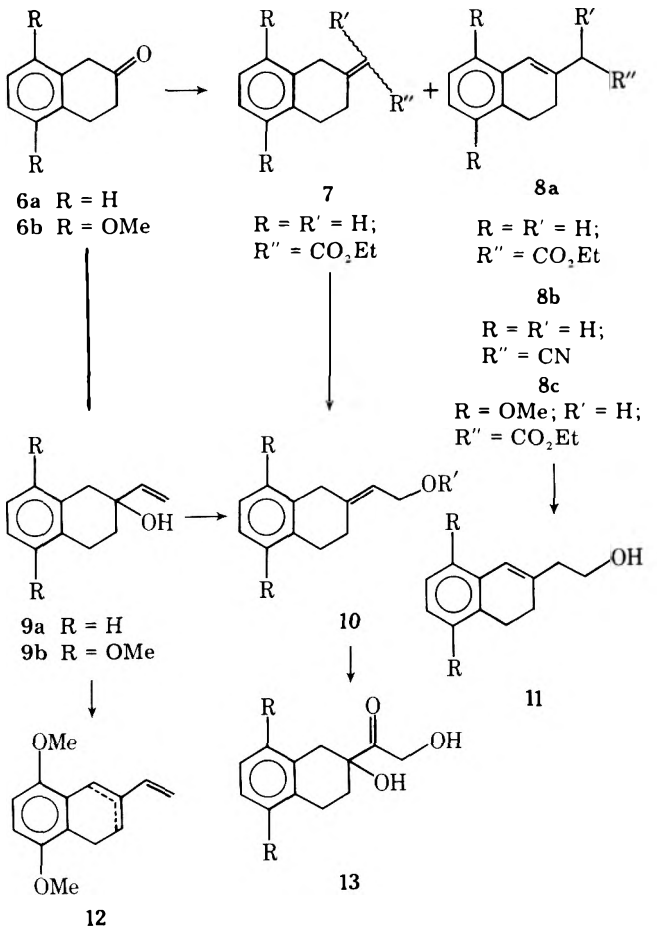
Due to the important biological activities of **1** and **2** considerable interest has been shown in their synthesis and several aspects have been explored.[1,5] Since practical syntheses of the daunosamine sugar moiety[5c,f] and a circuitous synthesis of the aglycone[5b] had been reported, the formal total synthesis of **1** was completed in 1974 with the report of stereospecific coupling of the aglycone and sugar moiety.[1c] In this paper, we describe the elaboration of the tetracyclic nonasymmetric ketone **5** to adriamycin (**2**). In our work, **5** was obtained by degradation of daunorubicin, but a total synthesis of **5** which was subsequently elaborated to (±)-daunomycinone was recently described by Kende et al.[5a] via a Diels–Alder sequence, an approach that has received much recent attention.[6]

Treatment of daunorubicin (**1**) with sodium dithionite (Scheme I) resulted in reductive cleavage of the glycoside bond to afford 7-deoxydaunomycinone (**3**) in quantitative yield. Reduction of the 13-carbonyl was achieved with $LiAl(t\text{-}BuO)_3H$ in THF to afford the 13-dihydro compound **4** as a diastereomeric mixture in 80% yield. Periodate cleavage of the glycol was unusually slow, requiring 2 equiv of $NaIO_4$ at 23 °C for 16 h to produce a 99% yield of **5** with 71% conversion of **4**.

Scheme I



Scheme II



Having the tetracyclic ketone **5** in hand, several problems remained to be solved to allow its successful elaboration to **2**. Methods for the elaboration of the dihydroxyacetone side chain from the 9-keto function and for the regio- and stereospecific hydroxylation of the 7 position needed to be developed. The dihydroxyacetone side chain had to be blocked in such a way as to direct the sugar moiety to the 7 position during coupling and to protect the side chain during the alkaline deprotection of the sugar. However, the protecting group must be removable under conditions compatible with the acid-sensitive glycoside bond.

A number of possible methods of side-chain elaboration were evaluated using β-tetralone (**6a**) and 5,8-dimethoxy-2-tetralone (**6b**)[7] as model compounds. In general, these methods could be classified either as two-carbon homologations in which the potential 13- and 14-carbon atoms are introduced in a single operation and the resultant intermediate is subsequently transformed by conventional operations to the desired target (Scheme II), or two sequential one-carbon homologations in which the side-chain carbon atoms are introduced in discrete steps.

In the first of the two-carbon homologation sequences that we explored the ketone was to be converted to an exocyclic α,β-unsaturated ester such as **7**. The ester could then be reduced, the primary hydroxyl protected, and the olefin oxidized with the OsO_4–*N*-methylmorpholine–H_2O_2 reagent[8] to afford **13**. The reaction of β-tetralone (**6a**) with the sodio anion of triethyl phosphonoacetate proceeded smoothly to afford a single homogeneous (TLC, GLC) product with spectral properties (NMR, IR, MS) in apparent agreement with those expected of **7**. Reduction of this material with $LiAlH_3OEt$[9] afforded a single product in good yield. However, in the ^1H NMR spectrum of this material the new methylene protons appeared as a triplet instead of the doublet expected for **10**.

Table I. ^1H NMR Analysis of the Products of the Wadsworth–Emmons Condensation

	Chemical shift, δ		
	Olefinic	Methylene singlet	
Compd	proton	Found	Calcd
8a	6.29	3.18	3.10
7	5.80	3.52	3.34
11	6.29		

This indicated that the reduction product was the alcohol **11** and cast doubt on the identity of the condensation product of the Wadsworth–Emmons reaction. Reexamination of the ^1H NMR spectrum (Table I) of this material indicated its correct structure to be **8a**. This was assigned on the basis of the identical chemical shifts of the olefinic protons of the ester and **11** and the correlation of the chemical shift of the methylene singlet of the product with that calculated for a methylene flanked by a phenyl group and a carbon–carbon double bond[10] (see Table I).

Isomerization of the olefinic double bond into conjugation with an aromatic moiety during the Wadsworth–Emmons reaction has previously been reported and successfully suppressed by modifying the reaction conditions.[11] In this case, upon lowering the reaction temperature from 23 to 0 °C a new product in approximately a 1:3 ratio with **8a** was detected by GLC. While separation on a preparative scale could not be achieved, the ^1H NMR spectrum of the mixture showed two new signals at δ 3:52 and 5.80 corresponding to the methylene and olefinic protons of **7**. The ratio of **7** to **8a** could be improved by the use of less polar solvents, e.g., ether or benzene, and further lowering of the reaction temperature, but the overall yield of ester fell to unacceptable levels.

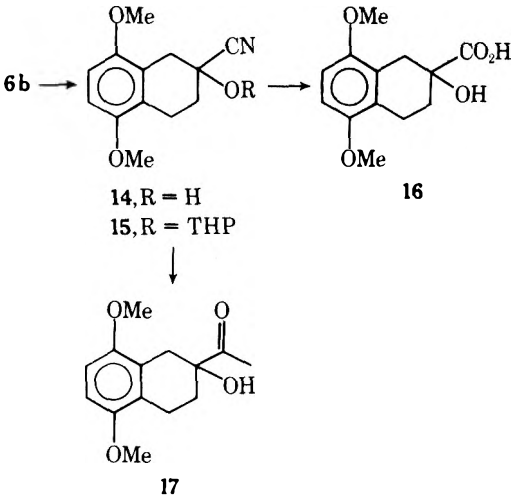
To evaluate the possibility of stabilizing the thermodynamically less favored exocyclic isomer through variation of R″, the reaction of β-tetralone with the anion of diethyl cyanomethylphosphonate in THF at 0 °C was examined and found to afford the endocyclic olefin **8b** exclusively. While the electron-releasing methoxy groups of **6b** might be expected to suppress the double-bond isomerization observed in the reactions of **6a**, the condensation of **6b** with the sodio anion of triethyl phosphonoacetate at 0 °C afforded only the endocyclic olefin **8c**.

Although the reaction of carbethoxymethylenetriphenylphosphorane with ketones is generally considered to be inferior to the Wadsworth–Emmons reaction as a method for the synthesis of α,β-unsaturated esters,[12] it was hoped that the absence of base would serve to suppress the isomerization of the olefinic bond. The phosphorane and β-tetralone were reacted under nitrogen at 110 °C without solvent to afford exclusively the endocyclic olefin **8a** in 76% yield. Reaction of β-tetralone with the lithium enolates of ethyl and *tert*-butyl trimethylsilylacetates[13] afforded only starting material.

Both the Wadsworth–Emmons and Wittig condensations appear to be excellent methods for effecting the required two-carbon homologation. However, at least in the models examined, the isomerization of the resultant olefin to the thermodynamically more stable endocyclic isomer poses serious problems in the subsequent synthetic steps leading to side-chain formation.

In another two-carbon homologation sequence that we explored, the keto function is transformed to a tertiary vinyl carbinol such as **9** via 1,2 addition. This intermediate could then be rearranged to an exocyclic olefin acetate **10** (R′ = Ac)[14] suitable for subsequent elaboration to the side chain. Reaction of vinylmagnesium chloride with **6a** and **6b** afforded the vinyl carbinols **9a** and **9b** in 34 and 45% yield, respectively, along with substantial amounts of unreacted ketone. The recovery

Scheme III

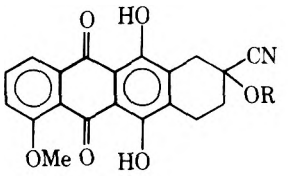


of starting material was probably due to base-catalyzed enolization of the starting ketone. Consistent with this explanation was the observation that only starting material could be recovered from the reaction of the more basic reagent, vinyllithium, with the model ketones. This problem was again encountered in the use of acyl anion equivalents such as 2-lithio-2-methyl-1,3-dithiane and α-methoxyvinyllithium[15] which also afforded only starting material upon reaction with **6a**.

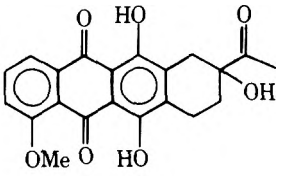
Initial attempts to effect allylic rearrangement of **9b** to **10** with HOAc afforded diene **12** as the major product. This result, together with the rather poor yield of the vinyl carbinols, caused us to drop this approach.

The ultimately successful route involved two sequential one-carbon homologations (Scheme III). 5,8-Dimethoxy-2-tetralone (**6b**) was readily converted to the cyanohydrin **14** which afforded the hydroxyacid **16** in high yield upon acid hydrolysis. However, reaction of **16** with methyllithium failed to yield any significant amounts of **17**. Conversion of **14** to its tetrahydropyranyl ether **15** was accomplished in 77% yield and subsequent reaction of **15** with excess methylmagnesium iodide produced **17** in 64% yield.[16] The trimethylsilyl and *tert*-butyldimethylsilyl protecting groups were less satisfactory; in the former case loss of the protecting group was observed during the Grignard reaction, while in the latter the silylation reaction was so slow as to render this approach impractical.

This sequence was also successful when applied to the tetracyclic ketone **5**. (±)-7-Deoxydaunomycinone (**20**) was obtained via the intermediates **18** and **19** in a 36% overall yield from **5**. In their synthesis of (±)-daunomycinone, Kende et al.[5a] elaborated the side chain via addition of ethynylmagnesium bromide to **5** followed by hydration of the triple bond.



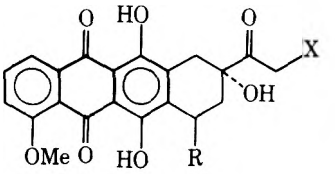
18, R = H
19, R = THP



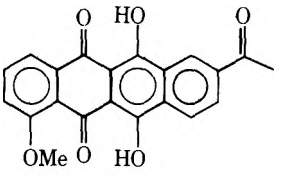
20

Hydroxylation of the 7 and 14 positions of **20** would afford (±)-adriamycinone which would lead to a mixture of diastereomers upon coupling with daunosamine. To avoid this complication, subsequent experiments were performed using 7-deoxydaunomycinone (**3**) obtained by reductive cleavage of **1**.

The 14-hydroxylation of **3** via ionic bromination with pyrrolidone hydrotribromide in THF to afford **21**, and subsequent reaction of **21** with 1 equiv of NaOH in aqueous acetone to produce 7-deoxyadriamycinone (**22**) proceeded readily. However, as **3** was more soluble than **22** in organic solvents, we chose to introduce the 7-hydroxyl first.



21, X = Br; R = H
22, X = OH; R = H
23, X = H; R = ~Br
24, X = H; R = ~OAc
25, X = H; R = ~OCOCF$_3$
26, X = H; R = ···OH
27, X = H; R = –OH
28, X = Br; R = ···OH
29, X = OH; R = ···OH
30, X = OC(Ph)$_2$-*p*-OMeC$_6$H$_4$; R = ···OH



31

A model for the hydroxylation of the 7 position of **3** (benzylic bromination, AgOAc displacement, transesterification with F_3AcOH, methanolysis) was first provided Goodman et al.[17] with a simplified daunomycinone analogue and by Wong et al.[5b] who used a closely related sequence in the first daunomycinone synthesis. Bromination of **3** with several reagents afforded, besides bromide **23**, considerable amounts of unreacted **3** and bis(anhydro)daunomycinone (**31**), presumably arising from aromatization of **23**. Efforts to achieve complete reaction resulted in increased yields of **31** at the expense of **23**. Although this problem was not fully overcome, the benzylic bromination was achieved most satisfactorily by using Br_2 (1.5 equiv) in refluxing CCl_4 with 2,2′-azobis(isobutyronitrile) (ABN) as catalyst. Wong[5b] postulated that steric hindrance about the 10 position allows benzylic bromination to proceed regiospecifically at the 7 position. 14-Bromo-7-deoxydaunomycinone (**21**), arising from ionic bromination of the 14 position, was not observed in the reactions of **3** with Br_2, NMe_4Br_3, or NBS in CCl_4. However, **21** was formed exclusively upon treatment of **3** with Br_2 or NMe_4Br_3 in $CHCl_3$, regardless of the presence of radical initiators.

The unstable bromide **23**, without isolation, could be converted to the acetate **24** with excess AgOAc in refluxing HOAc. However, subsequent transesterification to **25** (F_3AcOH, 48 h, 23 °C) was incomplete, as **24** was always detectable in the reaction mixture after methanolysis (MeOH, 23 °C, 4 h).

This problem was avoided by converting **23** directly to trifluoroacetate **25** with $NaOCOCF_3$ in Me_2SO[18] (16 h, 23 °C). Intermediates **23** and **25** were used without purification because of their instability. 7-Deoxydaunomycinone (**3**) was brominated, treated with $NaOCOCF_3$, and subjected to methanolysis as a continuous operation. Chromatography of the methanolysis product on silica gel afforded, in order of elution, bis(anhydro)daunomycinone (**31**), starting material (**3**, 17%), daunomycinone (**26**, 9%), and 7-*epi*-daunomycinone (**27**, 35%).

Characterization of **27** was based on its ^1H NMR spectra. The benzylic H-7 proton signal appeared as a multiplet at δ

5.42 ($\nu_{1/2}$ = 17 Hz) characteristic of an axial proton.[19] The spectrum of daunomycinone is similar except that the H-7 signal appears as a narrower ($\nu_{1/2}$ = 7 Hz) multiplet due to the equatorial orientation of H-7. The mass spectrum and elemental analysis of **27** showed it to be isomeric with daunomycinone.

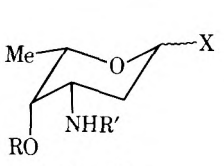
Anthracyclinones having an axial proton at C-7 have been epimerized with acid.[18] To obtain aglycone possessing the natural stereochemistry, the crude trifluoroacetate **25** was dissolved in F_3AcOH (23 °C, 1.5 h) before methanolysis. Silica gel chromatography of this crude product afforded **31**, starting material (**3**, 18%), daunomycinone (**26**, 35%), and 7-*epi*-daunomycinone (**27**, 6%). Reaction of **26** with bromine in $CHCl_3$[5h] afforded 14-bromodaunomycinone (**28**) which was treated directly with 1 equiv of NaOH in aqueous acetone to afford adriamycinone (**29**) in 87% yield.

The partial stereospecificity of the 7-hydroxylation can be explained by an S_N1 mechanism for the $NaOCOCF_3$ displacement. Approach of the trifluoroacetate anion to the planar benzylic carbonium ion arising from ionization of the bromide **23** should be more favorable from the side trans to the axial hydroxyl at C-9. Methanolysis would then result in the observed predominant formation of **27** over **26**.

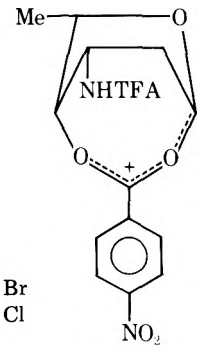
The problem of protecting the dihydroxyacetone side chain was solved via conversion of **29** to the monomethoxytrityl ether **30** in 84% yield. We elected to use **30** since it could be prepared in high yield without the formation of diastereomers, and probe experiments demonstrated that it could be removed without affecting the glycosidic bond. The highly lipophilic trityl moiety also facilitated the separation of the glycoside from the water-soluble sugar by-products of the coupling reaction by simple solvent extraction.

In alternative approaches to this problem, Arcamone et al.[5e] bridged the 9,14-diol system with an orthoester to provide side-chain protection during removal of an *N*-trifluoroacetyl group. The same investigators also employed a double ketal system in coupling work with 4-*epi*-daunosamine[5i] as well as daunosamine.[5e]

The sugar moiety was protected as previously described.[1c] Reaction of daunosamine (**32**) with *S*-ethyl trifluorothioacetate afforded *N*-trifluoroacetyldaunosamine (**33**) which upon treatment with *p*-nitrobenzoyl chloride in pyridine afforded the α anomer of **34** in 93% yield. Saturation of a suspension of **34** in CH_2Cl_2 with the appropriate hydrogen halide afforded **35** or **36** after filtration to remove the precipitated *p*-nitrobenzoic acid and evaporation. The crude 1-halo sugars so obtained were added to the reaction mixture without further purification.



32, R = R′ = H; X = OH
33, R = H; R′ = CF_3CO; X = OH
34, R = *p*-$NO_2C_6H_4CO$; R′ = CF_3CO; X = *p*-$NO_2C_6H_4CO_2$
35, R = *p*-$NO_2C_6H_4CO$; R′ = CF_3CO; X = Br
36, R = *p*-$NO_2C_6H_4CO$; R′ = CF_3CO; X = Cl
37, R = R′ = CF_3CO; X = Cl



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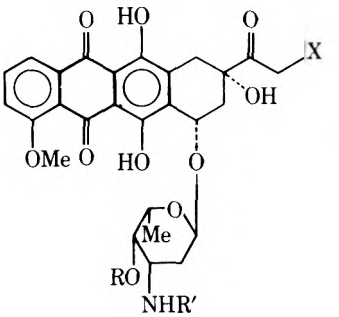
Previous work from this laboratory established that the daunosaminyl bromide derivative **35** coupled stereospecifically with daunomycinone, giving only the α anomer.[1c] Arcamone et al.[5e] found that the chloro derivative **37** provided a 7:3 ratio of α to β anomers in the same reaction.

Good precedent for steric control by a 4-*O*-*p*-nitrobenzoyl group in the coupling reactions of related sugars to give trans C-4, C-1 products is provided by the work of Dejter-Juszynski and Flowers.[20] They have also shown that a 4-*O*-acetyl group, while still exerting considerable steric control, is somewhat less effective in directing the steric course of the glycosidation.[21] Presumably, the carbonyl oxygen provides anchimeric assistance to the halide displacement, allowing the coupling to proceed via a 7-membered *p*-nitrobenzoyloxonium intermediate such as **38**. The poorer stereospecificity observed[5e,22] with the 4-*O*-trifluoroacetyl derivative **37** is consistent with this argument, as the greater electron withdrawing power of the trifluoromethyl group should inhibit participation of the carbonyl oxygen.

For the present work we have preferred to use **36**, retaining the *O*-*p*-nitrobenzoate for stereospecificity and the 1-chloro for greater stability toward elimination and adventitious hydrolysis during handling. The chloro sugar **36** is superior to **35** in the coupling with daunomycinone affording **39** in 77% yield, as opposed to the 53% yield obtained from **35**.



39, X = H; R = *p*-$NO_2C_6H_4CO$; R′ = CF_3CO
40, X = $OC(Ph)_2$-*p*-$OMeC_6H_4$; R = *p*-$NO_2C_6H_4CO$; R′ = CF_3CO
41, X = $OC(Ph)_2$-*p*-$OMeC_6H_4$ R = R′ = H

The protected aglycone **30** was condensed with **36** under Koenigs–Knorr conditions to afford exclusively α-glycoside **40**. The unpurified product was deacylated with 0.1 N NaOH in aqueous THF at 0 °C to afford **41** which could be separated from the water-soluble sugar by-products of the coupling reaction by extraction with $CHCl_3$.

Treatment of **41** with 80% HOAc afforded adriamycin (**2**) which was isolated as the hydrochloride in 40% yield from **30**. This material is identical in all respects, including biological activity as measured by inhibition of DNA and RNA synthesis of cultured L-1210 cells, with the natural product. The synthetic material provided ED_{50} values of 1.5 and 0.44 μM for DNA and RNA synthesis, respectively, as compared with 1.5 and 0.58 μM values from the natural product.

Experimental Section

Melting points are uncorrected. Ultraviolet–visible spectra, infrared spectra, and 60-MHz ^{1}H NMR measurement were made by the Pharmaceutical Analysis Department under the direction of Dr. Peter Lim. Measurements of 100-MHz ^{1}H NMR were performed by Mr. L. Cary using a Varian XL-100 spectrometer. The NMR spectra were measured in $CDCl_3$ with tetramethylsilane as an internal standard and the IR spectra were measured from Nujol mulls unless otherwise noted. Elemental microanalyses were provided by Ms. E. M. McCarthy (SRI) or the microanalytical laboratory of Stanford University. Mass spectra were recorded by Dr. D. W. Thomas on an LKB Model 9000 mass spectrometer at 70 eV unless otherwise stated.

Thin-layer chromatograms (TLC) were obtained on 250-μm silica gel G or H plates. Preparative layer chromatograms (PLC) were obtained on 20 × 20 × 0.2 silica gel 60 F-254 plates (E. Merck). Column chromatography was performed with Bio Sil A 200–305 mesh (Bio-Rad) or E. Merck prepacked silica gel 60 columns. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ immediately prior to use. Solvent extracts of aqueous solutions were dried over anhydrous Na_2SO_4. Petroleum ether refers to the fraction boiling from 30 to 60 °C, unless

otherwise stated. Solutions were concentrated under reduced pressure using a rotary evaporator.

7-Deoxydaunomycinone (3). To daunorubicin hydrochloride (1, 5.0 g, 8.87 mmol) in THF (100 mL)/MeOH (120 mL) under N_2 was added a solution of $Na_2S_2O_4$ (3.09 g, 17.8 mmol) and $NaHCO_3$ (5.96 g, 71.0 mmol) in H_2O (120 mL) over 5 min. The mixture was stirred for 15 min at 23 °C, poured into ice-water (250 mL), and extracted with CH_2Cl_2 (8 × 75 mL). The extracts were combined, dried, and evaporated to afford 3.85 g (99%) of **43**; mp 229–231 °C; IR 2.85 (OH), 5.85 (C=O), 6.19, 6.29 μm (H-bonded quinone); NMR δ 1.95 (m, 2 H, 8-H_2), 2.42 (s, 3 H, Ac), 3.00 (m, 4 H, 7 and 10-H_2), 3.84 (br s, 1 H, 9-OH), 4.10 (s, 3 H, OMe), 7.36 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.73 (t, 1 H, J = 8 Hz, 2 H), 7.99 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.37 (s, 1 H, phenolic OH), 13.79 (s, 1 H, phenolic OH); MS *m/e* (%), 383 (9), 382 M (33), 364 (6), 340 (21), 339 (100), 321 (13), 43 (13).

Anal. Calcd for $C_{21}H_{18}O_7 \cdot 0.5H_2O$: C, 64.45, H, 4.91. Found: C, 64.71; H, 4.75.

7-Deoxy-13-dihydrodaunomycinone (4). 7-Deoxydaunomycinone (**3**, 300 mg, 0.79 mmol) and LiAl(*t*-BuO)$_3$H (480 mg, 1.84 mmol) were stirred in THF (30 mL) under N_2 for 6 h. Additional LiAl(*t*-BuO)$_3$H (120 mg) was added, and after 16 h a third portion of LiAl(*t*-BuO)$_3$H (240 mg) was introduced. After the last addition, stirring was continued for 24 h. The reaction mixture was poured into 2 N HCl (50 mL) and heated on the steam bath for 1 h. The mixture was allowed to cool and extracted with CH_2Cl_2 (three 40-mL portions). The extracts were combined, dried, and evaporated. The residue was recrystallized from CH_2Cl_2/$CHCl_3$ to afford 161.6 mg of **4**. The mother liquors were evaporated and the residue was chromatographed (PLC silica gel, 93:7 $CHCl_3$/MeOH) to afford 35.4 mg of starting material **3** and an additional 79.5 mg of **4**. Combined yield was 240.1 mg (80%) of **4**: mp 230–233 °C; IR 2.85 (OH), 6.20, 6.30 μm (chelated quinone); MS *m/e* (%), 385 (18), 384 M (94), 340 (25), 339 (100); NMR δ 1.87 (two overlapping doublets, 3 H, 14-H_3), 2.06 (m, 2 H, 8-H_2), 2.63 (d, 1 H, J = 19 Hz, 10β-H), 2.8–3.1 (m, 3 H, 10α-H and 7-H_2), 3.79 (q, 1 H, 13-H), 4.11 (s, 3 H, OMe), 7.37 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.75 (t, 1 H, J = 8 Hz, 2-H), 8.03 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.48 (s, 1 H, phenolic OH), 13.84 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.61; H, 5.25. Found: C, 65.28; H, 5.39.

7,8-Dihydro-6,11-dihydroxy-4-methoxy-5,9(10*H*),12-naphthacenetrione (5). To 7-deoxy-13-dihydrodaunomycinone (**4**, 377.6 mg, 0.98 mmol) in THF (60 mL) was added $NaIO_4$ (462 mg, 2.16 mmol) in 50% aqueous MeOH (2 mL). The solution was stirred under N_2 for 16 h at 23 °C. The reaction mixture was concentrated to ca. 10 mL and extracted with CH_2Cl_2 (two 30-mL portions). The extracts were combined, dried, and evaporated. The residue was chromatographed (40 g of Bio Sil A, 98:2 $CHCl_3$/MeOH) to afford in order of elution 237.2 mg (99% yield, 71% conversion) of **4**: IR 5.82 (C=O), 6.15, 6.35 μm (H-bonded quinone); NMR δ 2.64 (t, 2 H, 8-H_2), 3.25 (t, 2 H, 7-H_2), 3.61 (s, 2 H, 10-H_2), 4.09 (s, 3 H, OMe), 7.38 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.77 (t, 1 H, J = 8 Hz, 2-H), 8.04 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.30 (s, 1 H, phenolic OH), 13.80 (s, 1 H, phenolic OH); MS 12 eV *m/e* (%) 338 M (100).

Anal. Calcd for $C_{19}H_{14}O_6 \cdot 0.5H_2O$: C, 65.7; H, 4.35. Found: C, 66.1; H, 4.49. Further elution afforded 110.6 mg of starting material **4**.

Ethyl 3,4-Dihydro-2-naphthylacetate (8a). Sodium hydride (0.865 g of 57% dispersion in mineral oil, 20.6 mmol) was placed in THF (60 mL) and cooled to 0 °C. Triethyl phosphonoacetate (4.60 g, 20.6 mmol) in THF (5.0 mL) was added dropwise with stirring. After the addition was complete, stirring was continued at 0 °C for 0.5 h when a homogenous solution formed. β-Tetralone (**6a**, 3.00 g, 20.6 mmol) in THF (5 mL) was added dropwise. After the addition was complete, stirring was continued at 0 °C for 0.5 h, at 23 °C for 3 h and at reflux for 0.5 h. The reaction mixture was allowed to cool and quenched with H_2O (200 mL), and the mixture was extracted with $CHCl_3$ (four 25-mL portions). The extracts were combined, dried, and evaporated. The residue was chromatographed (300 g of Bio Sil A, benzene) to yield 3.53 g (80%) of **8a**: IR (neat) 5.75 (C=O), 6.03 (C=C), 7.98, 8.45, 8.65 (COC), 9.65, 13.18 μm (Ar); NMR δ 1.23 (t, 3 H, $CO_2CH_2CH_3$), 2.31 (t, 2 H, 3-H_2), 2.81 (t, 2 H, 4-H_2), 3.18 (s, 2 H, CH_2CO_2), 4.14 (q, 2 H, $CO_2CH_2CH_3$), 6.29 (s, 1 H, 1-H), 7.03 (s, 4 H, Ar H's); MS *m/e* (%) 216 M (27), 143 (83), 142 (90), 141 (78), 128 (100), 115 (22).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.7; H, 7.44. Found: C, 77.3; H, 7.18.

2-Cyanomethyl-3,4-dihydronaphthalene (8b). Sodium hydride (0.433 g of 57% dispersion in mineral oil, 10.3 mmol) was placed in THF (60 mL) and cooled to 0 °C. Diethyl cyanomethylphosphonate (1.82 g, 10.3 mmol) in THF (5 mL) was added dropwise with stirring which was continued for 15 min at 0 °C when a homogeneous solution formed. β-Tetralone (**6a**, 1.50 g, 10.3 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h and at 25 °C for 2.5 h. The reaction mixture was poured into ice/H_2O (200 mL) and extracted with $CHCl_3$ (three 50-mL portions). The extracts were combined, dried, and evaporated. The residue was chromatographed (100 g of Bio Sil A, 1:1 petroleum ether/benzene) to afford 1.55 g (89%) of **8b**: IR (neat) 4.40 (CN), 6.72 (Ar), 13.16 μm; NMR δ 2.30 (t, 2 H, 3-H_2), 2.88 (t, 2 H, 4-H_2), 3.21 (d, 2 H, J = 1 Hz, CH_2CH), 6.52 (t, 1 H, J = 1 Hz, 1-H), 7.12 (s, 4 H, Ar H's); MS *m/e* (%) 170 (4), 169 M (29), 141 (10), 130 (9), 129 (100), 128 (28), 127 (11).

Anal. Calcd for $C_{12}H_{11}N \cdot 0.25H_2O$: C, 82.95; H, 6.68; N, 8.06. Found: C, 83.29; H, 6.79; N, 8.09.

Ethyl 3,4-Dihydro-5,8-dimethoxy-2-naphthylacetate (8c). In a procedure similar to that described above, 5,8-dimethoxy-2-tetralone (**6b**, 2.0 g, 9.72 mmol) was reacted with an equivalent amount of the sodio anion of triethyl phosphonacetate to afford 1.96 g (74%) of **8c**: IR (neat), 5.72 (C=O), 6.00 (C=C), 6.71, 7.95, 8.48, 8.62 (COC), 9.15, 9.25, 9.65, 12.60, 13.25, 13.95 μm (Ar); NMR δ 1.23 (t, 3 H, $CO_2CH_2CH_3$), 2.28 (m, 2 H, 3-H_2), 2.82 (m, 2 H, 4-H_2), 3.22 (s, 2 H, CH_2CO_2Et), 3.79 (s, 6 H, OMe), 4.17 (q, 2 H, $CO_2CH_2CH_3$), 6.68 (s, 3 H, 1-H and Ar H's); MS *m/e* (%) 277 (11), 276 M (67), 203 (63), 202 (26), 201 (15), 189 (16), 188 (53), 187 (21), 173 (25), 171 (19), 86 (65), 84 (100), 49 (17), 47 (20).

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.31. Found: C, 69.19; H, 7.11.

3,4-Dihydro-2-(2′-hydroxyethyl)naphthalene (11). To $LiAlH_4$ (0.6 g, 15.8 mmol) in ether (50 mL) was added EtOH (0.92 mL, 15.8 mmol) in ether (10 mL). This reagent was added in 0.5-mL portions at 0.5-h intervals to a stirred solution of ethyl 3,4-dihydro-2-naphthylacetate (**8a**, 107.1 mg, 0.496 mmol) in ether (5 mL). After 2.5 h, the reaction was complete as judged by TLC. Excess reagent was destroyed by addition of EtOAc (5 mL) followed by H_2O (5 mL). The mixture was filtered and diluted with $CHCl_3$. The organic phase was separated and the aqueous phase extracted with $CHCl_3$ (10 mL). The organic solutions were combined, dried, and evaporated to afford 59.8 mg (69%) of **11**: IR (neat) 2.95 (OH), 9.62, 13.22 μm (Ar); NMR δ 2.1–2.9 (m, 6 H, 1-, 3-, and 4-H_2's), 3.76 (t, 2 H, 2′-H_2), 6.26 (s, 1 H, 1-H), 7.02 (s, 4 H, Ar H's).

This material was further characterized as the *p*-nitrobenzoate: mp 93–94 °C; IR 5.78 (C=O), 6.17 (C=C), 7.25, 7.40, 7.85 (COC), 8.90, 9.05, 13.00, 13.90, 14.00 μm (Ar); NMR δ 2.1–3.0 (m, 6 H, 1′-, 3- and 4-H_2's), 4.52 (t, 2 H, 2′-H_2), 6.26 (s, 1 H, 1-H), 7.02 (s, 4 H, Ar H's), 8.19 (s, 4 H, PNB Ar H's); MS *m/e* (%) 323 M (1), 157 (11), 156 (100), 141 (21), 128 (29), 115 (14).

Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.29; N, 4.33. Found: C, 70.44; H, 5.57; N, 4.46.

1,2,3,4-Tetrahydro-2-hydroxy-2-vinylnaphthalene (9a). To vinylmagnesium chloride (1.00 mL of 2.3 M solution in THF, 2.23 mmol) under N_2 at 0 °C was added β-tetralone (150.4 mg, 1.03 mmol) dropwise and the mixture was stirred at 0 °C for 1 h and at 23 °C for 16 h. The reaction mixture was cooled to 0 °C and saturated NH_4Cl was added dropwise until vigorous reaction subsided. Additional saturated NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (two 10-mL portions). The extracts were combined, dried, and evaporated. The residue was chromatographed (PLC 9:1 $CHCl_3$/EtOAc) to afford 40.4 mg (39%) of **9a**: IR (neat) 3.10 (OH), 10.00, 10.80, 13.20, 13.50 μm (Ar); NMR δ 1.88 (t, 2 H, 3-H_2), 2.89 (m, 4 H, 1- and 4-H_2), 5.09 (dd, 1 H, J = 10 and 1.5 Hz, 2′-*cis*-H), 5.27 (dd, 1 H, J = 17 and 1.5 Hz, 2′-*trans*-H), 6.06 (dd, 1 H, J = 17 and 10 Hz, 1′-H), 7.09 (s, 4 H, Ar H's); MS *m/e* (%) 175 (3), 174 M (20), 159 (16), 156 (21), 145 (18), 141 (12), 129 (14), 128 (31), 119 (16), 117 (15), 115 (28), 105 (20), 104 (100), 103 (20), 91 (22), 85 (23), 83 (35), 78 (22), 55 (20).

This material was further characterized as the *p*-nitrobenzoate: mp 77 °C; IR 5.80 (C=O), 6.21 (Ar), 6.60 (NO_2), 13.95 μm (Ar).

Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.6; H, 5.29; N, 4.33. Found: C, 70.2; H, 5.51; N, 4.24.

1,2,3,4-Tetrahydro-2-hydroxy-5,8-dimethoxy-2-vinylnaphthalene (9b). To vinylmagnesium chloride (10 mL of 2.3 M solution in THF, 23.0 mmol) under N_2 at 0 °C was added 5,8-dimethoxy-2-tetralone (**6b**, 2.00 g, 9.72 mmol) in THF (5 mL) over 10 min. The solution was stirred at 0 °C for 1 h and at 23 °C for 3.5 h. The reaction mixture was cooled at 0 °C and the excess Grignard reagent destroyed by dropwise addition of saturated NH_4Cl (5 mL). Saturated NaCl (40 mL) was added and the mixture was extracted with EtOAc (three 15-mL portions). The extracts were combined, dried, and evaporated, and the residue was chromatographed (E. Merck silica gel 60 prepacked column (size C), 95:5 $CHCl_3$/EtOAc) to afford 0.39 g (20%) of **6b** and 0.95 g (42%) of **9b**: IR (neat) 3.10 (OH), 10.80 (CH=CH_2), 12.67, 13.15, 13.60, 13.95 μm (Ar); NMR δ 1.82 (t, 2 H, 3-H_2), 2.80 (m,

4 H, 1- and 4-H_2's), 3.86 (s, 6 H, OMe), 5.08 (dd, 1 H, J = 10.5 and 1.5 Hz, *cis*-CH=CH_2), 5.30 (dd, 1 H, J = 16.5 and 1.5 Hz, *trans*-CH=CH_2), 6.08 (dd, 1 H, J = 16.5 and 10.5 Hz, C**H**=CH_2), 6.63 (s, 2 H, Ar H's); MS *m/e* (%) 234 M (22), 216 (8), 164 (17), 149 (11), 75 (60), 73 (100).

This material was further characterized as the *p*-nitrobenzoate: mp 149–150 °C; IR 5.81 (C=O), 6.59 (NO_2), 13.80, 14.25 μm (Ar); MS 12 eV *m/e* (%) 383 M (25), 216 (100).

Anal. Calcd for $C_{21}H_{21}NO_6$: C, 65.78; H, 5.53; N, 3.65. Found: C, 65.60; H, 5.83; N, 3.54.

2-Cyano-1,2,3,4-tetrahydro-2-hydroxy-5,8-dimethoxynaphthalene (14). 5,8-Dimethoxy-2-tetralone (**6b**, 1.00 g, 4.85 mmol) and KCN (5 g) were placed in $CHCl_3$ (125 mL)/EtOH (37.5 mL) and cooled to 0 °C. HOAc (7.5 mL) was added over 10 min. The mixture was diluted with EtOH (25 mL) and stirred at 23 °C for 2 h. The mixture was diluted with H_2O (150 mL) and extracted with $CHCl_3$ (three 40-mL portions). The extracts were combined, dried, and evaporated. The residue was crystallized from toluene to afford 0.90 g (80%) of **14**: mp 117–119 °C; IR 2.92 (OH), 4.42 (CN), 13.95 μm (Ar); NMR δ 2.13 (t, 2 H, 3-H_2), 2.7–3.3 (m, 5 H, OH, 1 and 2-H_2's), 3.79 (s, 6 H, OMe), 6.68 (s, 2 H, Ar H's); MS *m/e* (%) 234 (7), 233 M (75), 218 (12), 206 (89), 164 (100), 163 (22), 149 (67), 91 (18).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.01; H, 6.49; N, 6.00.

1,2,3,4-Tetrahydro-2-hydroxy-5,8-dimethoxy-2-naphthoic Acid (16). 2-Cyano-1,2,3,4-tetrahydro-2-hydroxy-5,8-dimethoxynaphthalene (**14**, 1.00 g, 4.49 mmol) was placed in concentrated HCl (30 mL) at 0 °C. The mixture was stirred at 0 °C for 3 h and kept at 0 °C for an additional 20 h. The mixture was heated on a steam bath for 45 min and allowed to cool. The solution was extracted with CH_2Cl_2 (four 30-mL portions). The extracts were combined, dried, and evaporated. The residue was recrystallized from xylene to afford 0.77 g (71%) of **16**: mp 169–170 °C; IR 3.10 (OH), 5.82 (C=O), 12.70, 14.05 μm (Ar); NMR ($CDCl_3$/Me_2SO-d_6) δ 2.02 (t, 2 H, 3-H_2), 2.7–3.1 (m, 4 H, 1- and 3-H_2's), 3.77 and 3.81 (two singlets, 6 H, OMe), 6.68 (s, 2 H, Ar H's); MS *m/e* (%) 234 M (22), 216 (8), 164 (17), 149 (11), 75 (60), 73 (100).

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.38. Found: C, 61.78; H, 6.38.

2-Cyano-1,2,3,4-tetrahydro-5,8-dimethoxy-2-(2′-tetrahydropyranyloxy)naphthalene (15). 2-Cyano-1,2,3,4-tetrahydro-2-hydroxy-5,8-dimethoxynaphthalene (**14**, 109.4 mg, 0.464 mmol) was placed in dihydropyran (1.5 mL) with concentrated HCl (1 drop) and refluxed for 1.5 h. The reaction mixture was allowed to cool, diluted with ether (15 mL), washed with 10% NaOH (5 mL) and saturated NaCl (5 mL), and dried. The solvent was removed and the residue was chromatographed (PLC, 9:1 $CHCl_3$/EtOAc) to afford 113.8 mg (77%) of **15**: IR (neat) 4.41 (C≡N), 6.21 (Ar), 7.95 (COC), 12.55, 13.65, 14.00 μm (Ar); NMR δ 1.4–1.7 (m, 6 H, 3′-, 4′-, 5′-H_2's), 2.25 (m, 2 H, 3-H_2), 2.95 (m, 2 H, 4-H_2), 3.23 (s, 2 H, 1-H_2), 3.54 (m, 2 H, 6′-H_2), 3.86 (s, 6 H, OMe), 5.18 (m, 1 H, 2′-H), 6.62 (s, 2 H, Ar H's).

2-Acetyl-1,2,3,4-tetrahydro-2-hydroxy-5,8-dimethoxynaphthalene (17). 2-Cyano-1,2,3,4-tetrahydro-5,8-dimethoxy-2-(2′-tetrahydropyranyloxy)naphthalene (**15**, 106.1 mg, 0.335 mmol) in THF (1.5 mL) was added to MeMgI (0.4 mL of 2.5 M solution in ether, 1.00 mmol) under N_2 and was stirred at 23 °C for 16 h. The reaction mixture was added to 60% HOAc (10 mL) and heated on a steam bath for 0.75 h. The mixture was allowed to cool and extracted with $CHCl_3$ (two 10-mL portions). The extracts were combined, dried, and evaporated, and the residue was chromatographed (PLC, 85:15 $CHCl_3$/EtOAc) to afford 53.4 mg (64%) of **17** which could be crystallized from petroleum ether (60–110 °C): mp 97 °C; IR 2.95 (OH), 5.89 (C=O), 6.26 (Ar), 8.00 (COC), 12.60, 13.00, 14.00 μm (Ar); NMR δ 1.90 (m, 2 H, 3-H_2), 2.33 (s, 3 H, Ac), 2.90 (m, 5 H, 1- and 4-H_2 and OH), 3.78 and 3.81 (two singlets, 6 H, OMe), 6.66 (s, 2 H, Ar H's); MS 12 eV *m/e* (%) 250 M (100), 220 (58), 207 (51), 206 (36).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.20; H, 7.23. Found: C, 67.27; H, 7.11.

9-Cyano-7,8,9,10-tetrahydro-6,9,11-trihydroxy-4-methoxy-5,12-napthacenedione (18). 7,8-Dihydro-6,11-dihydroxy-4-methoxy-5,9(10*H*), 12-napthacenetrione (**5**, 45.3 mg, 0.134 mmol) and KCN (300 mg) were placed in 50% $CHCl_3$/EtOH (8 mL) and cooled at 0 °C. HOAc (0.4 mL) was added and the mixture was stirred at 23 °C for 5 h. The reaction mixture was diluted with H_2O (15 mL), the organic phase separated, and the aqueous phase extracted with $CHCl_3$ (10 mL). The organic solutions were combined, dried, and evaporated. The residue was chromatographed (8 g of Bio Sil A, 98:2 $CHCl_3$/MeOH) to afford 38.0 mg (77%) of **18**: mp 232–235 °C (dec); IR 2.93 (OH), 6.20, 6.31 μm (H-bonded quinone); NMR δ 2.1–2.4 (m, 2 H, 8-H_2), 2.8–3.4 (m, 5 H, 7 and 10-H_2's and 9-OH), 4.08 (s, 3 H, OMe), 7.36 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.74 (t, 1 H, J = 8 Hz, 2-H), 7.99 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.28 (s, 1 H, phenolic OH), 13.68 (s, 1 H, phenolic OH).

9-Cyano-7,8,9,10-tetrahydro-6,11-dihydroxy-4-methoxy-9-(2′-tetrahydropyranyloxy)-5,12-naphthacenedione (19). 9-Cyano-7,8,9,10-tetrahydro-6,9,11-trihydroxy-4-methoxy-5,12-napthacenedione (**18**, 37.0 mg, 0.11 mmol) was placed in 50% dihydropyran/THF (10 mL) with concentrated HCl (1 drop) and the solution was refluxed for 5 h. Pyridine (2 mL) was added and the solvents were removed. The residue was dissolved in $CHCl_3$ (10 mL), washed with H_2O (3 mL), dried, and evaporated. The residue was crystallized from $CHCl_3$/petroleum ether to afford 36.9 mg (90%) of **19**: mp 204–206 °C; IR 6.20, 6.30 μm (H-bonded quinone); NMR δ 1.64 (m, 6 H, 3′-, 4′-, and 5′-H_2's), 2.32 (m, 2 H, 8-H_2), 3.05 (m, 2 H, benzylic CH_2), 3.34, (t, 2 H, benzylic CH_2), 3.58 (m, 2 H, 6′-H_2), 4.10 (s, 3 H, OMe), 5.18 (m, 1 H, 2′-H), 7.35 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.75 (t, 1 H, J = 8 Hz, 2-H), 8.02 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.40 (s, 1 H, phenolic OH), 13.76 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{25}H_{23}NO_7$: C, 66.80; H, 5.16; N, 3.11. Found: C, 66.70; H, 5.25; N, 3.14.

(±)-7-Deoxydaunomycinone (20). Methylmagnesium iodide (0.4 mL of 2.5 M solution in ether, 1.00 mmol) was added under N_2 to a stirred solution of 9-cyano-7,8,9,10-tetrahydro-6,11-dihydroxy-4-methoxy-9-(2′-tetrahydropyranyloxy)-5,12-naphthacenedione (**19**, 15 mg, 0.033 mmol) in THF (1.5 mL). The mixture was stirred at 23 °C for 4 h and at 55 °C for 10 h. The reaction was quenched with 60% HOAc (10 mL) and the solution was heated on a steam bath for 0.75 h. The mixture was diluted with water (10 mL) and extracted with $CHCl_3$ (two 10-mL portions). The extracts were combined, washed with saturated $NaHCO_3$ (5 mL), dried, and evaporated. The residue was chromatographed (PLC, 85:15 $CHCl_3$/EtOAc) and crystallized from $CHCl_3$/petroleum ether to afford 5.7 mg (45%) of **20**: mp 230–232 °C; IR 2.85 (OH), 5.82 (C=O), 6.20, 6.30 μm (H-bonded quinone); NMR δ 1.95 (m, 2 H, 8-H_2), 2.42 (s, 3 H, Ac), 3.00 (m, 4 H, 7- and 10-H_2's), 3.74 (br s, 1 H, 9-OH), 4.10 (S= 3 H, OMe), 7.36 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.73 (t, 1 H, J = 8 Hz, 2-H), 7.99 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.37 (s, 1 H, phenolic OH), 13.79 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{21}H_{18}O_7 \cdot 0.5H_2O$: C, 64.45; H, 4.91. Found: C, 64.14; H, 4.56.

14-Bromo-7-deoxydaunomycinone (21). 7-Deoxydaunomycinone (**3**, 96.7 mg 0.253 mmol) and pyrrolidone hydrotribromide (132 mg, 0.265 mmol) were placed in THF (11 mL) and stirred at 23 °C for 24 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with H_2O (10 mL) and saturated NaCl (10 mL), dried, and evaporated. The residue was precipitated from CH_2Cl_2 with petroleum ether to afford 96.8 mg (83%) of **21**: mp 250–254 °C; IR 2.85 (OH), 5.74 (C=O), 6.19, 6.29 μm (H-bonded quinone); NMR (Me_2SO-d_6) δ 1.90 (m, 2 H, 8-H_2), 2.67 (m, 4 H, 7- and 10-H_2's), 3.85 (s, 3 H, OMe), 4.75 (s, 2 H, 14-H_2), 7.2–7.7 (m, 3 H, Ar H's), 13.07 (s, 1 H, phenolic OH), 13.57 (s, 1 H, phenolic OH); MS 12 eV *m/e* (%) 462 (14), 460 M (14), 340 (18), 339 (100).

Anal. Calcd for $C_{21}H_{17}BrO_7 \cdot H_2O$: C, 52.63; H, 4.01. Found: C, 52.80; H, 3.76.

7-Deoxyadriamycinone (22). 14-Bromo-7-deoxydaunomycinone (**21**, 99.0 mg, 0.215 mmol) and NaOH (10.3 mg, 0.258 mmol) were placed in 4:1 acetone/H_2O (50 mL) and refluxed under N_2 for 20 min. The acetone was removed and the residue diluted with H_2O (80 mL). The red precipitate was filtered and dried to afford 83.0 mg (97%) of **22**: IR 2.95 (OH), 5.79 (C=O), 6.20, and 6.30 μm (H-bonded quinone); NMR (Me_2SO-d_6) δ 1.84 (m, 2 H, 8-H_2), 2.6–2.9 (m, 4 H, 7- and 10-H_2's), 3.96 (s, 3 H, OMe), 4.5–4.9 (m, 3 H, 14-H_2 and OH), 5.60 (br s, 1 H, OH), 7.54 (br s, 1 H, 3-H), 7.76 (m, 2 H, 1- and 2-H), 13.48 (s, 1 H, phenolic OH), 14.02 (s, 1 H, phenolic OH); MS *m/e* (%) 398 M (20), 380 (4), 335 (100).

Anal. Calcd for $C_{21}H_{18}O_8 \cdot H_2O$: C, 60.58; H, 4.85. Found: C, 60.74; H, 4.51.

Daunomycinone (26). 7-Deoxydaunomycinone (**3**, 100 mg, 0.262 mmol), Br_2 (3.0 mL of 0.125 M solution in CCl_4, 0.375 mmol) and ABN (6.4 mg, 0.04 mmol) were placed in CCl_4 (20 mL) under N_2 and refluxed for 3 h. Additional Br_2 (0.19 mmol) was introduced and refluxing was continued for another hour. The solvent was removed and the residue was placed in Me_2SO (20 mL) with $NaOCOCF_3$ (200 mg) and stirred under N_2 for 16 h. The reaction mixture was poured into H_2O (50 mL) and extracted with $CHCl_3$ (three 15-mL portions). The extracts were combined, washed with H_2O (10 mL) and saturated NaCl (10 mL), dried, and evaporated. The residue was dissolved in F_3AcOH (10 mL) and stirred at 23 °C for 1.5 h. The solvent was removed and the residue dissolved in 4:1 MeOH/THF (20 mL) and stirred at 23 °C for 4 h. The solution was poured into H_2O (50 mL) and

extracted with $CHCl_3$ (three 15-mL portions). The extracts were combined, dried, and evaporated. The residue was chromatographed [E. Merck silica gel 60 prepacked column (size B), 99:1 to 97:3 CH_2Cl_2/MeOH] to afford in order of elution 17.7 mg (18%) of **3** and 37.0 mg (35%) of **26**: mp 215–217 °C; IR 2.90 (OH), 5.85 (C=O), 6.20, 6.31 μm (H-bonded quinone); NMR δ 2.05–2.35 (m, 2 H, 8-H_2), 2.48 (s, 3 H, Ac), 2.93 (d, 1 H, J = 19 Hz, 10 β-H), 3.25 (d, 1 H, J = 19 Hz, 10 α-H), 3.68 (s, 1 H, 9-OH), 4.14 (s, 3 H, OMe), 4.53 (s, 1 H, 7-OH), 5.36 (m, 1 H, $\nu_{1/2}$ = 7 Hz, 7-H), 7.40 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.79 (t, 1 H, J = 8 Hz, 2-H), 8.06 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.35 (s, 1 H, phenolic OH), 14.07 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{21}H_{18}O_8 \cdot H_2O$: C, 60.58; H, 4.85. Found: C, 60.96; H, 4.45.

Continued elution afforded 6.1 mg (6%) of 7-epidaunomycinone (**27**): mp 218–220 °C; IR 2.85 (OH), 5.85 (C=O), 6.20, 6.30 μm (H-bonded quinone); NMR δ 2.2–2.5 (m, 2 H, 8-H_2), 2.43 (s, 3 H, Ac), 2.90 (d, 1 H, J = 17 Hz, 10 β-H), 3.16 (d, 1 H, J = 17 Hz, 10 α-H), 3.82 (s, 1 H, 9-OH), 4.12 (s, 3 H, OMe), 4.33 (d, 1 H, 7-OH), 5.37 (m, 1 H, $\nu_{1/2}$ = 17 Hz, 7-H), 7.40 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.79 (t, 1 H, J = 8 Hz, 2-H), 8.06 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.26 (s, 1 H, phenolic OH), 14.33 (s, 1 H, phenolic OH); MS 12 eV m/e (%) 399 (22), 398 M (87), 380 (56), 362 (45), 355 (17), 339 (15), 338 (64), 337 (100); $[\alpha]_D$ − 184° (c 0.02, $CHCl_3$).

Anal. Calcd for $C_{21}H_{18}O_8 \cdot 0.25H_2O$: C, 62.61; H, 4.64. Found: C, 62.68; H, 4.51.

7-Epidaunomycinone (27). 7-Deoxydaunomycinone (**3**, 100 mg, 0.262 mmol), Br_2 (3.0 mL of 0.125 M solution in CCl_4, 0.375 mmol), and ABN (6.4 mg, 0.040 mmol) were placed in CCl_4 (20 mL) under N_2 and refluxed for 2 h. Br_2 (1.5 mL of 0.125 M solution in CCl_4) was added and refluxing was continued for 1 h. The solvent was removed and the residue was placed in Me_2SO (20 mL) with $NaOCOCF_3$ (200 mg) and stirred under N_2 for 16 h. The reaction mixture was poured into H_2O (50 mL) and extracted with $CHCl_3$ (three 15-mL portions). The extracts were combined, washed with H_2O (10 mL) and saturated NaCl (10 mL), dried, and evaporated. The residue was dissolved in 4:1 MeOH/THF (20 mL) and stirred at 23 °C for 4 h. The solution was poured into H_2O (50 mL) and extracted with $CHCl_3$ (three 15-mL portions). The extracts were combined, dried, and evaporated. The residue was chromatographed [E. Merck silica gel 60 prepacked column (size B), 99:1 to 97:3 CH_2Cl_2/MeOH] to afford in order of elution 17.2 mg (17%) of **3**, 9.1 mg (9%) of **26**, and 36.8 mg (35%) of **27**.

Adriamycinone (29). Daunomycinone (**26**, 10 mg, 0.025 mmol) was placed in $CHCl_3$ (1 mL). Br_2 (13.5 mg) in $CHCl_3$ (0.25 mL) was added and the solution stirred at 23 °C for 16 h. The solvent was removed and the residue was dissolved in 4:1 acetone/H_2O (5 mL). NaOH (1.1 mg, 0.028 mmol) was added and the blue solution was refluxed for 5 min when the red color returned. The solution was concentrated to ca. 2 mL, diluted with water (10 mL), and extracted with 1:1 $CHCl_3$/MeOH (three 10-mL portions). The extracts were combined, dried, and evaporated. The residue was crystallized from $CHCl_3$/MeOH/petroleum ether to afford 9.0 mg (87%) of **29**: IR 2.85 (OH), 5.75 (C=O), 6.15, 6.28 μm (H-bonded quinone); NMR δ 2.0–2.5 (m, 2 H, 8-H_2), 2.8–3.2 (m, 2 H, 10-H_2), 3.34 (m, 1 H, 9-OH), 4.09 (s, 3 H, OMe), 4.70 (d, 2 H, J = 16 Hz, 14-H_2), 5.34 (m, 1 H, $\nu_{1/2}$ = 8 Hz, 7-H), 7.38 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.76 (t, 1 H, J = 8 Hz, 2-H), 8.00 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.24 (s, 1 H, phenolic OH), 13.99 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{21}H_{18}O_9 \cdot 0.5H_2O$: C, 59.57; H, 4.54. Found: C, 59.63; H, 45.4.

14-*O*-*p*-Anisyldiphenylmethyladriamycinone (30). Adriamycinone (**29**, 369 mg, 0.90 mmol) was dissolved in pyridine (36 mL) and cooled to 5 °C. *p*-Anisylchlorodiphenylmethane (2.77 g, 9.48 mmol) was added in one portion with stirring, and the solution was kept at 5 °C for 5 days. The reaction mixture was poured into ice–water (200 mL) and extracted with $CHCl_3$ (two 100-mL portions). The extracts were combined, washed with 3 N H_2SO_4 (two 100-mL portions), saturated $NaHCO_3$ (100 mL), and water (100 mL), dried, and evaporated. The residue was crystallized from $CHCl_3$/petroleum ether to afford 520 mg (84%) of **30**: mp 198–203 °C; IR 2.90 (OH), 5.78 (C=O), 6.20, 6.30 μm (H-bonded quinone); NMR δ 2.08 (m, 2 H, 8-H_2), 2.78 (m, 2 H, 10-H_2), 3.83 (s, 3 H, Tr-OMe), 4.00 (s, 3 H, 4-OMe), 4.52 (s, 2 H, 14-H_2), 5.10 (m, 1 H, $\nu_{1/2}$ = 7 Hz, 7-H), 6.8–7.8 (m, 17 H, Ar H's), 13.00 (s, 1 H, phenolic OH), 13.58 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{41}H_{34}O_{10} \cdot 1.5H_2O$: C, 69.0; H, 5.23. Found: C, 69.1; H, 5.37.

2,3,6-Trideoxy-3-trifluoracetamido-α,β-L-*lyxo*hexopyranose (33). Sodium methoxide (7.0 g, 0.13 mol) was added to a solution of daunosamine hydrochloride (**32**, 23.5 g, 0.13 mol) in MeOH (400 mL) at 0 °C, and the mixture was stirred for 0.5 h. *S*-Ethyl trifluorothioacetate (25.3 g, 0.16 mol) was added and stirring was continued at 23 °C for 16 h. The reaction mixture was filtered and evaporated. The residue was triturated with hot acetone (250 mL) and filtered. The filtrate was dried and evaporated to afford 25 g of a solid residue. This was recrystallized from ethyl acetate to afford 18.9 g (68%) of **33**: mp 146–147 °C; IR 2.95–3.0 (OH, NH), 5.85 (C=O), 6.55 (amide II), 8.6 (CF_3) μm; NMR δ 1.2 (two overlapping d, 3 H, 6-H_3), 1.5–2.4 (m, 2 H, 2-H_2), 3.3–5.0 (m, 3 H, 3-, 4-, and 5-H's), 5.3 (m, 0.5 H, 1-H), 5.6 (m, 0.5 H, 1-H), 8.2 (br, 1 H, NH).

Anal. Calcd for $C_8H_{12}F_3NO_4$: C, 39.51; H, 4.98; N, 5.76. Found: C, 39.51; H, 5.00; N, 5.99.

2,3,6-Trideoxy-1,4-di-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-α-L-*lyxo*hexopyranose (34). *p*-Nitrobenzoyl chloride (40.4 g, 217.6 mmol) was added to a solution of 2,3,6-trideoxy-3-trifluoroacetamido-α,β-L-*lyxo*hexopyranose (**33**, 18.9 g, 77.7 mmol) in pyridine (600 mL) at 0 °C and stirred at 0 °C for 16 h. Water (50 mL) was added and the mixture was stirred for 0.5 h. The reaction mixture was poured into water (1.5 L) and extracted with $CHCl_3$ (four 1-L portions). The extracts were combined and washed successively with 3 N H_2SO_4 (two 2-L portions), H_2O (2 L), saturated $NaHCO_3$ (five 2-L portions), and H_2O (2 L), dried, and evaporated. The residue was recrystallized from acetone/$CHCl_3$/hexanes to afford 39.3 g (93%) of **34**: mp 202–203 °C; IR 2.98 (NH), 5.78 (C=O), 6.51 (aryl), 6.57 (NO_2), 8.67 μm (CF_3); NMR (Me_2SO-d_6) 1.13 (d, 3 H, 6-H_3), 2.08 (dm, 1 H, 2-H_{ax}), 2.58 (m, overlapped with Me_2SO-d_6 signal, 2-H_{eq}), 4.60 (m, 2 H, 3- and 5-H's), 5.50 (br s, 1 H, 4-H), 6.62 (br s, 1 H, 1-H), 8.42 (m, 8 H, Ar H's), 9.63 (d, 1 H, NH); $[\alpha]^{21}_D$ − 125° (c 0.03, 95% EtOH).

Anal. Calcd for $C_{22}H_{18}F_3N_3O_{10}$: C, 48.81; H, 3.34; N, 7.76. Found: C, 48.97; H, 3.76; N, 7.70.

4'-*O*-*p*-Nitrobenzoyl-3'-*N*-trifluoroacetyldaunorubicin (39). Daunomycinone (**26**, 99.5 mg, 0.25 mmol), $Hg(CN)_2$ (520 mg), $HgBr_2$ (236 Mg), and powdered molecular sieve 3A (1.2 g) were placed in THF (25 mL) and stirred at 50–55 °C for 2 h. Three 1 M equivalent portions of freshly prepared **36** in CH_2Cl_2 (2 mL) were added at 0, 4, and 22 h while the temperature was maintained at 50–55 °C. The chloro sugar **36** was prepared by bubbling anhydrous HCl into a suspension of 2,3,6-trideoxy-1,4-di-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-α-L-*lyxo*hexopyranose (**34**, 135 mg, 0.25 mmol) in CH_2Cl_2 (4 mL) at 0 °C for 3 min. The mixture was allowed to stand at 23 °C for 10 min, filtered to remove the precipitated *p*-nitrobenzoic acid, and evaporated. The residue was dissolved in CH_2Cl_2 (2 mL) and added to the reaction mixture. Additional $Hg(CN)_2$ (520 mg), $HgBr_2$ (236 mg), and powdered molecular sieve 3A (0.60 g) were added at 4 h. The total reaction time after the first addition of **36** was 25 h. The reaction mixture was filtered, the solids were washed with THF, and the washings and filtrate were combined and evaporated. The residue was triturated with $CHCl_3$ (75 mL), and filtered. The filtrate was washed with 30% KI (two 25-mL portions) and H_2O (50 mL), dried, and evaporated. The residue was chromatographed (PLC, six plates, 2:1 benzene/ethyl acetate) to afford 150 mg (77%) of **39**: IR 2.95 (NH, OH), 5.78 (C=O), 6.15, 6.30 (H-bonded quinone), 6.45 (amide II), 6.55 (NO_2), 8.55 (CF_3) μm; NMR δ 1.24 (d, 3 H, 6-H_3), 2.0–2.32 (m, 4 H, 8- and 2'-H_2's), 2.45 (s, 3 H, Ac), 2.95 (d, 1 H, J = 19 Hz, 10 β-H), 3.30 (d, 1 H, J = 19 Hz, 10 α-H), 4.10 (s, 3 H, OMe), 4.3–4.6 (m, 2 H, 3'- and 5'-H's), 5.33 (br s, 1 H, 7-H), 5.50 (m, 1 H, 4'-H), 5.67 (br s, 1 H, 1'-H), 6.20 (d, 1 H, NH), 7.39 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.79 (t, 1 H, J = 8 Hz, 2-H), 8.06 (dd, 1 H, J = 8 and 1 Hz, 1-H), 8.33 (m, 4 H, Ar H's), 13.09 (s, 1 H, phenolic OH), 14.07 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{36}H_{31}F_3N_2O_{14}$: C, 55.96; H, 4.04, N, 3.62. Found: C, 56.09, H, 4.42; N, 3.84.

Adriamycin Hydrochloride (2). 14-*O*-*p*-Anisyldiphenylmethyladriamycinone (**30**, 58.0 mg, 0.085 mmol), $Hg(CN)_2$ (250 mg), $HgBr_2$ (130 mg), and powdered molecular sieve 3A (500 mg) were placed in THF (9 mL) and refluxed for 2 h. Then 1 M equivalent portions of freshly prepared **36** were added at 3, 6, 11, 24, 28, 31, 36, 47, and 49 h while the mixture was maintained at 60 °C. The chloro sugar **36** was prepared as described in the previous experiment. Additional portions of $Hg(CN)_2$ (250 mg), $HgBr_2$ (130 mg), and molecular sieve 3A (500 mg) were added at 23 h. The total reaction time after the first addition of **36** was 50 h. The reaction mixture was filtered and evaporated. The residue was triturated with $CHCl_3$ (10 mL), filtered, washed with 30% KI, saturated $NaHCO_5$, and water, dried, and evaporated.

The residue was dissolved in THF (8 mL) and cooled to 5 °C. NaOH (17 mL of 0.2 N aqueous solution) was added and the solution was stirred at 5 °C for 5.25 h. After neutralization to pH 8 with 0.2 N HCl, the solution was extracted with 4:1 $CHCl_3$/MeOH, and the organic extract was washed with H_2O, dried, and evaporated.

The residue was dissolved in 80% HOAc (4 mL) and the solution was stirred at 23 °C for 16 h. The solution was lypophilized with temperature maintained below 0 °C, and the residue was dissolved in 2:1 MeOH/$CHCl_3$ (5 mL) and filtered. HCl (1.5 mL of a 0.1 N so-

lution in MeOH) was added to the filtrate followed by ether (50 mL). The precipitate was collected by centrifugation and decantation and reprecipitated from MeOH with ether to afford 20 mg (40%) of **2**: IR 3.00 (OH, NH), 5.83 (C=O), 6.20, 6.35 μm (H-bonded quinone); UV-vis (MeOH) λ_{max} (ε) 252 (25 391), 287 (9716), 478 (12 063), 492 (12 091), 531 (6913); NMR (Me_2SO-d_6) δ 1.18 (d, 3 H, 6′-H_3), 1.80 (m, 2 H, 2′-H_2), 2.12 (m, 2 H, 8-H_2), 2.78 (d, 1 H, J = 19 Hz, 10 β-H), 3.04 (d, 1 H, J = 19 Hz, 10 α-H), 3.61 (m, 2 H, 3′- and 4′-H's), 3.92 (s, 3 H, OMe), 4.17 (m, 1 H, 5′-H), 4.61 (s, 2 H, 14-H_2), 4.87 (br s, 1 H, 7-H), 5.28 (br s, 1 H, 1′-H), 5.47 (br s, 1 H, 9-OH), 7.57 (m, 1 H, 3-H), 7.80 (m, 2 H, 1- and 2-H's), 13.11 (s, 1 H, phenolic OH), 13.93 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{27}H_{29}NO_{11}$·HCl·0.75H_2O: C, 54.64; H, 5.35; N, 2.36. Found: C, 54.34; H, 5.03; N, 2.02.

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Registry No.—**1**, 20830-81-3; **1** HCl, 23541-50-6; **2**, 23214-92-8; **2** HCl, 25316-40-9; **3**, 32384-98-8; **4**, 40940-87-2; **5**, 59325-97-2; **6a**, 530-93-8; **6b**, 37464-90-7; **7**, 63625-93-4; **8a**, 63625-94-5; **8b**, 63625,95-6; **8c**, 63625-96-7; **9a**, 63625-97-8; **9a** PNB, 63625-98-9; **9b**, 63625-99-0; **9b** PNB, 63626-00-6; **11**, 63626-01-7; **11** PNB, 63626-02-8; **14**, 63626-03-9; **15**, 63626-04-0; **16**, 63626-05-1; **17**, 33628-85-2; **18**, 59325-99-4; **19**, 59326-00-0; **20**, 59367-18-9; **21**, 63626-06-2; **22**, 38554-25-5; **26**, 21794-55-8; **27**, 59325-98-3; **29**, 24385-10-2; **30**, 59326-04-4; **32** HCl, 19196-51-1; **33**, 52471-40-6; **34**, 63700-24-3; **36**, 63700-25-4; **39**, 52583-24-1; triethyl phosphonoacetate, 867-13-0; diethyl cyanomethylphosphonate, 2537-48-6; sodium triethylphosphonoacetate, 22822-85-1; vinyl chloride, 75-01-4; dihydropyran, 110-87-2; methyl iodide, 74-88-4; *p*-anisylchlorodiphenylmethane, 14470-28-1; *S*-ethyl trifluorothioacetate, 383-64-2; *p*-nitrobenzoyl chloride, 122-04-3; pyrrolidone hydrotribromide, 52215-12-0.

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Macrocyclic Spermidine Alkaloids from *Maytenus serrata* and *Tripterygium wilfordii*[1a]

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Four new spermidine alkaloids, celacinnine (**1**), celallocinnine (**2**), celafurine (**3**), and celabenzine (**4**), have been isolated in studies of *Maytenus serrata* (Hochst., ex A. Rich.) R. Wilczek and *Tripterygium wilfordii* Hook. The 13-membered macrocyclic structures of the alkaloids were elucidated by chemical degradation and by a study of the spectral properties of the alkaloids and their derivatives.

The twigs of *Maytenus serrata* (Hochst., ex A. Rich.) R. Wilczek (Celastraceae) have yielded two novel spermidine alkaloids, celacinnine (**1**) and celallocinnine (**2**), as the principal basic components.[2] Celacinnine (**1**) has also been isolated from the roots of *Tripterygium wilfordii* Hook (Celastraceae), together with the related alkaloids celafurine (**3**) and celabenzine (**4**).[2] We report herein our detailed studies on the isolation and structural elucidation of these four alkaloids. Studies of the fruit of *M. serrata* in these laboratories have yielded the nicotinoyl sesquiterpene alkaloids maytoline, maytine, and maytolidine,[3] and the highly active tumor-inhibitory ansa-macrolide maytansine,[4] but these compounds could not be detected in the twigs and no spermidine alkaloids were detected in the fruit. A series of complex nicotinoyl sesquiterpene alkaloids has been previously reported from the roots of *T. wilfordii*.[5]

Table I. NMR Spectra of Spermidine Alkaloids and Derivatives from *M. serrata* and *T. wilfordii*[a]

Compd	Registry no.	C-7 (2 H)	C-8 (1 H)	CH_2	Aryl-H	Acyl groups
1	53938-05-9	7.50 d (7.0)	6.00 t (7.0)	6.2–7.0 br m (9 H) 7.2–8.6 br m (7 H)	2.5–2.8 m (10 H)	2.23 d (1 H), 3.12 d (1 H) (15.5) (15.5)
2	53990-48-0	7.55 d (7.0)	6.10 t (7.0)	5.9–7.0 br m (9 H) 7.4–8.8 br m (7 H)	2.5–2.8 m (10 H)	3.40 d (1 H), 3.96 d (1 H) (13) (13)
3	53938-09-3	7.58 d (7.0)	6.13 t (7.0)	6.2–8.9 br m (16 H)	2.75–2.95 m (5 H)	2.40 d (1 H), 2.69 t (1 H), 3.54 d (1 H) (1.5) (1.5) (1.5)
4	53938-08-2	7.58 d (7.0)	6.12 t (7.0)	6.2–8.9 br m (16 H)	2.6–2.9 m (10 H)	
5	53938-06-0	7.55 d (7.0)	6.03 t (7.0)	br m	2.7–2.8 m (10 H)	
7[b]	63301-66-6	7.60 m	6.00 br d (12)	6.4–8.8 m	2.5–3.0 m (10 H)	2.40 d (1 H), 3.32 d (1 H) (15) (15)
8[c]	53938-07-1	7.10 m	4.32 br d (12)	6.0–8.5 m	2.5–3.0 m (10 H)	2.26 d (1 H), 3.16 d (1 H) (15) (15)

[a] Spectra are of $CDCl_3$ solutions. Chemical shifts are given in τ units. Coupling constants in hertz are given in parenthesis; d, doublet; t, triplet; s, singlet; br m, broad multiplet; br d, broad doublet. [b] Peak at τ 7.98 s (3 H) *N*-methyl. [c] Peak at τ 7.53 s (3 H) CH_3CON–.

In the present study the ground dried twigs of *M. serrata*[6] were extracted with aqueous ethanol and the extract was partitioned between ethyl acetate and water. The ethyl acetate soluble material was chromatographed on SilicAR CC-7 and then on neutral alumina to give a crystalline alkaloid fraction. Recrystallization gave the major alkaloid, celacinnine (**1**, $C_{25}H_{31}N_3O_2$). TLC of the mother liquors yielded additional **1** and an isomeric alkaloid, celallocinnine (**2**). Both alkaloids gave strong positive reactions with either Dragendorff's reagent or iodoplatinic acid.

The ground dried roots of *T. wilfordii*[6] were extracted with 95% ethanol and the extract was partitioned between ethyl acetate and water. The ethyl acetate soluble material was extracted with aqueous citric acid solution, which was then treated with base and extracted with ethyl acetate to yield a basic fraction. Successive chromatography of the basic fraction on neutral alumina and silica gel, TLC purification on alumina and silica gel, and crystallization yielded **1**, celafurine (**3**, $C_{21}H_{27}N_3O_3$), and celabenzine (**4**, $C_{23}H_{29}N_3O_2$).

Similarity among the spectra of the four alkaloids suggested that **1**–**4** differed only in the acyl side chain. In each case the infrared spectrum contained two amide carbonyl bands at 6.02–6.06 and 6.19–6.25 μm and the mass spectrum contained prominent ions with *m/e* 274 ($C_{16}H_{24}N_3O$), 160 ($C_{11}H_{14}N$), 146 (C_9H_8NO), and 131 (C_9H_7O).[7] The NMR spectra (see Table I) showed few distinctive signals, but all four alkaloids appeared to contain 16 aliphatic protons (τ 5.9–8.9), at least five aryl protons, and a spin-coupled CH_2–CH system [τ 7.5 (2 H) and 6.1 (1 H), J = 7 Hz].

The NMR spectrum of **1** also contained an AB quartet (J = 15.5 Hz) at τ 2.23 and 3.12, and signals for a second monosubstituted aromatic ring. These signals, together with the ultraviolet absorption band at λ_{max} 277 nm (ϵ 23 000), suggested the presence of a *trans*-cinnamoyl group [cf., *N,N*-dimethyl-*trans*-cinnamide: UV λ_{max} 278 nm (ϵ 22 400);[8] NMR τ 2.17 and 3.54 (J = 15.5 Hz)[9]]. The NMR spectrum of the isomeric alkaloid **2** contained an AB quartet (J = 13 Hz) at τ 3.40 and 3.96, and the UV spectrum contained absorption bands at λ_{max} 255 and 264 (infl) nm (ϵ 11 800, 9500), suggesting a *cis*-cinnamoyl group [cf., *cis*-cinnamide, UV λ_{max} 254 nm (ϵ 10 600);[10] and methyl *cis*-cinnamate, NMR τ 3.1 and 4.1 (J = 12.4 Hz)[11]]. Hydrogenation of both **1** and **2** yielded dihydrocelacinnine (**5**), which lacked the strong ultraviolet absorption and contained no olefinic proton signals in the NMR spectrum. Although the mass spectra of **1** and **2** both contained peaks at *m/e* 131 (C_9H_7O) characteristic of a cinnamoyl group, this peak was also present in the spectrum of the other alkaloids, including **5** and its dideuterio isomer **6**, and can therefore result from a double fragmentation (vide infra).

The NMR spectrum of **3** contained intercoupled one-proton signals at τ 2.40 (d), 2.69 (t), and 3.54 (d), and the base peak in the mass spectrum of **3** appeared at *m/e* 95 ($C_5H_3O_2$), consistent with the presence of a β-furoyl group.[12,13] β-Furoic acid and its derivatives occur rarely in nature; they have been isolated primarily from the Celastraceae[14] and include two of the nicotinoyl sesquiterpene alkaloids, wilforgine and wilfortrine, from *T. wilfordii*.[5]

The NMR spectrum of alkaloid **4** contained ten aromatic but no olefinic proton signals, and the mass spectrum contained an intense peak at *m/e* 105 (C_7H_5O). These data suggested that a benzoyl group was present.

The unsaturated acyl groups appeared to be attached by an amide linkage to a common $C_{16}H_{24}N_3O$ nucleus, which contained both an aromatic ring and a saturated amide group. The relationship of the nitrogen functions was established by chemical degradation; vigorous acidic hydrolysis of **1** followed by acetylation of the reaction mixture yielded triacetylspermidine (**9**). A similar cleavage of a benzylic secondary amine has been reported in the acid hydrolysis of tetrahydro-*seco*-chaenorhine.[15] Hydrogenation of **1** gave **5**, so the single remaining unidentified unsaturation represented by the molecular formula could be attributed to the presence of a cyclic structure. The residue left after subtracting the acyl and spermidine units from the empirical formulas of the alkaloids corresponded in each case to a phenylpropionyl group. The NMR chemical shifts (Table I) of the CH_2–CH group protons were nearly identical with analogous peaks in *N*-methyl-β-phenyl-β-alanine methyl ester [τ 6.03 (CH), 7.50 (CH_2)], indicating that a β-amino-β-phenylpropionamido group was present in the alkaloids.

Acetylation of the basic nitrogen in **1** with acetic anhydride in pyridine gave *N*-acetylcelacinnine (**8**), whose NMR spectrum contained signals at τ 4.38 and 7.08 (J = 7 Hz). Comparison with the spectra of *N*-acetyl-β-phenyl-β-alanine methyl ester, τ 4.52 and 7.14 (J = 7 Hz), and *N*-acetyl-β-phenyl-α-alanine methyl ester, τ 5.12 and 6.91 (J = 7 Hz), confirmed that the basic amino group was in the β position of the phenylpropionamide and that in the original alkaloid it was not the site of the unsaturated acyl group. A similar shift of the CH signal upon acetylation, from τ 6.16 to 4.47 (dd, J = 10, 6 Hz), has been reported for a model β-phenyl-β-alanine derivative studied during the elucidation of the structure of the spermine alkaloid chaenorhine.[15] From the optical rotation of **1**–**4**, no assignment of the stereochemistry at C-8 could be made.

At this point, data for the structure of **1** were also consistent

Scheme I. Mass Spectral Fragmentation of Celaccinnine and Its Derivatives

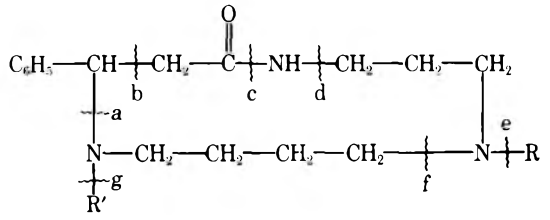


Table II. Mass Spectra of Spermidine Alkaloids and Derivatives from *M. serrata* and *T. wilfordii*[a]

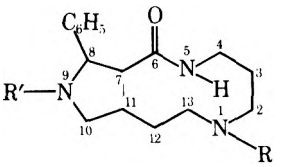
	m/e							
Compd	M+	i	ii	iii	iv	v	vi	vii
1[b,c]	405	333	274	260	160	159	146	131[d]
	(23)	(1)	(100)	(17)	(21)	(16)	(29)	(90)
3[e]	369	297	274	224	160	159	146	131
	(47)	(18)	(29)	(52)	(30)	(20)	(38)	(14)
4[f]	379	307	274	234	160	159	146	131
	(24)	(4)	(57)	(4)	(25)		(25)	(12)
5[c]	407	335	274	262	160	159	146	131
	(100)	(10)	(65)	(23)	(41)	(51)	(67)	(16)
6[c,g]	409	337	274	264	160	159	146	131
	(100)	(9)	(81)	(22)	(44)	(71)	(82)	(22)
7	419		288		160	159	146	131
	(28)		(97)		(98)	(1)	(8)	(100)
8	447		316					131
	(38)		(80)					(100)

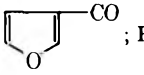
[a] Relative abundances are given in parentheses. Fragmentations refer to Scheme I: i = $M^+ - C_3H_6NO$; ii = $M^+ - e$; iii = $M^+ - vi$; iv, v = b + g + f; vi = a + d; vii = a + c. [b] Spectrum of 2 was quantitatively identical with 1 with minor variations in relative abundances. [c] All assignments confirmed by HRMS. [d] Note that for 1 the peak at *m/e* 131 is not characteristic of the acyl group. [e] Base peak *m/e* 95 assigned to $C_5H_3O_3$ (furoyl). [f] Base peak *m/e* 105 assigned to C_7H_5O (benzoyl). [g] Registry no.: 63301-67-7.

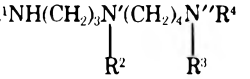
with structures **14, 15,** and **16.** Previous workers have reported that mass spectral fragmentation of triacetylspermidine (**9**) involves preferential fission of the three-carbon chain, with little involvement of the four-carbon chain.[16] Mild acid hydrolysis of **1,** followed by esterification and acetylation, yielded the triacyl spermidine **17,** resulting from hydrolysis of the saturated amido group. The mass spectrum of **17** contained peaks at *m/e* 345, 333, and 319 corresponding to ions **18, 19,** and **20,** respectively, resulting from cleavage of the three-carbon chain. The ester derived from **15** would be expected to have the same fragments. However, fission of the three-carbon chain in esters derived from alternative structures **14** and **16** should give rise to a much different fragmentation pattern.

N-Methylation of **1** gave **7,** whose methiodide was converted by Hofmann degradation to **10.** Alternatively, **10** was synthesized by partial cinnamoylation of spermidine,[17] separation of *N,N'*-dicinnamide **11,** and methylation. Both derived and synthetic **10** gave identical spectra. Mass spectral peaks at *m/e* 155, 143, and 129 corresponded to preferential fragmentation to give **21, 22,** and **23,** respectively. Although conversion of **1** to **10** confirmed the orientation of the spermidine unit, this transformation did not exclude **15** as a possible structure for the starting material.

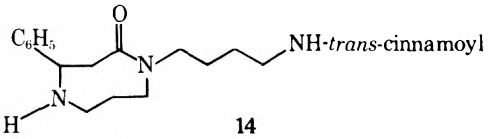
Macrocyclic structure **1** was ultimately assigned to celaccinnine on the basis of high-resolution mass spectral data. Principal fragmentations of the alkaloids and their derivatives are shown in Scheme I and Table II. The peaks at *m/e* 131 (vii, C_9H_7O) and 146 (vi, C_9H_8NO) were present in all four alkaloids as well as in the dihydro and dideuterio derivatives. The



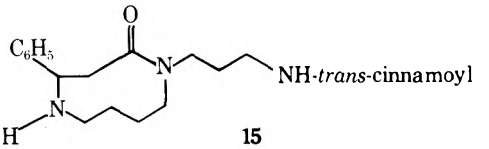
1, R = *trans*-PhCH=CHCO; R' = H
2, R = *cis*-PhCH=CHCO; R' = H
3, R =  ; R' = H
4, R = PhCO; R' = H
5, R = $PhCH_2CH_2CO$; R' = H
6, R = PhCHDCHDCO; R' = H
7, R = *trans*-PhCH=CHCO; R' = CH_3
8, R = *trans*-PhCH=CHCO; R' = CH_3CO



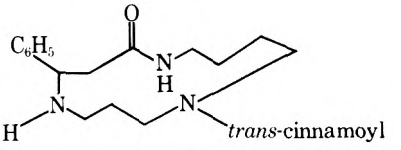
9, $R^1 = R^2 = R^3$ = Ac; R^4 = H
10, $R^1 = R^2$ = *trans*-cinnamoyl; $R^3 = R^4$ = Me
11, $R^1 = R^2$ = *trans*-cinnamoyl; $R^3 = R^4$ = H
12, $R^1 = R^3$ = *trans*-cinnamoyl; $R^2 = R^4$ = H
13, $R^1 = R^4$ = H; $R^2 = R^3$ = *trans*-cinnamoyl



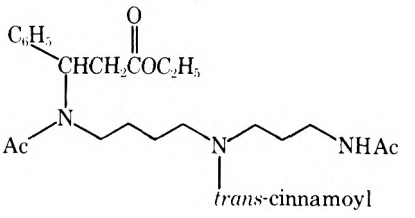
14



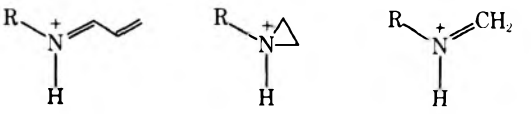
15



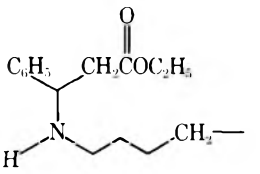
16



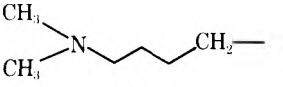
17



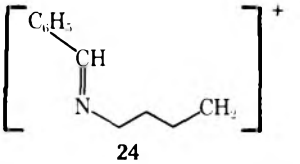
18, R = R' **19,** R = R' **20,** R = R'
21, R = R'' **22,** R = R'' **23,** R = R''



R'



R''



24

presence of the *m/e* 146 peak in compounds **3–6**, which do not contain a cinnamide moiety, and the absence of a peak at *m/e* 148 ($C_9H_{10}NO$) for **5** and *m/e* 150 ($C_9H_8D_2NO$) for **6** suggest that the *m/e* 146 peak arises from elimination of the β-amino amide to yield a dicinnamoyl spermidine, which then undergoes cleavage at the C-4–N-5 bond. Although a triple cleavage might generate a similar *m/e* 146 peak for **15**, the $M^+ - C_9H_8NO$ peak (iii) observed in **1**, **5**, and **6** would not be possible for **15** and its derivatives.

Peaks at $M^+ - C_3H_6NO$ (i), attributed to a double cleavage in which the ring amide and either the C-7 or C-4 methylene groups are lost, provide additional support for assignment of structure **1** to celacinnine. No reasonable rationalization for loss of this fragment was possible for alternative structure **15**, and high-resolution mass spectroscopy clearly established that the *m/e* 333 peak did not result from loss of $C_4H_{10}N$, an alternative fragment which might arise from either **1** or **15**.

Loss of the acyl side chain (cleavage e) gave a peak (ii) at *m/e* 274, which changed to *m/e* 288 and 316 in the corresponding *N*-methyl (**7**) and *N*-acetyl (**8**) derivatives. Prominent peaks in all the spectra at *m/e* 160 (iv, $C_{11}H_{14}N$) and 159 (v, $C_{11}H_{13}N$) can be derived by cleavage b with loss of the substituent on N (cleavage g), followed by fragmentation f to give ion **24**.

A number of closely related spermidine alkaloids have been reported, including periphylline[18] and maytenine (**12**),[19,20] from Celastraceae species, and the *Lunaria* alkaloids.[20] A second series of alkaloids based on spermine, including homaline[20] and chaenorhine,[15] has many similarities. Most such alkaloids appear to originate from dicinnamic acid amides of the tri- or tetraamine, but in a few cases other acyl groups have been incorporated. Unlike many other alkaloids, these compounds do not seem to be associated with a particular plant family.

Experimental Section

Melting points were determined on a Hoover Uni-Melt melting point apparatus and are uncorrected. Values of $[\alpha]_D$ were obtained on a Perkin-Elmer 141 polarimeter. CD spectra were measured on a modified JELCO instrument.[21] UV spectra were determined on a Beckman DK-2A ratio recording spectrophotometer or a Coleman Hitachi EPS-3T spectrometer, IR spectra on a Perkin-Elmer 257 spectrophotometer, and NMR spectra on a Varian HA-100 spectrometer. MS were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer and high-resolution mass spectra (HRMS) on an AEI MS-902 mass spectrometer. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Celacinnine (1) and Celallocinnine (2) from *M. serrata*. The ground dried twigs of *Maytenus serrata* (1.5 kg) were extracted with cold aqueous EtOH (1:1) for 3 days. Evaporation yielded an extract (178 g), which was partitioned between EtOAc and H_2O. The EtOAc-soluble fraction (20 g) was chromatographed on SilicAR CC-7 (Mallinckrodt, 500 g); elution with $CHCl_3$ followed by 5% MeOH/$CHCl_3$ yielded the alkaloid fraction (1.7 g). The alkaloid fraction was chromatographed on neutral alumina (activity I, Woelm, 20 g) and eluted with C_6H_6 followed by $CHCl_3/C_6H_6$ (1:1). The resulting crystalline fractions (310 mg) were rechromatographed on alumina and repeatedly crystallized from hexane/$CHCl_3$ to give fine needles of celacinnine (**1**, 31 mg): mp 203–204 °C; $[\alpha]^{25}_D$ −19° (*c* 0.16, $CHCl_3$); CD max (MeOH) 230, 275 nm ($\Delta\epsilon$ −2.0, 1.7); UV (MeOH) λ_{max} 223 (infl), 277 nm (ϵ 16 000, 23 000); IR ($CHCl_3$) 2.89, 3.00, 6.06, 6.25, 6.45, 6.67 μm; IR (KBr) 3.0 (br), 6.02, 6.24, 6.46, 6.67, 13.0, 14.3 μm; MS *m/e* 405.2423 (M^+ calcd for $C_{25}H_{31}N_3O_2$, 405.2416).

Anal. Calcd for $C_{25}H_{31}N_3O_2$: C, 74.04; H, 7.71; N, 10.36. Found: C, 73.71; H, 7.66; N, 10.19.

The combined mother liquors (300 mg) from a number of isolations were separated by TLC on silica gel (10% MeOH/EtOAc) to give two basic fractions having R_f 0.60 and 0.55, respectively. The higher R_f fraction on crystallization from $Et_2O/CHCl_3$ yielded **1** (117 mg). The lower R_f fraction (46 mg) was recrystallized from EtOAc/Et_2O/hexane to give needles of celallocinnine (**2**, 13 mg): mp 172–173 °C; $[\alpha]^{25}_D$ −24° (*c* 0.23, $CHCl_3$); CD max (MeOH) 225, 255, 275 nm ($\Delta\epsilon$ −1.0, 0.3, −0.16); UV (MeOH) λ_{max} 255, 264 (infl) nm (ϵ 11 800, 9500); IR ($CHCl_3$) 2.76 2.90, 6.02, 6.20 μm; MS *m/e* 405 (M^+).

Anal. Calcd for $C_{25}H_{31}N_3O_2$: C, 74.04; H, 7.71. Found: C, 74.09; H, 7.76.

Celacinnine (1), Celafurine (3), and Celabenzine (4) from *T. wilfordii*. The ground dried roots of *Tripterygium wilfordii* (21 kg) were extracted with refluxing 95% EtOH for 2 days. Evaporation yielded an extract (2 kg), which was partitioned between EtOAc and H_2O. The EtOAc-soluble fraction (722 g) was extracted with 0.5 M citric acid, which was then made basic by addition of NH_4OH. Extraction of the basic solution with EtOAc and subsequent concentration at reduced pressure yielded a crude mixture of alkaloids (14.8 g), a portion (12.4 g) of which was separated by TLC on alumina (10% MeOH/EtOAc). The major component, R_f 0.5–0.7, was recovered to yield an enriched alkaloid fraction (6.5 g), and a portion (4.7 g) of the enriched fraction was chromatographed on a silica gel column (Merck, 70–325 mesh, 500 g). Slow elution with EtOAc yielded a mixture of the alkaloids (1.27 g) from which TLC on alumina (EM, Type T, 10% MeOH/EtOAc) gave two fractions, R_f 0.45 and 0.50. The lower band (300 mg) was recovered and crystallized from EtOAc to yield celafurine (**3**, 250 mg): mp 154–155 °C; $[\alpha]^{25}_D$ −11° (*c* 0.11, $CHCl_3$); UV (95% EtOH) λ_{max} 222 (infl), 232 (infl), 285 nm (ϵ 10 000, 6960, 1230); IR ($CHCl_3$) 2.91, 3.00, 6.04, 6.19, 6.65, 6.99, 8.35 μm; MS *m/e* 369.2063 (M^+ calcd for $C_{21}H_{27}N_3O_3$, 369.2052).

Anal. Calcd for $C_{21}H_{27}N_3O_3$: C, 68.35; H, 7.32; N, 11.38. Found: C, 68.09; H, 7.40; N, 11.19.

TLC of the higher band on silica (ChromAR 7GF, Mallinckrodt) with 10% MeOH/EtOAc gave two closely spaced bands having R_f 0.45 and 0.50, respectively. The higher R_f fraction (140 mg) was crystallized from EtOAc to yield celacinnine (**1**, 120 mg). The lower R_f fraction crystallized from EtOAc to yield celabenzine (**4**, 28 mg): mp 156–158 °C; $[\alpha]^{25}_D$ 0° (*c* 0.14, $CHCl_3$); UV (95% EtOH) λ_{max} 258 (infl), 264 (infl), 268 (infl) nm (ϵ 1390, 935, 685); IR ($CHCl_3$) 2.90, 3.00, 6.04, 6.20, 6.48, 6.99, 7.60, 8.95 μm; MS *m/e* 379.2202 (M^+ calcd for $C_{23}H_{29}N_3O_2$, 379.2260).

Anal. Calcd for $C_{23}H_{29}N_3O_2$: C, 72.82; H, 7.65; N, 11.08. Found: C, 72.79; H, 7.64; N, 11.07.

Dihydrocelacinnine (5). A. From Celacinnine (1). A solution of celacinnine (37 mg) in EtOAc (10 mL) was hydrogenated over 10% Pd/C for 4 h. The product was crystallized from EtOAc/Et_2O/hexane to give dihydrocelacinnine (**5**, 12.5 mg): mp 172–173 °C; UV (MeOH) λ_{max} 253, 260, 265, 269 nm (ϵ 520, 600, 520, 380); IR ($CHCl_3$) 2.78, 6.03, 6.14 μm; MS *m/e* 407.2574 (M^+ calcd for $C_{25}H_{33}N_3O_2$, 407.2573).

Anal. Calcd for $C_{25}H_{33}N_3O_2$: C, 73.67; H, 8.16; N, 10.31. Found: C, 73.91; H, 7.92; N, 10.20.

B. From Celallocinnine (2). A solution of celallocinnine (12 mg) in EtOAc (5 mL) was hydrogenated over 5% Pd/C for 4 h. The product was crystallized twice from EtOAc/Et_2O/hexane to give dihydrocelacinnine (**5**, 3.3 mg), identical with material from A on comparison by TLC, UV, IR, NMR, and MS.

Dideuteriocelacinnine (6). A solution of celacinnine (16 mg) in EtOAc (5 mL) was hydrogenated using deuterium over 10% Pd/C for 5 h (uptake 0.95 mol). The product was crystallized from EtOAc/Et_2O/hexane to give dideuteriocelacinnine (**6**, 9.6 mg): mp 174–175 °C; UV (MeOH) λ_{max} 254, 260, 265, 269 nm (ϵ 630, 680, 630, 580); IR ($CHCl_3$) 2.90, 6.02, 6.13, 10.9 μm; isotopic purity by MS, 95% (M^+:M^+ − 2) MS *m/e* 409.2713 (100%; M^+ calcd for $C_{25}H_{31}D_2N_3O_2$, 409.2698).

Vigorous Hydrolysis of Celacinnine. A solution of celacinnine (**1**, 58 mg) in 2 N HCl (3 mL) in a sealed tube was heated to 150 °C. After 17 h the solution was cooled and extracted with EtOAc (two 10-mL portions). The aqueous solution was neutralized ($NaHCO_3$), then washed with $CHCl_3$ (three 10-mL portions) and evaporated to dryness under vacuum. The residue was dissolved in dry MeOH and saturated with HCl gas. After evaporation the residue was dissolved in pyridine (2 mL) and acetic anhydride (0.5 mL) and kept at room temperature overnight. The solution was worked up to yield an oil, which was separated by TLC on silica gel (25% MeOH/EtOAc). The major component, R_f 0.2, was triacetylspermidine (**9**, 2.0 mg), identical with an authentic sample by TLC (silica gel, 25% MeOH/EtOAc and 5% HOAc/acetone) and by MS.

Mild Hydrolysis of Celacinnine. A solution of celacinnine (15 mg) in 6 N HCl (6 mL) was heated to 100 °C in a sealed tube for 2 h. The cooled solution was neutralized ($NaHCO_3$) and freeze-dried, and the residue dissolved in dry EtOH saturated with HCl gas and stirred. After evaporation, the product was dissolved in pyridine (1 mL) and acetic anhydride (0.2 mL) and allowed to stand at room temperature for 12 h. Evaporation of the pyridine followed by TLC of the residue on silica gel (EtOH/EtOAc) yielded degradation product **17**, R_f 0.7, as a pale yellow oil: IR 5.78, 6.00, 6.18, 7.25, 8.38 μm; NMR τ 2.25 (d, 1 H, *J* = 15.5 Hz), 2.6–2.9 (m, 10 H), 3.15 (d, 1 H, *J* = 15.5 Hz), 4.30 (dd, 1 H, *J* = 3, 12 Hz), 6.00 (q, 2 H, *J* = 7 Hz), 6.0–8.5 (m, 17 H), 7.56

(s, 3 H), 7.85 (s, 3 H), 8.82 (t, 3 H, J = 7 Hz); MS m/e 535.3044 (M^+ calcd for $C_{31}H_{41}N_3O_5$, 535.3036).

***N*-Acetylcelacinnine (8).** Celacinnine (20 mg) was dissolved in pyridine (2 mL) and acetic anhydride (0.5 mL) was added. The mixture was stirred at room temperature (24 h), $CHCl_3$ (25 mL) was added, and the solution was washed with H_2O (three 10-mL portions). The $CHCl_3$ fraction was dried (Na_2SO_4) and the solvent evaporated. Chromatography of the residue on alumina (10% MeOH/EtOAc) yielded *N*-acetylcelacinnine (**8**, 14 mg) as a white amorphous powder: IR 6.00, 6.10, 6.18, 6.33 μm; MS m/e 447.2476 (M^+ calcd for $C_{27}H_{33}N_3O_3$, 447.2514).

***N*-Methylcelacinnine (7).** Celacinnine (**1**, 18 mg) was dissolved in EtOH (1 mL) and methyl iodide (0.5 mL) was added. The mixture was heated at 65 °C for 20 h. After removal of solvent, chromatography of the residue on silica gel (10% MeOH/EtOAc) yielded *N*-methylcelacinnine (**7**, 13 mg): UV (MeOH) λ_{max} 224 (infl), 279 nm (ϵ 14 200, 22 100).

Hofmann Degradation of *N*-Methylcelacinnine. A solution of **7** (9 mg) and methyl iodide (1.5 mL) in acetone (1 mL) was heated at 65 °C for 24 h. After evaporation of the solvent, distilled water (1 mL) and silver oxide (10 mg, freshly prepared) were added to the residue and the mixture was stirred at room temperature for 20 h. The solution was filtered and the filtrate was concentrated to dryness. The residue was heated at 140 °C for 20 h and then separated by TLC on silica gel (10% MeOH/EtOAc) to yield the degradation product (**10**, 1 mg): MS m/e (rel intensity) 433 (3), 334 (27), 302 (13), 257 (33), 243 (98), 188 (85), 187 (100), 155 (10), 143 (12), 131 (100), 129 (21).

Synthesis of Degradation Product 10. Spermidine (5 g) was added to a suspension of barium hydroxide (6 g) in EtOH (200 mL), and cinnamoyl chloride (8.5 g) was added in small portions with stirring and cooling over 1 h. The mixture was then stirred at room temperature overnight. The solution was filtered and the filtrate was concentrated to dryness. Chromatography on alumina (Woelm, neutral, 200 g) using CH_2Cl_2 as eluent gave tricinnamoylspermidine (4.7 g), and elution with CH_2Cl_2/MeOH (1:1) gave a mixture of three products. Rechromatography of the mixture on alumina (15% MeOH/CH_2Cl_2) yielded *N,N'*-dicinnamoylspermidine (**11**, 248 mg): mp 127 °C; UV (MeOH) λ_{max} 223, 276 nm (ϵ 29 600, 41 000); IR (KBr) 2.90, 3.03, 6.06, 6.22, 6.45 μm; MS m/e (rel intensity) 405 (M^+, 5), 336 (7), 335 (6), 314 (5), 274 (9), 245 (13), 205 (36), 188 (30), 131 (100), 127 (29), 115 (4), 103 (98), 101 (4). Additionally, bands were obtained for maytenine (**12**, 2.3 g)[17] and for *N',N''*-dicinnamoylspermidine (**13**, 9 mg): mp 107 °C; UV (MeOH) λ_{max} 223, 278 nm (ϵ 27 300, 40 500); IR (KBr) 2.90, 3.08, 5.97, 6.15, 6.45; MS m/e (rel intensity) 405 (M^+, 4), 387 (4), 335 (8), 300 (8), 274 (10), 257 (10), 245 (14), 231 (10), 205 (36), 188 (34), 159 (56), 153 (16), 131 (100), 127 (26), 115 (6), 103 (98), 101 (5).

A solution of the dicinnamoylspermidine **11** (20 mg) and methyl iodide (0.6 mL) in EtOH (1 mL) was kept at room temperature for 3 days and then heated at 100 °C for 3 days. The product was chromatographed on alumina (15% MeOH/CH_2Cl_2) to yield **10** (6 mg), identical by MS with material from the Hofmann degradation of *N*-methylcelacinnine.

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Registry No.—**10**, 63301-68-8; **11**, 63301-69-9; **13**, 63301-70-2; **17**, 53938-10-6; spermidine, 124-20-9; cinnamoyl chloride, 17082-09-6.

References and Notes

(1) (a) Supported by grants from the National Cancer Institute, U.S. Public Health Service (CA 11718 and CA 125059), and the American Cancer Society (CI-102K). (b) Deceased October 19 1976. (c) School of Natural Resources, University of the South Pacific, Box 1168, Suva, Fiji.
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W-7783, a Unique Antifungal Antibiotic

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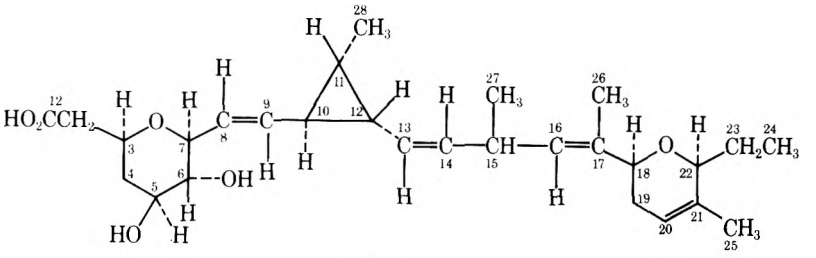
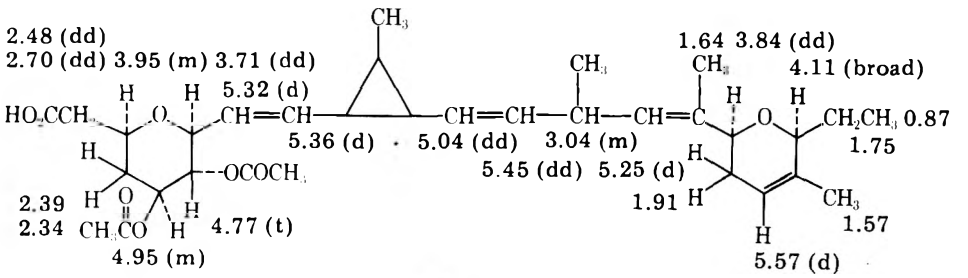
W-7783, $C_{28}H_{42}O_6$, an antifungal antibiotic with a unique structure, is produced by a myxobacteriale *Polyangium cellulosum* var. *fulvum*. The structure was deduced from chemical and spectral evidence including single-crystal x-ray analysis.

The structure of W-7783 (5,6-dihydroxypolyangioic acid),[2] an antifungal antibiotic produced by growth under appropriate conditions from a soil inhabiting myxobacteriale *Polyangium cellulosum* var. *fulvum*,[3a] has been deduced from chemical and spectral data including single-crystal x-ray analysis. W-7783 shows in vitro[3a] and in vivo activity[3b] against a variety of pathogenic fungi including *Histoplasma capsulatum* and *Coccidioides immitis*. *Histoplasmois* and *coccidioidomycosis* are treated at the present time with the highly toxic agent amphotericin B requiring iv administration and prolonged hospitalization. W-7783 (**1**, see Scheme I) represents a completely novel type of antibiotic. It is an orally active

Scheme I

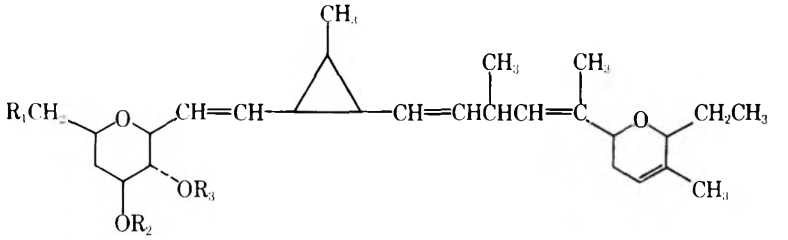


A L C



2

Scheme II



1. $R_1 = CO_2H$, $R_2 = R_3 = H$
2. $R_1 = CO_2H$, $R_2 = R_3 = COCH_3$
3. $R_1 = CO_2CH_3$, $R_2 = R_3 = H$
4. $R_1 = CO_2CH_3$, $R_2 = R_3 = COCH_3$
5. $R_1 = CH_2OH$, $R_2 = R_3 = H$
6. $R_1 = CH_2OCOCH_3$, $R_2 = R_3 = COCH_3$
7. $R_1 = CH_2OCOH$, $R_2 = R_3 = COH$
8. $R_1 = CH_2Br$, $R_2 = R_3 = COH$
9. $R_1 = CH_2Br$, $R_2 = R_3 = H$

antifungal agent, with a unique chemical structure, and is produced by a type of organism previously unexplored in the search for therapeutic agents.

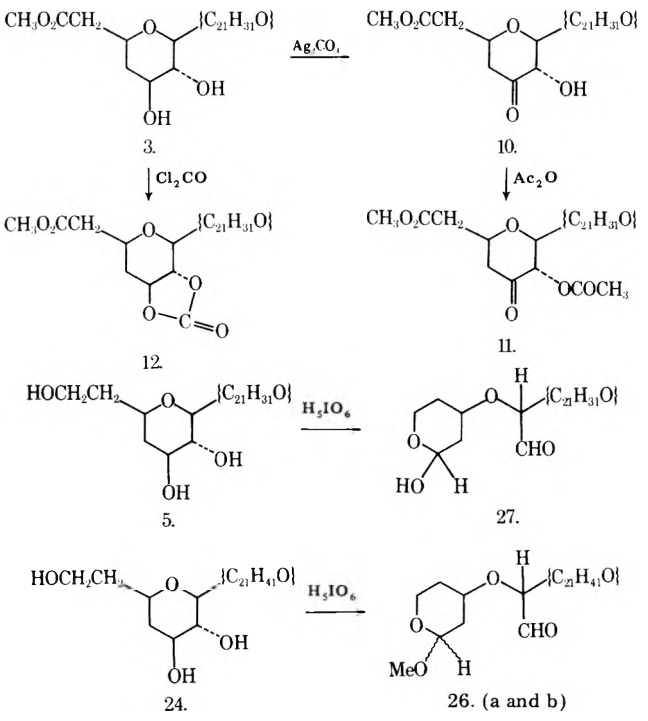
The molecular ion in the mass spectrum indicated a molecular formula $C_{28}H_{42}O_6$ (474). The infrared spectrum showed a carbonyl band at 1720 cm^{-1} and the ultraviolet spectrum indicated the molecule contained no conjugated functions. Acid **1** was converted to diacetate **2** and monomethyl ester **3** (Scheme II). The ester was converted to diacetate **4**, which showed no hydroxyl stretching in the infrared spectrum, indicating **1** is a dihydroxymonocarboxylic acid. Reduction of acid **1** or ester **3** with lithium aluminum hydride gave triol **5**, which was acetylated to give triacetate **6**. The ester was catalytically hydrogenated to give octahydro ester **19** indicating **1** contains four double bonds and thus three rings.

The ^{13}C NMR spectrum of **1** showed a carbonyl C (δ 175.1) and confirmed the presence of four double bonds (vinyl C resonances at δ 139.4, 136.0, 135.4, 129.9, 125.5, 124.1, and 121.3). The eighth vinyl C resonance was not clearly observed above the background. In the coupled spectrum these resonances were all doublets with the exception of the resonance at δ 135.4 (singlet). The presence of six carbons adjacent to oxygen (δ 80.7, 78.2, 78.1, 75.9, 72.3, and 71.7) was observed and all were doublets in the coupled spectrum. Two of these resonances represent the carbons attached to two secondary hydroxyl groups. Thus, the other four resonances must represent two ether linkages of the type >ĊHOĊH<. The spectrum also showed four methylene carbons (δ 40.3, 38.3, 30.2, and 25.6), four methine carbons (δ 35.0, 30.5, 29.0, and 21.6), and five methyl carbons (δ 21.2, 18.9, 13.0, 12.3, and 8.2).

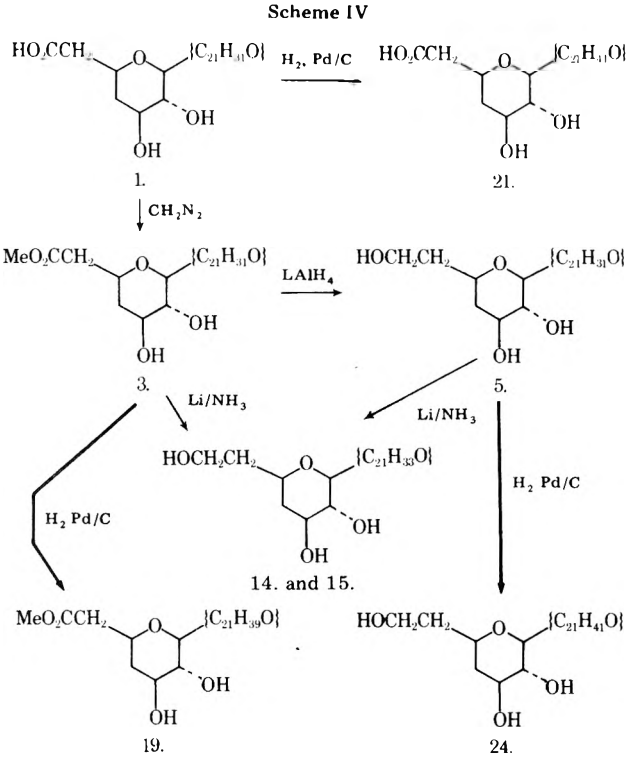
The ^1H NMR spectrum of diacetate **2** showed six vinyl protons (δ 5.57, 5.45, 5.36, 5.32, 5.25, and 5.04) and two vinyl methyl groups (δ 1.64 and 1.57), confirming the presence of four double bonds. Two protons (δ 4.95 and 4.77) on carbons next to acetoxy and the four protons (δ 4.11, 3.95, 3.84, and 3.71) of the two ether systems were observed. Other important features were a resonance at δ 3.04 characteristic of a proton on a bisallylic carbon and two quartets (δ 2.70 and 2.48) assigned to a methylene group next to the carboxylic acid function. The five methyl groups indicated by the ^{13}C NMR spectrum were also observed and assigned the following environments: two $CH_3C{=}C$ (δ 1.64 and 1.57), two CH_3CH (δ 1.01), and one CH_3CH_2 (δ 0.87).

The important mass spectral fragmentations of ester **3** are shown in Scheme V. Fragments at 171, 215, and 197 indicate a highly oxygenated fragment connected to a double bond ($C_8H_{13}O_5CH{=}CH$-). ^1H NMR decoupling experiments on diacetate **2** together with chemical evidence indicate this gragment has the structure (ring A) shown in Scheme I. Irradiation at δ 3.71 (C_7H) decouples δ 5.32 (d to s, C_8H) and δ 4.77 (t to d, C_6H). Irradiation at δ 3.95 (C_3H) decouples at C_2 2.48 (dd to d) and 2.70 (dd to d). Irradiation at δ 5.32 (C_8H) decouples at δ 3.71 (dd to d, C_7H). Irradiation at δ 4.95 (C_5H) collapses δ 2.34 (C_4H) and 2.39 (C_4H). The vicinal nature of the hydroxyl groups was deduced in several ways. Triol **5** was oxidized to aldehyde **27** with periodic acid (a reagent specific for vicinal diols). This oxidation was not reproducible with **5**

Scheme III



Scheme IV



and only small yields of **27** Were occasionally isolated. The reaction was reproducible with triol **24**, which was oxidized to isomeric acetals **26a** and **26b** under the same conditions. ^{1}H NMR and mass spectra indicate **26** has the structure shown in Scheme III.

Ester **3** formed cyclic carbonate **12**, with phosgene in pyridine showing a carbonyl band at 1820 cm^{-1} (five membered ring) in the IR. Ester **3** was oxidized with silver carbonate on Celite to ketone **10**, which was converted to acetate **11**. The ^{1}H NMR of **11** showed the following resonances not present in the NMR of **2**, at δ 2.54 (d, 1, J = 16 Hz) and at δ 2.65 (d, 1, J = 16 Hz) due to the C_4 hydrogens (now next to the newly generated carbonyl group) and at δ 5.00 (d, 1, J = 5 Hz) due to the C_6H which has moved downfield due to the presence of the adjacent carbonyl group and is no longer split by the hydrogen at C_5.

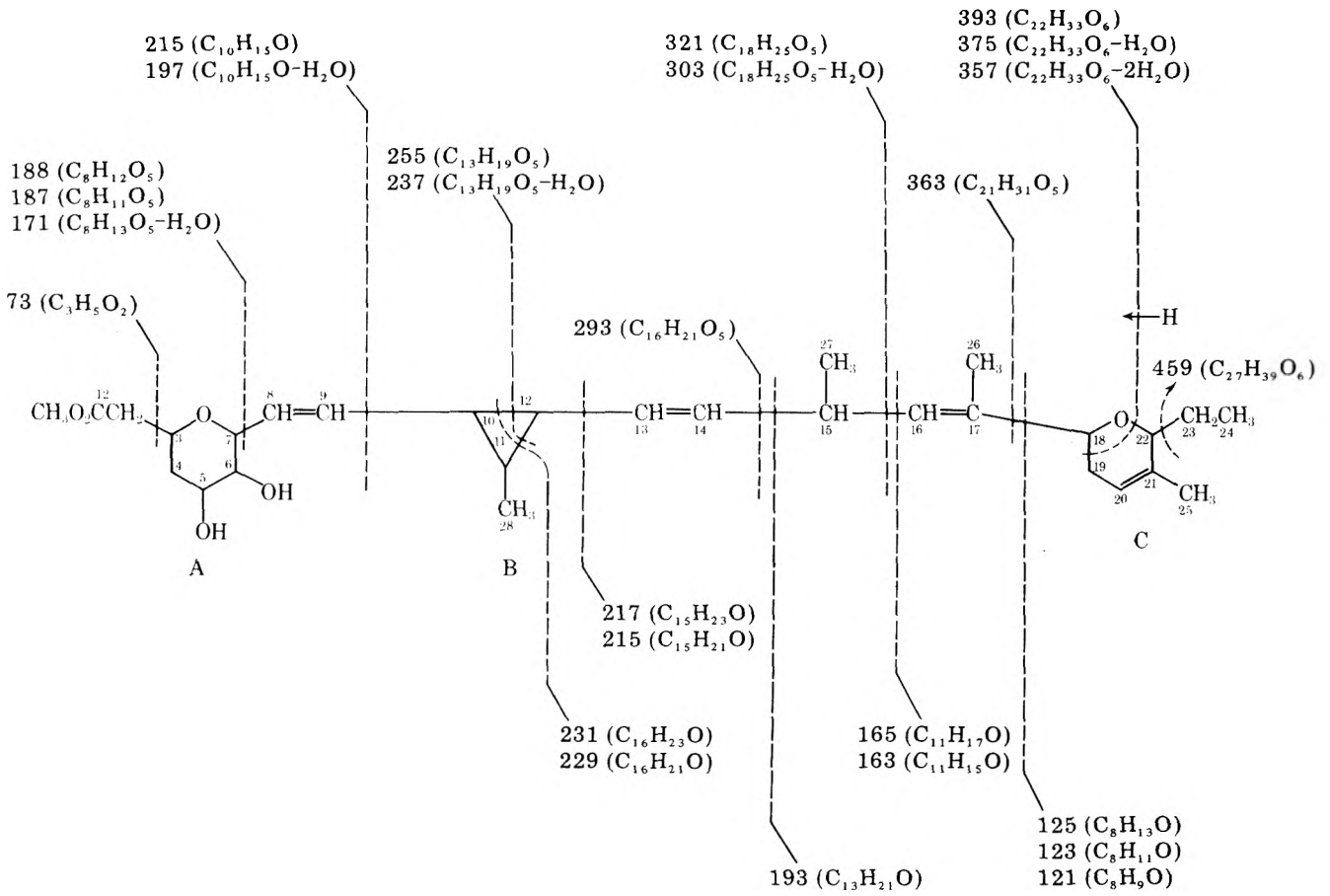
The mass spectrum also shows prominent fragments containing one oxygen at 125 ($C_8H_{13}O$), 165 (-CH=C(CH$_3$)-$C_8H_{13}O$) and 193 (-CH(Me)C=C(CH$_3$)$C_8H_{13}O$). Irradiation at δ 3.04 decouples at δ 5.45 (dd to d, C_{14}H) and 5.25 (d to s, C_{16}H) establishing the system CH=CHCH(Me)CH=C(Me)- in the molecule. The coupling constants and mass spectral fragments rule out the C_8–C_9 double bond from being part of this system and thus it constitutes the C_{13} to C_{17} portion as shown in **1**. This leaves a C_4H_6 moiety to link G_9 and C_{13}. The $C_8H_{13}O$ fragment must contain a CH–O–CH, a CH=CCH$_3$, an ethyl group, and a –CH$_2$–, for none of these groups could be fitted into the C_4H_6 fragment and make sense in light of the spectral evidence presented above. The $C_8H_{13}O$ fragment must contain a ring as well as the double bond, and the arrangement shown as ring C in **1** is the only one which fits the ^{1}H NMR evidence. Neither C_{18}H nor C_{22}H is coupled to C_{20}H and neither is a singlet. Irradiation at δ 1.91 decouples δ 3.84 (dd to d, C_{18}H) and 5.57 (d to s, C_{20}H). Irradiation at δ 4.11 (C_{22}H) simplifies the pattern at δ 1.75. The only carbons not now accounted for in the ^{13}C NMR spectrum are one methyl and three methines, and they must constitute the C_4H_6 fragment.

In addition to the straightforward chemistry described above, certain anomalous reactions were observed. Thus, catalytic hydrogenation of ester **3** gave the expected octahydro ester **19**, but hydrogenation of acid **1** or triol **5** under the same conditions gave decahydro compounds **21** and **24**. All the reduced compounds gave the expected acetates, indicating that no C–O–C bonds had been reduced and thus the extra molecule of hydrogen was introduced by C–C bond breaking in a ring.

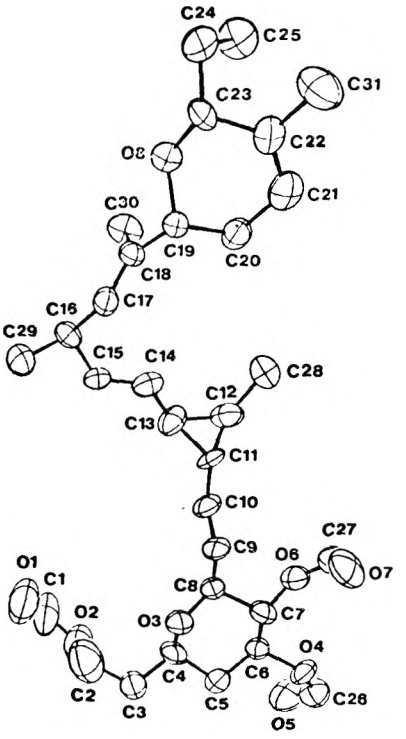
Reduction of ester **3** or triol **5** with lithium in liquid ammonia gave dihydrotriols **14** and **15**[4] and tetraol **13**. Initially, a triple bond to double bond transformation was suspected (acetylation indicates no extra hydroxyl groups are generated), but the ^{1}H NMR indicated six vinyl hydrogens (as in the unreduced compound). All the vinyl hydrogens had undergone shifts (all crowded around δ 5.41 to 5.18) except C_{20}H, further indicating it to be off in a ring by itself. The only type of C–C bonds broken by lithium in liquid ammonia are those in which the negative charges formed by bond breaking are stabilized by adjacent conjugation, and the bond broken is under strain.[5] Thus, the system –C=CC_{10}–C_{12}C=C– must be present in **1**, and the C_{10}–C_{12} bond must be part of a ring and be under strain. A possible arrangement for the C_4H_6 fragment is cyclopropane ring B, and this conveniently provides the double bond strained single bond–double bond system needed to explain the lithium in liquid ammonia reductions and anomalous catalytic hydrogenations. Attempts to obtain further evidence by cleaving the system with ozone gave a complex mixture from which no pure compounds were obtained.

To distinguish the proposed structure **1** from other alternatives that were considered, it was necessary to carry out an x-ray structure determination. In order to do the x-ray crystallography, a large number of derivatives were prepared, almost all of which were oils or gums. Triol **5** formed crystalline compounds with aryl isocyanates and they could be recrystallized to give analytically pure samples **28** and **29**, but no suitable crystals for x-ray analysis could be grown. The bromodiformate **8** was prepared from triol **5** with Ph_3PBr_2 and DMF.[6] This would have been the ideal compound for x-ray work. It could be recrystallized from ethanol by cooling and filtering the crystals, but attempts to obtain larger crystals by slow evaporation of the solvent resulted in hydrolysis to noncrystalline bromodiol **9**. The main product from the re-

Scheme V



Scheme VI



action of triol 5 with Ph_3PBr_2 and DMF was triformate 7.

Unequivocal proof of the structure and stereochemistry of 1 was provided by single-crystal x-ray analysis[7] of polyangi-1,5,6-triol triformate (7) which crystallized from ethanol in the monoclinic system, space group $P2_1$, a = 15.671 (4), b = 5.309 (2), c = 19.995 (4) Å, β = 110.80° (2), z = 2. There were 2439 independent reflections measured on a Syntex P1 diffractometer using graphite monochromated Cu-K_α radiation. The structure was solved by direct methods and refined by full-matrix least-squares to an R value of 0.087.

The x-ray structure indicates that the double bonds at C_8–C_9, C_{13}–C_{14}, and $C_{16}C_{17}$ are all trans with respect to the chain. Ring A is in a chair conformation and the substituents at 3, 5, 6, and 7 are all equatorial. The substituents at 3, 5, and 7 are cis with respect to each other and trans to the 6 substituent. On the cyclopropane ring the methyl group is cis to the C_{12} substituent and trans to the C_{10} substituent. In ring C, the ethyl group and the C_{18} substituent are both equatorial and cis to each other. A computer drawing of the x-ray structure of triformate 7 is shown in Scheme VI.[8]

Experimental Section[9]

Melting points were measured with a Thomas-Hoover capillary melting-point apparatus without correction. ^1H NMR spectra were run in $CDCl_3$ on a Perkin-Elmer R-12B 60 MHz or Varian HR-220[10] spectrometer with Me_4Si used as internal standard. The ^{13}C NMR spectrum was run in $CDCl_3$ on a Varian XL-100 at 25.2 MHz in the pulsed fourier transform mode. Mass spectra[11] were obtained with an AE1 MS-902 instrument. TLC was performed on silica gel plates (Quantum) using iodine vapors for visualization.

Isolation of W-7783 (1). The crude acid was extracted from the fermentation medium with ethyl acetate and purified by preparative TLC with the solvent system ethyl acetate–2-propanol–water (85:10:5). The pure acid (homogeneous by TLC0 was obtained as a gum, which could be ground to give an off-white amorphous powder: IR (film) 3600–3200 (br, OH), 2800–2400 (OH), 1720 cm^{-1} (CO); ^{13}C NMR δ 175.1 (s, c=O), 139.4 (d, H-C=), 136.0 (d, H-C=), 135.4 (s, C=), 129.9 (d, H-C=), 125.5 (d, H-C=), 124.1 (d, H-C=), 121.3 (d, H-C=), 80.7 (d, H-C-O), 78.2 (d, H-C-O), 78.1 (d, H-C-O), 75.9 (d, H-C-O), 72.3 (d, H-C-O), 71.7, (d, H-C-O), 40.3 (t, CH_2), 38.3 (t, CH_2), 35.0 (d, CH), 30.5 (d, CH), 30.2 (t, CH_2), 29.0 (d, CH), 25.6 (t, CH_2), 21.6 (d, CH), 21.2 (q, CH_3), 18.9 (q, CH_3), 13.0 (q, CH_3), 12.3 (q, CH_3), 8.2 (q, CH_3); mass spectrum m/e (rel intensity) 474 (20), 456

(13), 445 (30), 379 (18), 279 (20), 193 (100). Found M^+ 474.3009; $C_{28}H_{42}O_6$ requires 474.2981.

Anal. Calcd for $C_{28}H_{42}O_6 H_2O$: C, 68.26; H, 9.00. Found: C, 68.07; H, 8.78.

Methyl 5,6-Dihydroxypolyangioate (3). Excess diazomethane in ether was added to W-7783 (100 mg) in ethanol (10 mL). The solution was allowed to stand at room temperature for 15 min. A few drops of acetic acid were added and the solvents were removed at reduced pressure to give a yellow oil. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) to give a colorless oil (90 mg): IR (film 3600–3200 (br, OH), 1730 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 488 (6), 470 (2), 460 (11), 459 (47), 393 (14), 375 (10), 363 (7), 357 (6), 321 (10), 305 (3), 303 (6), 294 (7), 293 (12), 279 (7), 277 (9), 255 (17), 237 (27), 231 (8), 229 (9), 217 (8), 215 (10), 215 (3), 211 (48), 197 (16), 193 (69), 188 (10), 171 (52), 165 (64), 163 (44), 159 (100), 152 (79), 139 (45), 135 (48), 129 (90), 127 (74), 125 (83), 124 (26), 123 (81), 122 (32), 121 (30), 120 (19), 119 (8), 73 (17). Found: M^+ 488.3240; $C_{29}H_{44}O_6$ requires 488.3238.

5,6-Dihydroxypolyangioic acid, Diacetate 2. Acetic anhydride (1 mL) was added to a solution of W-7783 (100 mg) in pyridine (2 mL). The reaction mixture was allowed to stand at room temperature overnight. A few drops of water were added and the solvents were removed at reduced pressure to give a brown oil. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) to give a colorless oil (homogeneous by TLC) (84 mg, 71%): IR (film) 1745 (CO), 1720 cm^{-1} (CO); ^1H NMR δ 5.57 (d br, 1, $C_{20}H$), 5.45 (dd, 1, J = 15.5 and 6.2 Hz, $C_{14}H$), 5.36 (d, 1, C_9H), 5.32 (d, 1, C_8H), 5.25 (d, 1, J = 9.2 Hz, $C_{16}H$), 5.04 (dd, 1, J = 15.5 and 8.2 Hz, $C_{13}H$), 4.95 (m, 1, C_5H), 4.77 (t, 1, J = 9.5 and 9.5 Hz, C_6H), 4.11 (br, $C_{22}H$), 3.95 (m, 1, C_3H), 3.84 (dd, 1, J = 2.2 and 10.5 HZ, $C_{18}H$), 3.71 (dd, 1, J = 5.7 and 9.5 Hz, C_7H), 3.04 (m, 1, $C_{15}H$), 2.70 (dd, 1, J = 5.5 and 16.0 HZ, C_2H), 2.48 (dd, 1, J = 5.5 and 16.0 Hz), 2.39 (m, 1, C_4H), 2.34 (m, 1, C_4H), 2.00 (s, 3, CH_3CO), 1.98 (s, 3, CH_3CO), 1.64 (s, 3, CH_3C=), 1.57 (s, 3, CH_3C=), 1.01 (m, 6, 27-CH_3 and 28-CH_3), 0.87 (t, 3, 24-CH_3); mass spectrum *m/e* (rel intensity) 558 (10), 529 (32), 463 (14), 345 (7), 245 (32), 193 (100), 165 (57), 125 (70). Found: $M^+ - 29$, 529.2939; $C_{30}H_{41}O_8$ requires 529.2801.

Methyl 5,6-Dihydroxypolyangioate, Diacetate 4. Prepared from methyl 5,6-dihydroxypolyangioate (100 mg) by the general method described for the preparation of acetate 2. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) to give a colorless oil (80 mg): IR (film) 1740 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 572 (23), 543 (53), 477 (29), 259 (35), 193 (100).

Polyangi-1,5,6-triol 5. Lithium aluminum hydride (100 mg) was added to a solution of W-7783 (100 mg) in THF (20 mL). The reaction mixture was refluxed with stirring under nitrogen for 3 h. The mixture was cooled in an ice bath, and a few drops of water were added, followed by magnesium sulfate (50 mg). The inorganic solids were filtered off and thoroughly washed with ethyl acetate. The filtrate and washings were evaporated to give a colorless oil. The product was purified by preparative TLC with the solvent system ethyl acetate–2-propanol–water (85:10:5) to give a colorless oil (75 mg, 77%) (homogeneous by TLC): IR (film) 3400–3200 cm^{-1} (br, OH); mass spectrum *m/e* (rel intensity) 460 (6), 442 (5), 431 (52), 365 (6), 347 (26), 329 (10), 195 (75), 193 (100), 167 (100), 165 (100), 152 (100), 125 (100), 123 (100). Found: 123 (100). Found: M^+ 460.3223; $C_{28}H_{44})_5$ requires 460.3189.

Polyangi-1,5,6-triol, Triacetate 6. Acetic anhydride (1 mL) was added to a solution of **5** (30 mg) in pyridine (2 mL). The reaction mixture was allowed to stand at room temperature overnight. A few drops of methanol were added and the solvents were removed at reduced pressure to give a colorless oil. The product was purified by preparative TLC with the solvent system ethyl acetate– cyclohexane (4:1) to give a colorless oil (homogeneous by TLC) (30 mg, 79%): IR (film) 1740 cm^{-1} (CO); ^1H NMR δ 5.58 (d br, 1, $C_{20}H$), 5.46 (dd, 1, $C_{14}H$), 5.37 (d, 1, C_9H), 5.35 (d, 1, C_8H), 5.25 (d, 1, $C_{16}H$), 5.06 (dd, 1, $C_{13}H$), 4.97 (m, 1, C_5H), 4.77 (t, 1, C_6H), 4.13 (m, 3, $C_{22}H + C_1$, 2 H), 3.86 (dd, 1, $C_{18}H$), 3.68 (dd, 1, C_7H), 3.62 (m, 1, C_3H), 3.07 (m, 1, $C_{15}H$), 2.16 (m, 1, C_4H), 2.10 (m, 1, C_4H), 2.04 (s, 3, CH_3CO), 2.03 (s, 3, CH_3CO), 1.99 (s, 3, CH_3CO), 1.64 (s, 3, CH_3C=), 1.59 (s, 3, CH_3C=), 1.05 (m, 6, 27-CH_3 and 28-CH_3), 0.89 (t, 3, 24-CH_3); mass spectrum *m/e* (rel intensity) 586 (10), 557 (50), 491 (20), 431 (6), 371 (20), 193 (100).

Methyl 5,6-Dihydroxypolyangioate, 5,6-Cyclic Carbonate (12). A solution of 12% phosgene in benzene (2 mL) was added to methyl 5,6-dihydroxypolyangioate (40 mg) in pyridine (2 mL). The resulting mixture was allowed to stand at room temperature overnight. The reaction mixture was cooled, diluted with ice-cold water, and extracted with ether. The extracts were dried ($MgSO_4$) and evaporated to give a brown oil. The oil was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (1:2) to give a colorless oil (29 mg, 69%) (homogeneous by TLC): IR (film) 1820 (CO), 1735 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 514 (7), 485 (20), 419 (13), 193 (100), 165 (80), 125 (50). Found: M^+ 514.2902; $C_{30}H_{42}O_7$ requires 514.2930.

Methyl 6-Hydroxy-5-oxopolyangioate (10). Silver carbonate on celite (2.0 g) was added to a solution of methyl 5,6-dihydroxypolyangioate (200 mg) in toluene (100 mL). The reaction mixture was refluxed under nitrogen with vigorous stirring. Further portions of silver carbonate on celite were added (total amount added 5.0 g) until TLC indicated an absence of starting material in the reaction mixture. The inorganic solids were filtered off and washed with ethyl acetate. The filtrate and washings were evaporated under reduced pressure to give a brown oil. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) to give a yellow oil (95 mg, 48%) (homogeneous by TLC): IR (film) 3600–3300 (br, OH), 1740 (CO), 1720 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 486 (20), 468 (22), 457 (21), 391 (42), 373 (20), 275 (35), 193 (60), 165 (100).

Methyl 5-Oxo-6-hydroxypolyangioate Acetate (11). Acetic anhydride (1 mL) was added to a solution of methyl 6-hydroxy-5-oxopolyangioate (40 mg) in pyridine (3 mL). The solution was allowed to stand at room temperature overnight. The reaction mixture was cooled, diluted with methanol, and evaporated at reduced pressure to give a yellow oil. The product was purified by preparative TLC with chloroform as the solvent system to give a yellow oil (31 mg) (homogeneous by TLC): IR (film) 1740 (CO), 1720 cm^{-1} (CO); ^1H NMR δ 5.57 (d br, 1, $C_{20}H$), 5.48 (dd, 1, $C_{14}H$), 5.42 (d, 1, C_9H), 5.40 (d, 1, C_8H), 5.26 (d, 1, $C_{16}H$), 5.08 (dd, 1, $C_{13}H$), 4.99 (d, 1, J = 10 Hz, C_6H), 4.11 (m, 2, $C_{22}H$ and C_3H), 4.00 (dd, 1, C_7H), 3.85 (dd, 1, $C_{18}H$), 3.70 (s, 3, OMe), 3.05 (m, 1, $C_{15}H$), 2.77 (dd, 1, C_2H), 2.65 (d, 1, J = 15 Hz, C_4H), 2.57 (dd, 1, C_2H), 2.54 (d, 1, J = 15 Hz, C_4H), 2.15 (s, 3, CH_3CO), 1.64 (s, 3, CH_3C=), 1.59 (s, 3, CH_3C=), 1.06 (m, 6, 27-CH_3 and 28-CH_3), 0.89 (t, 3, 24-CH_3).

Reduction of Methyl 5,6-Dihydroxypolyangioate with Lithium/Liquid Ammonia. Lithium (enough to maintain a blue color for 30 min) was added to a solution of methyl 5,6-dihydroxypolyangioate (160 mg) in anhydrous liquid ammonia (35 mL) and absolute ethanol (3 mL). The solution was stirred for 30 min. The ammonia was allowed to evaporate and the residue was diluted with water. The resulting aqueous solution was extracted with chloroform. The extracts were dried ($MgSO_4$) and evaporated to give a yellow oil. The oil was fractionated by preparative TLC (ethyl acetate) into three compounds. **Tetraol (13)** (12 mg), a colorless oil (most polar): IR (film) 3600–3200 cm^{-1} (br, OH). **Dihydropolyangi-1,5,6-triol (14)** (20 mg), a colorless oil: IR (film) 3600–3200 cm^{-1} (br, OH); mass spectrum *m/e* (rel intensity) 462 (25), 444 (9), 433 (28), 367 (37), 349 (36), 331 (22), 313 (14), 195 (20), 193 (100), 167 (60), 165 (86), 125 (60), 123 (85). **Isodihydropolyangi-1,5,6-triol (15)** (44 mg), a colorless oil: IR (film) 3600–3200 cm^{-1} (br OH); mass spectrum *m/e* (rel intensity) 462 (26), 444 (11), 433 (44), 367 (66), 349 (55), 331 (22), 313 (13), 195 (70), 193 (85), 167 (81), 165 (100), 125 (80), 123 (80).

Tetraol, Tetraacetate 16. Tetraol (13) was acetylated under the conditions described above to give tetraacetate 16 (colorless oil): IR (film) 1740 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 632 (7), 630 (15), 603 (27), 543 (7), 537 (40), 477 (88), 417 (16), 375 (20), 357 (20), 315 (20), 297 (40), 195 (65), 193 (80), 167 (74), 165 (100), 125 (65), 123 (65).

Dihydropolyangi-1,5,6-triol, Triacetate 17. Triol 14 was acetylated under the conditions described above to give 17 (colorless oil0: IR (film) 1740 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 588 (19), 559 (25), 493 (69), 479 (14), 433 (18), 419 (12), 391 (14), 373 (26), 359 (6), 313 (18), 259 (33), 195 (69), 193 (100), 167 (60), 165 (73), 125 (80), 123 (60).

Isodihydropolyangi-1,5,6-triol, Triacetate 18. Triol 15 was acetylated under the conditions described above to give 18 (colorless oil): IR (film) 1740 cm^{-1} (CO); ^1H NMR δ 5.58 (d br, 1, $C_{20}H$), 5.41–5.18 (m, 5, vinyl), 4.96 (m, 1, C_5H), 4.79 (t, 1, C_6H), 4.17 (t, 2, C_1H), 4.11 (br, $C_{22}H$), 3.85 (m, 1, $C_{18}H$), 3.55 (m, 1, C_3H), 3.33 (m, 1, C_7H), 3.02 (m, 1, $C_{15}H$), 2.05 (s, 3, CH_3CO), 2.04 (s, 3, CH_3CO), 2.01 (s, 3, CH_3CO), 1.65 (d, 3, 26-CH_3), 1.58 (s, 3, 25-CH_3), 27-CH_3 and 28-CH_3 signals are complex, indicating a mixture of isomers; mass spectrum *m/e* (rel intensity) 588 (26), 559 (18), 493 (100), 433 (25), 419 (14), 391 (17), 373 (13). Found: M^+ 588.3706; $C_{34}H_{52}O_8$ requires 588.3696.

Methyl Octahydro-5,6-dihydroxypolyangioate (19). A solution of methyl 5,6-dihydroxypolyangioate (150 mg) in absolute ethanol (20 mL) was hydrogenated over 10% palladium on carbon at atmospheric pressure for 3 h. The catalyst was filtered off and washed with

ethanol. The filtrate and washings were evaporated to give a colorless oil. The oil was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) to give a colorless oil (72 mg, 47%) (homogeneous by TLC): IR (film) 3600–3300 (br, OH), 1740 cm^{-1} (CO); mass spectrum spectrum *m/e* (rel intensity) 498 (0.5), 496 (4.5), 494 (1.8), 167 (37), 154 (100), 127 (14), 109 (11). Found: M^+ 496.3792; $C_{29}H_{52}O_6$ requires 496.3764.

Methyl Octahydro-5,6-dihydroxypolyangioate, 5,6-Diacetate 20. Acetic anhydride (1 mL) was added to a solution of methyl octahydro-5,6-dihydroxypolyangioate (15 mg) in pyridine (2 mL). The reaction mixture was allowed to stand at room temperature overnight. Methanol was added and the solvents were removed at reduced pressure to give a colorless oil. The product was purified by preparative TLC to give a colorless oil (14 mg, 80%) (homogeneous by TLC): IR 1740 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 582 (5), 580 (20), 578 (7), 520 (15), 460 (15), 367 (12), 337 (17), 214 (45), 197 (35), 167 (100), 154 (100), 127 (50), 109 (45).

Decahydropolyangin (21). A solution of W-7783 (50 mg) in absolute ethanol (20 mL) was hydrogenated over 10% palladium on charcoal for 4 h. The catalyst was filtered off and washed with ethanol. The filtrate and washings were evaporated to give a colorless oil. The oil was purified by preparative TLC with the solvent system ethyl acetate–2-porpanol–water (85:10:5) to give a colorless oil (20 mg, 39%) (homogeneous by TLC): IR (film) 3600–3200, 2800–2400 (br OH), 1715 cm^{-1} (CO).

Methyl Decahydro-5,6-dihydroxypolyangioate (22). Acid **21** was methylated with diazomethane to give methyl ester **22**: IR (film) 3600–3200 (br, OH), 1740 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 498 (4), 373(2), 339 (7), 167 (9), 154 (63), 127 (100), 109 (34).

Methyl Decahydro-5,6-dihydroxypolyangioate, Diacetate 23. Ester **22** was acetylated by the method described above to give diacetate **23**: IR (film) 1745 (CO), 1735 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 582 (8), 522 (4), 506 (1), 367 (5), 223 (5), 201 (4), 167 (8), 154 (36), 127 (100), 109 (36). Found: M^+ 582.4130; $C_{33}H_{58}O_8$ requires 582.4131.

Decahydropolyangi-1,5,6-triol (24). A solution of polyangi-1,5,6-triol (47 mg) in absolute ethanol (20 mL) was hydrogenated over 10% palladium on charcoal for 3 h. The catalyst was filtered off and washed with ethanol. The filtrate and washings were evaporated to give a colorless oil. The product was purified by preparative TLC with the solvent system ethyl acetate–2-propanol–water (85:10:5) to give a colorless oil (40 mg): IR (film) 3600–3200 cm^{-1} (br OH); mass spectrum *m/e* (rel intensity) 470 (4), 339 (7), 315 (4), 297 (6), 154 (15), 127 (100), 109 (60).

Decahydropolyangi-1,5,6-triol, Triacetate 25. Triol **24** was acetylated by the method described above to give triacetate **25**: IR (film) 1745 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 596 (6), 536 (5), 520 (2), 476 (3), 462 (4), 441 (4), 381 (4), 237 (4), 215 (4), 199 (18), 167 (7), 154 (25), 127 (100), 109 (42). Found: M^+ 596.4355; $C_{34}H_{60}O_8$ requires 596.4288.

Oxidation of Decahydropolyangi-1,5,6-triol with Periodic Acid. A solution of periodic acid (60 mg) in water (1 mL) was added to **24** (80 mg) in methanol (5 mL). The reaction mixture was allowed to stand at room temperature for 20 h, concentrated at reduced pressure, diluted with water, and extracted with chloroform. The extracts were dried ($MgSO_4$) and evaporated to give a yellow oil. The oil was fractionated by preparative TLC (chloroform) into two pure components. **26a** (20 mg) (colorless oil): IR (film) 1735 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 482 (5), 453 (20), 450 (12), 432 (5), 421 (30), 309 (20), 154 (100), 127 (100). **26b** (14 mg) (colorless oil): IR (film) 1735 cm^{-1} (CO); ^1H NMR δ 9.5 (d, 1, CHO), 3.2 (s, 3, OMe); mass spectrum *m/e* (rel intensity) 482 (5), 464 (5), 453 (14), 432 (24), 421 (32), 154 (100), 127 (100).

Oxidation of Polyangi-1,5,6-triol with Periodic Acid. A solution of periodic acid (40 mg) in water (1 mL) was added to **5** (10 mg) in methanol (2 mL). The reaction mixture was stirred for 1 h at room temperature and worked up as described above to give **27** (2 mg) as a colorless oil: IR (film) 3600–3200 (br, OH), 1730 cm^- (CO); mass spectrum *m/e* (rel intensity) 458 (16), 440 (40), 429 (16), 422 (86), 411 (18), 404 (26), 393 (18), 375 (8), 363 (12), 357 (14), 345 (26), 327 (24), 297 (20), 263 (20), 229 (66), 193 (100).

Polyangi-1,5,6-triol, Triphenylcarbamate 28. A solution of polyang-1,5,6-triol (40 mg) and phenyl isocyanate (60 mg) in toluene (5 mL) was refluxed under nitrogen for 2 h. The solvent was removed under reduced pressure to give an oil. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (1:2) to give a crystalline solid. Recrystallization from ethyl acetate gave white crystals (39 mg, 55%): mp 178–181 °C; IR (Nujol) 3300 (NH), 1705 cm^{-1} (CO).

Anal. Calcd for $C_{49}H_{59}N_3O_8$: C, 71.95; H, 7.27; N, 5.14. Found: C, 71.71; H, 7.34; N, 5.36.

Polyangi-1,5,6-triol, Tri-4-bromophenylcarbamate (29). A solution of polyangi-1,5,6-triol (200 mg) and 4-bromophenyl isocyanate (350 mg) in toluene (50 ML) was refluxed under nitrogen for 4 h. The reaction was worked up as described above to give a white powder. Recrystallization from ethyl acetate gave white crystals (95 mg, 21%): mp 184–190 °C; IR (nujol) 3300 (NH), 1705 cm^{-1} (CO).

Anal. Calcd for $C_{49}H_{56}Br_3N_3O_8$: C, 55.80; H, 5.35; N, 3.98; Br, 22.73. Found: C, 55.67; H, 5.57; N, 3.69; Br, 22.54.

Polyangi-1,5,6-triol, Triformate 7, and 1-Bromopolyangi-5,6-diol, Diformate 8. Bromine (0.16 g, 0.001 mol) was added to a solution of triphenylphosphine (0.262 g, 0.001 mol) in DMF (2.5 mL) at 0 °C under nitrogen. A solution of polyangi-1,5,6-triol (115 mg, 0.00025 mol) in DMF (1 mL) was added to the above triphenylphosphine dibromide solution at 0 °C. The reaction mixture was stirred at 0 °C for 4 h and stored in a freezer for 4 days. The reaction mixture was poured into a brine and extracted with ether. The extracts were dried ($MgSO_4$) and evaporated to give a white solid. The product mixture was separated into four fractions by preparative TLC with the solvent system ethyl acetate–cyclohexane (1:10). (1) **Triphenylphosphine oxide** (most polar). (2) **Polyangi-1,5,6-triol, triformate (7).** A colorless oil (73 mg, 54%), which crystallized on standing. Recrystallization from ethanol gave white crystals: mp 94–95 °C; IR (Nujol) 1735 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 544 (56), 515 (100), 449 (64), 419 (25), 357 (36), 259 (45), 193 (100), 165 (50), 152 (90), 125 (80). Found: M^+ 544.3089; $C_{31}H_{44}O_8$ requires 544.3036. (3) **1-Bromopolyangi-5,6-diol, Diformate 8.** A colorless oil (38 mg, 26%), which crystallized on standing. Recrystallization from methanol gave white crystals: mp 80–83 °C; IR (Nujol) 1735 cm^{-1} (CO); mass spectrum *m/e* (rel intensity) 580 (20), 578 (20), 541 (50), 539 (50), 485 (25), 483 (25), 193 (100), 165 (50), 152 (100), 125 (100), 123 (100). (4) **Triphenylphosphine** (least polar). **1-Bromopolyangi-5,6-diol (9).** A solution of 1-bromopolyangi-5,6-diol diformate (12 mg) in ethanol (3 mL) was allowed to stand at room temperature overnight. The ethanol was removed at reduced pressure to give a colorless oil. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (1:1) to give diol **9** (a colorless oil homogeneous by TLC) (5 mg, 46%): IR (film) 3600–3200 cm^{-1} (br, OH); mass spectrum *m/e* (rel intensity) 524 (100), 522 (100), 506 (50), 504 (50), 495 (50), 493 (50), 429 (25), 472 (25). Found: M^+ 522.2450; $C_{28}H_{43}Br^{79}O_4$ requires 522.2351.

Registry No.—**1**, 58857-02-6; **2**, 63511-83-1; **3**, 62711-77-7; **4**, 63511-84-2; **5**, 63511-77-3; **6**, 63511-79-5; **7**, 63511-85-3; **8**, 63511-86-4; **9**, 63511-87-5; **10**, 63511-88-6; **11**, 63511-89-7; **12**, 63511-90-0; **14–15**, 63511-78-4; **17–18**, 63511-80-8; **27**, 63533-50-6; **28**, 63511-91-1; **29**, 63511-82-0; phenylisocyanate, 103-71-9; 4-bromophenyl isocyanate, 2493-02-0.

References and Notes

(1) (a) Uniroyal, Inc., Middlebury, Conn. 06749; (b) ICI North America, Wilmington, Delaware.

(2) The trivial chemical name 5,6-dihydroxypolyangioic acid is suggested for this system. This facilitates the naming of derivatives and epimers. Ambruticin is the suggested USANC name.

(3) (a) S. M. Ringel et al., *J. Antibiot.* **30**, 371 (1977); (b) H. B. Levine and S. M. Ringel, Proceedings of the Third International Coccidioidomycosis Symposium, June 1977.

(4) The exact nature of these compounds is under investigation.

(5) For an example of reductive ring opening with Na in liquid NH_3, see P. G. Gassman and X. Creary, *Chem. Commun.* 1214 (1972).

(6) R. K. Boeckman, Jr., and B. Ganem, *Tetrahedron Lett.*, 913 (1974).

(7) X-ray analysis performed by Molecular Structure Corp., College Station, Texas 77840.

(8) In this drawing the carbons and oxygens are numbered consecutively from the first formate and not systematically as in the previous figures and discussion.

(9) Many of the compounds described were gums or oils, which slowly decomposed at room temperature. The homogeneity of each compound was checked by TLC in at least two solvent systems. Molecular formulas were determined by high-resolution mass spectroscopy where possible. In cases where high resolution was not possible, the molecular composition of the low-resolution molecular ion was obvious from either the composition of the starting material or from a subsequent transformation product.

(10) 22-MHz ^1H NMR spectra were performed by Morgan-Schaffer Corp., Montreal, Canada.

(11) A high-resolution mass spectrum of methyl 5,6-dihydroxypolyangioate (**3**) with a computer printout of molecular compositions of fragment ions was performed at Battelle Institute, Columbus, Ohio 43201.

Kinetics of the Reaction of Bromine with 5-Bromo-2(1*H*)-pyrimidinones: Evidence for the Involvement of Covalent Hydrates

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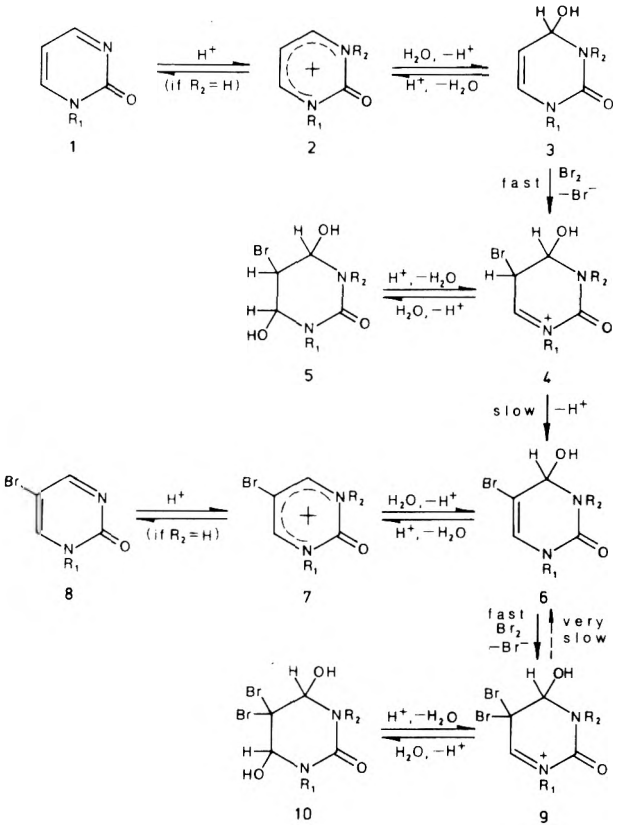
The kinetics of bromination of 5-bromo-2(1*H*)-pyrimidinone, 5-bromo-1-methyl-2-pyrimidinone, and 5-bromo-1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium bromide have been measured in 2–13 N aqueous sulfuric acid. In these media all three substrates exist (>99%) as cations. The order of reaction, the acidity dependence of the rates, and the reactivities of the substrates are all consistent with a mechanism in which the rate-determining step involves attack by molecular bromine upon the covalent hydrate (or pseudobase) of the substrates.

We have previously presented evidence that the bromination of simple 2(1*H*)-pyrimidinones carried out in aqueous acidic media proceeds in several discrete steps,[1] as shown in Scheme I. In the first step, the covalent hydrates (or pseudobase) **3**, in equilibrium with substrates **1** (or **2**), react *rapidly* with bromine to give **4** and hence the observable[1] intermediates **5**. These nonaromatic intermediates undergo *slow* acid-catalyzed[1] dehydration via **4** to give the isolable 5-bromo derivatives **8** (or **7**). In the presence of a sufficiency of bromine a further reaction takes place, presumably via the covalent hydrates (or pseudobase) **6**, to give 5,5-dibromo derivatives[1] **10**.

Scheme I



We hoped that by using more concentrated acidic media we would be able to study the first steps of the reaction (**2** ⇄ **3** → **4** ⇄ **5**), and thus obtain more direct evidence of the intermediacy of the covalent hydrate **3**. For the cation **2** ($R_1 = R_2$ = Me) the equilibrium constant[2] $K_{ROH} = [3][H^+]/[2] = 10^{-7}$. Thus, in strong acid the concentration of **3** should be very low, and hence the rate of bromine consumption might be reduced to a measurable quantity. However, the conversion **5** → **6** ⇄ **7** is acid catalyzed,[1] and in strong acid it seems that its rate is sufficiently fast that **6** can compete with **3** for bromine. Consequently, in strong acid the rate of disappearance of bromine follows complex kinetics which we have not pursued. We were, however, able to study the bromination **7** → **10** (R_1, R_2 = H, or Me) for which the covalent hydrates (or pseudobase) **6** were previously proposed[1] as the actual intermediates undergoing electrophilic attack.

Results and Discussion

We have studied the kinetics of the reaction between bromine and the substrates 5-bromo-2(1*H*)-pyrimidinone (**8**, R_1 = H), 5-bromo-1-methyl-2-pyrimidinone (**8**, R = Me), and 5-bromo-1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium (**7**, $R_1 = R_2$ = Me) bromide in 2–13 N aqueous sulfuric acid, in which all three substrates largely (>99%) exist as cations.[3] In media of acidity greater than 15 N sulfuric acid, a quantitative reaction between bromine and the substrates was not observed. At these acidities, bromine could be detected even in the presence of a tenfold excess of substrate. This we presume to be due to the onset of the acid-catalyzed reverse reaction[4] **10** → **9** → **6** → **7** which we observed earlier.[1] However, at acidities less than 15 N sulfuric acid the reaction with bromine proceeds to completion, and the decrease in UV absorbance due to bromine (or substrate) follows first-order kinetics if the substrate is present in excess (about tenfold).

Substrate Dependence. In the presence of an excess of substrates, good pseudo-first-order rate constants (k_1^{obsd}) were obtained for the bromination of all three substrates. By varying the substrate concentration it was shown that the reactions are in fact second order (see Table I).

The conditions of our experiments were not truly pseudo-first-order in that the excess of substrate over bromine was not very large (5- to 13-fold). However, one can still obtain useful results under these circumstances. For a second-order reaction $\ln[(b - x)/(a - x)] = \ln(b/a) - (a - b)k_2t$. If $b < a \gg x$, this may be simplified to $\ln(b - x) = \ln b - (a - b)k_2t$. Thus, during the earlier stages of the reaction, when $a \gg x$ is most valid, the disappearance of the component b follows a first-order law for which the apparent pseudo-first-order rate constant $k_1^{obsd} = (a - b)k_2$. In the present work, therefore, second-order rate constants were calculated from $k_2^{obsd} = k_1^{obsd}/([7] - [Br_2]_0)$. This approach has been used previously by Bell,[5a] and by us.[5b,c]

Acidity Dependence. Table II shows the second-order rate constants that were obtained for reactions carried out in various concentrations of sulfuric acid. For all three substrates the rate of bromination decreases markedly with increasing acidity, and presumably this reflects the diminishing concentration of the covalent hydrates (or pseudobase) **6**.

Since the equilibrium **7** ⇄ **6** is a type of carbenium ion–carbinol interconversion, we have chosen to use the acidity function H_R (derived from the ionization of carbinols)[6] as the measure of acidity. Plots of $\log k_2^{obsd}$ vs. H_R give good straight

Table I. Substrate Dependence of the Rates of Bromination of 7 at 30 °C

7		$[7] \times 10^4$,	$[Br_2]_0 \times 10^5$,	$k_1^{obsd} \times 10^2$,	k_2^{obsd}[a],	Av k_2^{obsd},
R_1	R_2	M	M	s^{-1}	$M^{-1}\,s^{-1}$	$M^{-1}\,s^{-1}$
H	H[b]	2.0	4.9	5.19	344	
			4.1	5.00	314	332 ± 18[c]
		4.0	5.6	11.7	340	
			5.4	11.4	329	
Me	H[d]	2.0	4.0	7.91	494	
			2.0	8.72	484	
		3.0	3.0	13.2	489	
			3.0	13.0	481	488 ± 12[c]
			3.0	13.4	496	
		4.0	3.0	17.6	476	
			3.0	18.4	497	
Me	Me[d]	2.0	2.7	2.91	168	
			2.7	2.86	165	
		3.0	4.5	4.08	160	
			4.5	4.14	162	162 ± 6[c]
		4.0	5.5	5.50	159	
			5.5	5.55	161	
			5.5	5.39	156	

[a] $k_2^{obsd} = k_1^{obsd}/([7] - [Br_2]_0)$. [b] In 7.4 N H_2SO_4. [c] Maximum deviation from average. [d] In 5.55 N H_2SO_4.

Table II. Acidity Dependence of the Rates of Bromination[a] of 7 at 30 °C

7		$[H_2SO_4]$,		k_2^{obsd},		
R_1	R_2	N	$-H_R$	$M^{-1}\,s^{-1}$	log k_2^{obsd}	No. of runs
H	H	5.90	1.99	1210	3.083	2
		7.01	2.58	492	2.692	4
		7.40	2.75	332	2.521	4
		8.64	3.44	103	2.013	5
		10.0	4.14	24.6	1.391	3
Me	H	5.55	1.79	488	2.688	7
		6.50	2.30	197	2.294	4
		8.05	3.10	46.4	1.667	3
		9.95	4.14	7.25	0.860	2
Me	Me	2.00	0.11	3830	3.583	4
		2.76	0.45	1890	3.276	3
		4.00	1.02	622	2.794	8
		5.55	1.79	162	2.210	7
		9.50	3.90	4.10	0.6128	6
		11.4	4.93	0.610	−0.2147	2
		13.3	5.94	0.120	−0.9208	2

[a] Each k_2^{obsd} is the average of the number of runs indicated in the last column.

Table III. Least-Squares Analysis of log k_2^{obsd} vs. H_R for 7 → 10

7		Intercept = log k_2K	Slope = m		No. of
R_1	R_2	(SD)	(SD)	Corr coeff	pts
H	H	4.69 (0.02)	0.79 (0.03)	0.9984	5
Me	H	4.08 (0.001)	0.78 (0.001)	0.9999	4
Me	Me	3.62 (0.01)	0.77 (0.007)	0.9998	7

lines with slopes about 0.78 (see Table III). These observations, we believe, are completely compatible with the intermediacy of the species **6**.

Electrophilic attack upon the cations **7** is unlikely,[7] and would not result in the observed inverse dependence of rate upon acidity. The cation **7** ($R_1 = R_2 = Me$) almost certainly reacts via the observable[1b] pseudobase **6** ($R_1 = R_2 = Me$), this being an enamine and thus highly susceptible to electrophilic attack. In view of the similarity in their rates of bromination, and in the acidity dependences, it is reasonable to propose that the other two substrates **7** ($R_1 = R_2 = H$) and **7** ($R_1 = Me$, $R_2 = H$) react via their covalent hydrates **6** ($R_1 = R_2 = H$) and **6** ($R_1 = Me$, $R_2 = H$),[10] respectively.

For the proposed mechanism

$$H_2O + 7 \overset{K}{\rightleftharpoons} H^+ + 6 \xrightarrow[Br_2]{k_2} 9 \rightarrow 10$$

we should have

$$k_2^{obsd} = k_2K/h_x \quad (1)$$

and

$$\log k_2^{obsd} = \log k_2K + H_x \quad (2)$$

where $K = [6]h_x/[7]$, and $H_x = -\log h_x$ is the acidity function, defined like H_R,[6] governing the equilibrium. Equations 1 and 2 are derived assuming $[7] \gg [6]$ (or $h_x \gg K$) which is justifiable, since for **7** ($R_1 = R_2 = Me$) we have previously measured[1b] $K = 10^{-3.08}$.

The observed data in Table II can be expressed in the form log k_2^{obsd} = intercept + mH_R (see Table III) which is in accord with eq 2 in view of the known linear relationship between acidity functions.[11] Accordingly, the data also support the proposed mechanism.

Relative Reactivities. Finally, we consider the reactivities of the substrates **7** in terms of the mechanism proposed above. Assuming that $H_x = mH_R$, we can equate the intercepts in Table III with the term log k_2K from eq 2. Except for the dimethyl cation **7** ($R_1 = R_2 = Me$) the term k_2K is not separable, and so we compare these terms for the three substrate cations.

cation **7**	$R_1 = R_2 = H$	$R_1 = Me$, $R_2 = H$	$R_1 = R_2 = Me$
k_2K, s^{-1} (30 °C)	4.9×10^4	1.2×10^4	4.2×10^3
rel	11.7	2.86	1.00

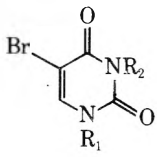
Methyl substitution should increase k_2, but decrease K for steric and electronic reasons.[2] It appears that the second effect is dominant.[12] This is not unreasonable, since it is known that steric factors play a significant role in the equilibria **2** ⇄ **3**,[2] and the presence of the 5-bromo substituent in **7** should enhance the hindrance to hydroxyl attachment resulting from methyl substitution.[2]

A similar order of reactivity was observed earlier in the H–D exchange of the cations **2** in aqueous acid.[13] For this reaction we proposed that the rate-determining step involved electrophilic attack by D^+ upon **3**.[13]

cation **2**	$R_1 = R_2 = D$	$R_1 = R_2 = Me$
k_2K, s^{-1} (107 °C)	4.7×10^{-5}	7.2×10^{-6}
rel	6.5	1.0

For the dimethyl cation **7** ($R_1 = R_2 = Me$) the equilibrium constant[1b] $K \simeq 10^{-3}$, and so $k_2 \simeq 4 \times 10^6$ $M^{-1}s^{-1}$. This value for the attack of bromine upon the pseudobase **6** ($R_1 = R_2 = Me$) seems to us quite reasonable. The enol of acetone reacts with bromine with $k_2 \simeq 10^7$ $M^{-1}s^{-1}$ at 25 °C.[14] A simple enamine should be more reactive than this,[15] but in **6** the enamine moiety would be deactivated by the presence of the 5-bromo substituent and by the carbonyl group in conjugation with the N_1 lone pair.

It is, perhaps, noteworthy that similarly substituted 5-bromouracils (**11**), which have a carbonyl group at position 4, are much less reactive.[16]



11

$R_1 = R_2 = H$, $k_2 = 64$ $M^{-1}s^{-1}$

$R_1 = R_2 = Me$, $k_2 \simeq 19$ $M^{-1}s^{-1}$

In summary, we feel that the relative and the absolute reactivities of the substrates **7** are understandable in terms of the proposed mechanism involving **6**. It may be noted that of the species **1**–**10** in Scheme I only **4** and **9** have not been directly observed.[1]

Experimental Section

The origin of the compounds used in this study, their UV spectral data, and their pK values can be found elsewhere.[1b] UV measurements were made on a Cary 14 instrument and on an Aminco DW-2.

Sulfuric acid solutions were either commercial standard volumetric solutions, or were made by dilution of concentrated sulfuric acid (38 N) and were checked by titration against a standard sodium hydroxide solution.

Values of H_R were obtained by interpolation from the data (at 30 °C) of Arnett and Bushick[6] using "Wt % H_2SO_4" calculated from "normality" and the known densities of sulfuric acid–water mixtures.[17]

Constant temperature was maintained by circulation of water at 30.00 ± 0.05 °C through the cell holders of the spectrophotometer. Reagent solutions were equilibrated at 30 °C prior to their use in kinetic experiments.

The rate of the reaction between the substrates **7** and bromine was measured by monitoring the decrease in absorbance due to bromine or the substrate[18] at a convenient UV wavelength. A solution of the final product mixture with an absorbance approximately equal to A_∞ was used as a reference to largely offset the absorbance due to the unreacted excess of substrate.

Reactions were initiated by adding 50 or 100 μL of bromine solution to a 1-cm cell and then adding 3 mL of substrate solution. Between 10 and 15 absorbance values were taken over 2 half-lives, and pseudo-first-order rate constants (k_1^{obsd}) were obtained from least-squares analysis of ln $(A - A_\infty)$ vs. time. Only those data which gave correlation coefficients ≥0.9995 were accepted. The rate constants reported in the text are the averages of two to eight individual runs.

Second-order rate constants (k_2^{obsd}) were obtained from[5] $k_2^{obsd} = k_1^{obsd}/([7] - [Br_2]_0)$ as explained in the text. Since the loss of bromine from aqueous solutions is appreciable over extended periods of time, the actual bromine concentration for a given kinetic run was estimated from the total change in absorbance due to the decrease in the substrate concentration assuming $[Br_2]_0 = [7]_0 - [7]_\infty$.

Up to 0.01 M KBr had a negligible effect upon the rates. Since $[Br^-]$ did not exceed 10^{-3} M during any of the kinetic experiments, its effect upon the rate constants (due to tribromide ion formation) was ignored.

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Registry No.—**7** ($R_1 = R_2 = Me$) bromide, 38353-08-1; **8** ($R_1 = H$), 38353-06-9; **8** ($R_1 = Me$), 14248-01-2; bromine, 7726-95-6.

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(6) E. M. Arnett and R. D. Bushick, *J. Am. Chem. Soc.*, **86**, 1564 (1964).
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(8) A. R. Katritzky and C. D. Johnson, *Angew. Chem., Int. Ed. Engl.*, **6**, 608 (1967).
(9) R. P. Bell and D. R. Marshall, *J. Chem. Soc.*, 2195 (1964); C. Barnett and J. Warkentin, *J. Chem. Soc., B*, 1572 (1968).
(10) We prefer the covalent hydrate **6** ($R_1 = Me$, $R_2 = H$) rather than **6** ($R_1 = H$, $R_2 = Me$) for steric reasons. For the cations **2** the hydroxyl group is attached preferentially to the position adjacent to the least bulky substituent.[2] The presence of the 5-bromine probably enhances this preference.[2]
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(15) The iodination of acetone shows apparent acid catalysis by primary and secondary (but not tertiary) ammonium ions. This has been attributed to rate-determining formation of an enamine which reacts rapidly with iodine. M. L. Bender and A. Williams, *J. Am. Chem. Soc.*, **88**, 2504 (1966).
(16) O. S. Tee and C. G. Berks, unpublished results.
(17) "International Critical Tables", Vol. **3**, 1928, p 56.
(18) Even though the change in substrate absorbance is relatively small it can be measured successfully on the more sensitive Aminco DW-2. Rates measured by following bromine decrease and substrate decrease agree very well.

Electrophilic Additions to Multiple Bonds.[1] 2. Medium Effect on Bromine Additions to Alkenes

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The rates of addition of bromine to a series of alkenes were obtained in acetic acid and in tetrachloroethane at 25 °C. Solvent effects on alkene reactivity have been evaluated by examination of relative rates with respect to ethylene in these two and five other solvents, covering a range of dielectric constants from about 2 to 80. The structural effects on reaction rates, for the bromination of alkenes, are approximately constant in all hydroxylic solvents, but are drastically enhanced in nonpolar solvents. The importance of specific solvation of the cyclic bromonium ion like transition state is examined.

The effect of solvent on the rate of bromine additions to alkenes has recently received increased attention.

It is well established that a change from a less to a more polar solvent results in an increase in the observed rate of bromination of a particular compound.[2] For example, the rate of bromine addition to 1-pentene varies from 1.17×10^{-3} M^{-1} s^{-1} in Freon 112 (1,2-difluorotetrachloroethane) to 11.3 M^{-1} s^{-1} in acetic acid and 2.5×10^{7} M^{-1} s^{-1} in water.[3]

Less well established experimentally is the effect of solvent upon the structural effects on the observed rates. Two different effects have been reported. Solvent independence of substituent effects on the rates of bromination of alkenes has been reported by Dubois.[3] On the other hand, reduced structural effects on rates of bromination of unsaturated compounds with a change of solvent from more polar to less polar were also reported recently.[4] The low selectivity of bromine addition to alkenes and alkynes in Freon 113 (1,1,2-trichlorotrifluoroethane) at −35 °C compared to high selectivity in methanol at 25 °C was interpreted by Olah in terms of a change in the structure of the rate-determining transition state of bromination from an alkene–bromine π complex in nonpolar media to a bromonium ion like σ complex in polar solvents.[4]

We would like to present experimental data that clearly establish that the structural effects on rates of bromination of alkenes are strongly reduced when going from nonhydroxylic to hydroxylic solvents and remain almost constant in the latter media.

Results and Discussion

The kinetic equation for polar additions of bromine to alkenes is presented in general form by eq 1, where [A] = [alkene]:[5]

$$-d[Br_2]/dt = k_2[Br_2][A] + k_3[Br_2]^2[A] + k_3'[Br_3^-][A] \quad (1)$$

In the absence of bromide ion and at low bromine concentrations ($[Br_2] < 10^{-3}$ M) in acetic acid, eq 1 reduces to the form:

$$-d[Br_2]/dt = k_2[Br_2][A] \quad (2)$$

In TCE, however, even under these conditions, only a third-order rate dependence is found:

$$-d[Br_2]/dt = k_3[Br_2]^2[A] \quad (3)$$

Even at the lowest bromine concentration at which we are able to measure rates ($[Br_2] = 2 \times 10^{-4}$ M), *no* second-order rate dependence is found.

The reason for this change in kinetic order is believed to be that protic solvents (such as methanol or acetic acid) can solvate the leaving bromide ion, thus stabilizing the ionic rate-determining transition state. In solvents which are not capable of such stabilization (e.g., TCE), a second bromine molecule may serve this function and the process then becomes third order (the Ad_E2–Br_2 assisted mechanism).[6] The second bromine molecule may then catalytically aid the Br–Br bond cleavage by formation of the more charge-dispersed tribromide ion.

The rate constants obtained in both solvents are collected in Tables I and II.

Separate experiments, carried out in the presence of oxygen or isoamyl nitrite, correspond to an ionic addition mechanism, and no contribution of a radical pathway was detected.

The logarithms of the rate constants correlate fairly well with the sum of Taft's polar substituent constants, $\Sigma\sigma^*$, for the alkyl groups substituted on the ethylene system. This remains in agreement with the commonly accepted model of a highly electron-deficient, bridged bromonium ion like transition state for the reaction. Nevertheless, steric effects upon the rate cannot be ignored, as demonstrated by the values of the k_{cis}/k_{trans} ratio which are generally greater than unity for pairs of geometrically isomeric alkenes (Table II). One of us has shown previously[8] that the initial enthalpy difference between the ground states of cis and trans isomers of 1,2-dialkyl-substituted ethylenes was increased at the transition state of bromination. This ruled out earlier assumptions about the partial loss of the ground-state energy difference between cis and trans isomers in the rate-determining transition state of addition. It may be possible to account for the somewhat faster rate of addition to the cis alkene relative to the trans isomer on the basis of steric interactions between the incoming electrophile and the alkyl groups on the double bond.[8,9]

Table I. Specific Rate Constants[a] for the Addition of Bromine to Terminal Alkenes in CH_3COOH and in CCl_2H–CCl_2H at 25.0 °C

Alkene	k_2, M^{-1} s^{-1} in CH_3COOH	k_3, M^{-2} s^{-1} in TCE
$H_2C{=}CH_2$	0.221 ± 0.002	14.3 ± 0.69
$H_2C{=}CH(CH_3)$	17.6 ± 0.2	7820 ± 137
$H_2C{=}CH(C_2H_5)$	27.9 ± 0.4	3090 ± 26
$H_2C{=}CH(C_3H_7)$	16.5 ± 0.2	2930 ± 22
$H_2C{=}CH(i\text{-}C_3H_7)$	19.3 ± 0.2	4940 ± 30
$H_2C{=}CH(t\text{-}C_4H_9)$	10.2 ± 0.1	5680 ± 53
$H_2C{=}CH(CH_2\text{-}t\text{-}C_4H_9)$		479.0 ± 5.9
$H_2C{=}C(CH_3)_2$	1510 ± 33	345 000 ± 3500
$H_2C{=}CCH_3(C_2H_5)$	3410 ± 27	
$H_2C{=}C(C_2H_5)_2$	3350 ± 51	
$H_2C{=}CC_2H_5(i\text{-}C_3H_7)$	1330 ± 34	

[a] The rate constants are the average of two to nine independent kinetic runs.

Table II. The Specific Rate Constants[a] for the Addition of Bromine to Geometrically Isomeric Alkenes in CH_3COOH and in CCl_2H–CCl_2H at 25.0 °C

Alkene		k_2, M^{-1} s^{-1} in CH_3COOH	k_c/k_t	$k_3 \times 10^{-5}$, M^{-2} s^{-1}, in TCE	k_c/k_t
$CH_3CH{=}CHCH_3$	cis	1230 ± 20	1.31	5.38 ± 0.06	1.06
	trans	940 ± 9		5.05 ± 0.05	
$CH_3CH{=}CH(C_2H_5)$	cis	2530 ± 30	1.42	14.8 ± 0.15	1.20
	trans	1780 ± 20		12.3 ± 0.11	
$CH_3CH{=}CH(i\text{-}C_3H_7)$	cis	1300 ± 20	1.71	15.9 ± 0.10	1.36
	trans	760 ± 10		11.7 ± 0.10	
$CH_3CH{=}CH(t\text{-}C_4H_9)$	cis	1020 ± 20	3.40	19.3 ± 0.12	2.11
	trans	300 ± 4		9.16 ± 0.05	
$C_2H_5CH{=}CHC_2H_5$	cis	2830 ± 30	1.20	28.7 ± 0.20	1.01
	trans	2350 ± 10		28.4 ± 0.20	
$C_2H_5CH{=}CH(i\text{-}C_3H_7)$	cis	1340 ± 30	1.03	28.1 ± 0.18	1.03
	trans	1300 ± 30		27.4 ± 0.18	
$C_2H_5CH{=}CH(t\text{-}C_4H_9)$	cis	1250 ± 20	2.27	32.7 ± 0.32	1.71
	trans	550 ± 10		19.1 ± 0.15	
$(i\text{-}C_3H_7)CH{=}CH(i\text{-}C_3H_7)$	cis	270 ± 15	0.61	12.3 ± 0.11	0.22
	trans	440 ± 5		55.1 ± 0.84	
$(t\text{-}C_4H_9)CH{=}CH(t\text{-}C_4H_9)$	cis	517 ± 8	47.0		
	trans	11 ± 0.1		0.538 ± 0.005	

[a] The rate constants are the average of two to seven independent kinetic runs.

Table III. The Solvent Dependence of Bromination Rates on Alkene Structure

Alkene	Registry no.	k^{rel} in Freon 112[a]	k^{rel} in TCE[b]	k^{rel} in CH_3COOH[b]	k^{rel} in MeOH[c]	k^{rel} in MeOH/H_2O[d] (7/3)	k^{rel} in H_2O[e]	k^{rel} in Freon 113[f]
$H_2C{=}CH_2$	74-85-1	1.0	1.0	1.0	1.0	1.0	1.0	1.0
$H_2C{=}CH(CH_3)$	115-07-1		5.5×10^2	8.0×10	6.1×10	2.5×10	2.6×10	1.4×10
$H_2C{=}CH(C_2H_5)$	106-98-9		2.2×10^2	1.3×10^2	9.6×10			2.0×10
$H_2C{=}CH(C_3H_7)$	109-57-1	1.3×10^3	2.0×10^2	7.5×10	6.9×10	2.3×10	6.4×10	1.2×10
$H_2C{=}CH(i\text{-}C_3H_7)$	563-45-1		3.5×10^2	8.8×10	5.6×10	2.2×10	2.2×10	
$H_2C{=}CH(t\text{-}C_4H_9)$	558-37-2		4.0×10^2	4.6×10	2.7×10			
$H_2C{=}CH(CH_2\text{-}t\text{-}C_4H_9)$	762-02-9		3.3×10					
$H_2C{=}C(CH_3)_2$	115-11-7		2.4×10^4	6.9×10^3	5.4×10^3	5.4×10^3		2.0×10^2
$H_2C{=}CCH_3(C_2H_5)$	563-46-2			1.5×10^4				
$H_2C{=}C(C_2H_5)_2$	760-21-4			1.5×10^4				
$H_2C{=}CC_2H_5(i\text{-}C_3H_7)$	7357-93-9			6.0×10^3				
cis-$CH_3CH{=}CHCH_3$	590-18-1		3.8×10^4	5.6×10^3	2.6×10^3	1.8×10^3		3.2×10^2
trans-$CH_3CH{=}CHCH_3$	624-64-6		3.5×10^4	4.3×10^3	1.7×10^3	1.1×10^3		2.0×10^2
cis-$CH_3CH{=}CHC_2H_5$	627-20-3	1.1×10^5	1.0×10^5	1.1×10^4	4.1×10^3	2.3×10^3		8.8×10^2
trans-$CH_3CH{=}CHC_2H_5$	646-04-8		8.6×10^4	8.1×10^3	2.6×10^3			
cis-$C_2H_5CH{=}CHC_2H_5$	7642-09-3		2.0×10^5	1.3×10^4	6.4×10^3			8.5×10^2
trans-$C_2H_5CH{=}CHC_2H_5$	13269-52-8		2.0×10^5	1.1×10^4	3.7×10^3			6.8×10^2
cis-$CH_3CH{=}CH(i\text{-}C_3H_7)$	691-38-3		1.1×10^5	5.9×10^3	1.5×10^3	1.4×10^3		
trans-$CH_3CH{=}CH(i\text{-}C_3H_7)$	674-76-0		8.1×10^4	3.5×10^3	1.2×10^3	1.1×10^3		
cis-$CH_3CH{=}CH(t\text{-}C_4H_9)$	762-63-0		1.3×10^5	4.6×10^3	1.3×10^3	9.3×10^2		
trans-$CH_3CH{=}CH(t\text{-}C_4H_9)$	690-08-4		6.4×10^4	1.4×10^3	1.6×10^2	1.3×10^2		
cis-$C_2H_5CH{=}CH(i\text{-}C_3H_7)$	15840-60-5		2.0×10^5	6.1×10^3				
trans-$C_2H_5CH{=}CH(i\text{-}C_3H_7)$	692-24-0		1.9×10^5	5.9×10^3				
cis-$C_2H_5CH{=}CH(t\text{-}C_4H_9)$	690-92-6		2.3×10^5	5.7×10^3	2.0×10^3	1.3×10^3		
trans-$C_2H_5CH{=}CH(t\text{-}C_4H_9)$	690-93-7		1.3×10^5	2.5×10^3	2.1×10	1.6×10^2		
cis-$(i\text{-}C_3H_7)CH{=}CH(i\text{-}C_3H_7)$	10557-44-5		8.6×10^4	1.2×10^3				
trans-$(i\text{-}C_3H_7)CH{=}CH(i\text{-}C_3H_7)$	692-70-6		3.8×10^5	2.0×10^3				
cis-$(t\text{-}C_4H_9)CH{=}CH(t\text{-}C_4H_9)$	692-47-7			2.4×10^3				
trans-$(t\text{-}C_4H_9)CH{=}CH(t\text{-}C_4H_9)$	692-48-8		3.8×10^3	5.2×10				
$CH_3CH{=}C(CH_3)_2$	513-35-9	2.1×10^6			1.3×10^5	2.7×10^3		2.3×10^3
$(CH_3)_2C{=}C(CH_3)_2$	563-79-1	5.2×10^7			9.2×10^5			5.7×10^3

[a] Data from ref 3, k_2 for $CH_2{=}CH_2$ was calculated from the equation taken from ref 7 and k_2 for $CH_2{=}CH_2$ in methanol.[11] [b] This paper. [c] Data from ref 11. [d] Data taken from ref 12, k_2 for $CH_2{=}CH_2$ being calculated on the basis of appropriate equation[12] and k_2 ($CH_2{=}CH_2$) in methanol.[11] [e] Data taken from ref 13. [f] Data taken from ref 4.

Table IV. Observed Proton Magnetic Resonance Parameters for Products from the Bromination of Olefin Pairs in Acetic Acid

Compound			Dibromoalkane[c]					Bromoacetoxyalkane[f]				
R^1	R^2	cis trans	Stereochemistry	Registry no.	Chemical shifts, δ, ppm H^1	H^2	Coupling constants, Hz, $J_{H^1H^2}$	Stereochemistry	Registry no.	Chemical shifts, δ, ppm H^1	H^2	Coupling constants, Hz, $J_{H^1H^2}$
CH_3	CH_3	cis	dl	598-71-0	4.45	4.45	3.2	threo	19773-39-8	4.10	4.95	4.0
		trans	meso	5780-13-2	4.23	4.23	7.6	erythro	37906-78-8	4.21	4.90	6.0
C_2H_5	CH_3	cis	threo	22415-73-2	4.13	4.35	3.0	threo	63569-56-2	4.83–5.20	4.83–5.20	*a*
		trans	erythro	22415-74-3	3.88–4.45	3.88–4.45	*a*	erythro	63569-57-3	4.73–5.19	4.73–5.19	*a*
C_2H_5	C_2H_5	cis	dl	16230-28-7	3.98–4.28	3.98–4.28	*a*	threo	63569-58-4	3.95	4.87	3.4
		trans	meso	16230-27-6	3.90–4.28	3.90–4.28	*a*	erythro	63569-59-5	3.81–4.30	4.85	6.0
i-C_3H_7	i-C_3H_7	cis	dl	40084-92-2	3.70–3.85	3.70–3.85	8.2[d]	threo	40084-95-5	3.91	4.87	5.0[b]
		trans	meso	40084-93-3	4.16	4.16	11.8[d]	erythro	40084-94-4	3.91	5.08	10.2[b]
C_3H_7	CH_3	cis	threo	58608-83-6	3.77	4.25	3.5	threo	63569-60-8	3.6–4.0	5.03	6.5
		trans	erythro	58608-84-7	4.15	4.26	10	erythro	63569-61-9	4.8–5.1	4.8–5.1	*a*
i-C_3H_7	C_2H_5	cis	threo	63569-54-0	3.77	4.07	3.0	threo	63569-62-0	5.0[d]	4.0[e]	6.0
		trans	erythro	63569-55-1	4.03–4.23	4.03–4.23	*a*	erythro	63569-63-1	3.95	5.00	4.0
t-C_4H_9	CH_3	cis	threo	7694-05-5	3.85	4.40	1.3	threo	63569-64-2	3.87	5.20	1.5
		trans	erythro	7694-04-4	4.40	4.61	*a*	erythro	63569-65-3	4.4	5.1–5.36	*a*
t-C_4H_9	C_2H_5	cis	threo	40084-97-7	3.93	3.9–4.3	1.6[b]	threo	63569-66-4	3.80	5.00	1.1[b]
		trans	erythro	40084-96-6	4.23	4.38	1.9[b]	erythro	63569-67-5	3.99	4.7–5.1	3.1[b]
t-C_4H_9	t-C_4H_9	cis	dl	40085-00-5	4.17	4.17	1.0[b]	threo	40085-01-6	3.97	4.95	1.0[b]
		trans	d									

[a] The value of the coupling constants is nonmeasureable. [b] Data taken from ref 8. [c] The regiochemistry of the product: (i-C_3H_7)-BrHC-CH($OCOCH_3$)(C_2H_5). [d] The reaction product is a complex mixture, but neither the *dl*-dibromide nor *threo*-acetoxy bromide could be detected 8. [e] $R^1H^1C(Br)$-$(Br)CH_2R^2$. [f] $R^1H^1C(OCOCH_3)$-$(Br)CH^2R^2$.

If the particularly sterically hindered *trans*-di-*tert*-butylethylene is excluded,[10] the values of ρ^* for additions in acetic acid and TCE are -2.8 ± 0.3 and -4.1 ± 0.3, respectively.

Relative rates ($k^{rel} = k^{alkene}/k^{ref\ alkene}$) are a more sensitive measure of selectivity than the reaction constants ρ^*, which involve logarithmic relationships. The relative rates of bromine addition to alkenes compared to ethylene in seven solvents are presented in Table III. For all alkenes studied, the selectivity of bromination decreases in solvent order: Freon 112 > TCE > CH_3COOH > MeOH > 70% MeOH/30% H_2O > H_2O > Freon 113.

This surprising result is not only in disagreement with Olah's postulate about bromination selectivity of alkenes in polar and nonpolar solvents, but is inconsistent with the proposed change in the mechanism of bromination in polar and nonpolar solvents (σ- and π-complex type transition state). Further, the solvent order shown above does not follow any known solvent polarity scale.[14]

Our rate data in acetic acid and in TCE, as well as the reported data in all but the last column of Table III, were obtained by direct kinetic measurements, while the relative rates in Freon 113 represent values obtained by competition experiments.[4]

It has been frequently pointed out[1,15] that relative rates obtained by the competitive technique can be influenced by several external factors (rate of mixing, concentrations, etc). This tends to result in a smaller span of rate constants compared to those obtained from direct kinetic measurements. In addition, the decrease of ρ values with an increase of temperature is a general feature of the addition of halogens to alkenes;[16] thus, kinetic data obtained at −35 °C in Freon 113 should show *increased* selectivity with respect to those at +25 °C.

It is also possible that the additions in Freon 113 at −35 °C in the dark proceed at least partly via radical mechanisms.[17] This would explain the high reaction rates and low selectivity observed. It has been reported that the free-radical bromination is facilitated by a decrease in temperature.[18] Bromine addition to the double bond of [4.3.1]propell-3-ene in CH_2Cl_2 at −78 °C in the dark has been demonstrated to be of a radical nature.[19] It has been pointed out that the radical character of the addition does not have to be externally induced, but "a solely free-radical reaction initiated by interaction between reactants" [20] may occur.

The rate data in Freon 113 at −35 °C simply do not make any sense in terms of an ionic mechanism. However, if the data in Freon 113 are neglected, the interpretation of the remaining results concerning the role of solvent in determining the selectivity of bromination of alkenes becomes much clearer, and remains in agreement with the general organic reactivity–selectivity principle; in the better solvents, an increased reactivity and decreased selectivity is expected to occur.

In our opinion, there is no need to invoke different rate-determining transition-state structures for additions in polar and nonpolar media. The widely accepted cyclic bromonium ion like transition state accounts very well for the observed rates and exclusive antistereospecificity of the reaction in both polar and nonpolar solvents.[21]

The stereochemistry of the present additions was investigated by means of spectroscopic (NMR) analysis of the vicinal

dibromides formed as reaction products. For all 1,2-disubstituted ethylene derivatives, both in acetic acid and in TCE, exclusive antiaddition (>99%) was found. In acetic acid some bromoacetoxy products were also observed, in amounts not exceeding 5%, which is significantly less than the amounts of bromomethoxy compounds found for brominations in methanol.[22]

Structural effects on bromination rates in different solvents correlate linearly. Unfortunately, the limited number of data in H_2O as well as in Freon 112 do not allow the use of the most or least polar solvent as a reference for all the correlations. However, the rate data of each column in Table III correlate linearly with the appropriate rate data of the other columns. The slopes are close to unity for the hydroxylic solvents, and significantly higher for the nonpolar solvents, e.g.,

$$\log k_2^{rel}(CH_3COOH) = 1.09 \log k_2^{rel}(MeOH) + 0.15 \quad (4)$$

where $r = 0.971$, $s = 0.06$

$$\log k_3^{rel}(TCE) = 1.32 \log k_2^{rel}(MeOH) + 0.51 \quad (5)$$

where $r = 0.895$, $s = 0.16$

$$\log k_2^{rel}(\text{Freon 112}) = 1.23 \log k_2^{rel}(MeOH) + 0.37 \quad (6)$$

where $r = 0.992$, $s = 0.09$

Thus, although increased reactivity and decreased selectivity with a change from less to more polar solvent is observed for all the solvents of Table III (except for the data in Freon 113), the trend in slope does not show any uniform character. The larger slope value in the correlations 5 and 6 indicates a much larger charge development in the transition state of bromination in TCE and Freon 112 than in MeOH. This can be interpreted in terms of the absence of specific solvation of the transition state in nonhydroxylic solvents. This results in relative localization of the positive charge and therefore higher sensitivity to the electron-releasing effects of the substituents on the double bond.

The relative rate data presented in Table III indicate not only a general medium effect on the transition state of the reaction, but also a marked difference in the mode of solvation in nonpolar solvents with respect to the hydroxylic solvents.

The linear character of the correlations of structural effects in different solvents provides an additional argument in favor of a common σ-complex-like rate-determining transition-state structure in all solvents investigated.

We conclude that structural effects on reaction rates of bromination of alkenes are approximately constant in all hydroxylic solvents but are drastically enhanced when the reaction medium is changed to nonhydroxylic halogenated hydrocarbon-type solvent. This strongly indicates the importance of specific solvation of the transition states. Thus, it appears that the solvent has two roles in the rate-determining transition state. It solvates the departing bromide ion (electrophilic solvation) and specifically solvates the carbon portion (nucleophilic solvation).

Unfortunately, the detailed nature of the solvent–transition-state interactions cannot be evaluated on the basis of the present results. However, the importance of electrophilic solvation in bromination is emphasized by the fact that a termolecular process operates in nonprotic solvents like TCE, which are not capable of such solvation, so that the second bromine molecule has to serve the solvent function in removing the bromide ion.

Experimental Section

Reagents. The alkenes were commercially available (Chemical Samples) and their purity was verified by GLC and NMR. Acetic acid was purified by refluxing for several hours with chromium trioxide and acetic anhydride and then distilled through a column.[23] 1,1,2,2-Tetrachloroethane was purified as previously described.[24]

Kinetics. The rate constants were measured on a Durrum-Gibson stopped-flow spectrophotometer, as previously described.[6]

In order to inhibit the possible radical reaction, oxygen was passed through the TCE prior to preparing the solutions for a few control kinetic runs. No change of the reaction rate was observed.

The rates of bromine addition to 1-pentene and *cis*-3-hexene in TCE and in the presence of the radical inhibitor (isoamyl nitrite, concentration 5×10^{-3} M) were measured. The observed rates were not slower than in the regular TCE experiments.

Product Analysis. Identification of products from the addition of bromine in acetic acid to some cis and trans pairs of alkenes was carried out under conditions where the second-order process is dominant.[6] The products were isolated by pouring the reaction mixture into water, extraction with pentane, and washing with saturated $NaHCO_3$ solution and then water. The extracts were dried over $MgSO_4$ and the solvent was removed on a rotary evaporator at room temperature. The quantitative yield of products indicated 1:1 alkene–bromine adduct formation. IR and NMR spectra of the reaction mixture were in full agreement with the structure of the corresponding vicinal dibromides obtained in previous studies.[8]

In TCE, analyses were performed both by NMR and infrared spectroscopy on the reaction mixtures themselves. The magnitude of the vicinal coupling constant between the bromomethine hydrogens has been used as a criterion for distinguishing meso-*dl* and erythro-threo diastereomeric pairs of dibromoalkanes.[25] The stereochemistry of acetoxybromides was assigned on the basis of dimethine coupling constants and rotamer population by similar arguments as those for dibromoalkanes. Percentage compositions were determined from integrated areas of appropriate peaks or from peak-height ratios.

Erythro- and *threo*-acetoxy bromides used for identification as model compounds were prepared by addition of acetyl hypobromite to some alkenes.[26] NMR data necessary for product determination are collected in Table IV.

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Registry No.—Bromine, 7726-95-6.

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Nucleophilic Reactivities Toward Substituted Aryl Trimethylacetates: Conflicting Steric Effects of Ground-State Activation and Transition-State Crowding

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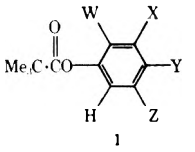
The hydroxide ion and imidazole catalyzed hydrolyses of a series of leaving-group-substitued aryl trimethylacetates have been studied at 25 °C in 10% (v/v) acetonitrile–water. The ρ value for hydroxide ion catalysis (*vs.* σ) is 0.99, with a low correlation coefficient (r = 0.962). The Brønsted plot for dependence of log k_{HO^-} on the pK_a of the conjugate acid (slope, β_{LG}) indicates that 2,3-dimethylphenyl trimethylacetate is some 25-fold less reactive than predicted; 2-chloro-4-nitro- and 2,4-dinitrophenyl esters are 3.5- and 5-fold inhibited, respectively. These deviations are ascribed to steric hindrance. Imidazole catalysis is nucleophilic even for esters with ortho substituents and the β_{LG} value was −1.16, indicating a high dependence on leaving group pK_a. The transition state for imidazole catalysis is suggested to incorporate some degree of bond cleavage between the acyl and leaving groups. The unusually high reactivity of trimethylacetylimidazole toward imidazole is suggested to be caused by steric destruction of resonance in the ground state.

Yeast carboxypeptidase Y, a protease which sequentially cleaves amino acid residues from the C terminus of proteins and peptides, has recently been shown to possess esterase activity toward aryl trimethylacetates.[1b-3] During a study of this reactivity, it became essential to obtain rate data for attack on these esters by nucleophilic species to serve as standards of reference for the enzymatic reactions. To this end, we have prepared a series of aryl-substituted trimethylacetates covering a wide range of reactivity, **1a–i** in Table I, and have studied their hydrolyses catalyzed by hydroxide ion, imidazole, and some other species. The results have led to a dissection of the steric effects which the bulky trimethylacetyl



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group can exert in the reactions of the title esters. A recent communication[4] has appeared discussing the effect of substituent variation in bridged and non-bridged trialkyl acetate 4-nitrophenyl esters.

Results

Solvolysis Catalyzed By Hydroxide Ion. Reactions of all esters studied were first order in hydroxide ion concentration so that slopes of k_{obsd} (the observed pseudo-first-order rate constant when [HO$^-$]≫ [ester]) vs. stoichiometric hydroxide ion concentration yielded values of the second-order rate constant k_{HO^-} (recorded in Table II). Values of ifk_{HO^-} for monosubstituted meta and para derivatives obeyed a Hammett relationship with Hammett σ values (eq 1, Figure 1). The relatively low correlation coefficient for this equation is characteristic of such reactions (cf. phenyl acetates,[5] phenyl benzoates[6,16]).

$$\log k_{HO^-} = 0.99\ (\pm 0.10)\ \sigma - 0.92\ (\pm 0.05) \qquad (r = 0.962) \qquad (1)$$

When k_{HO^-} values were analyzed in terms of a Brønsted-type relationship for leaving-group dependence (by plotting log k_{HO^-} vs. the pK_a of the conjugate acid of the leaving group), esters with ortho substituents were found to be considerably less reactive than meta and para derivatives (see eq 2). 2,3-Dimethylphenyl trimethylacetate is some 25-fold less reactive than the Brønsted plot (Figure 2) predicts, while the (2-chloro, 4-nitro) and 2,4-dinitro esters are 3.5- and 5-fold less labile. The slope of the Brønsted (leaving group) plot for meta and para derivatives is −0.36.

$$\log k_{HO^-} = 2.64 - 0.36\ pK_{LG} \qquad (r = 0.969) \qquad (2)$$

Solvolysis in Imidazole Buffers. Repetitive scanning of the reaction during imidazole-catalyzed solvolysis of 4-nitrophenyl trimethylacetate [imidazole buffer containing 90% free base (0.0763 M) and 10% (v/v) acetonitrile at an ionic strength of 0.1] provided evidence of a two-stage reaction course, as the isosbestic point for the initial part of reaction was 249 nm, but was 241 nm by the end of the reaction. For the 4-nitrophenyl esters, the variation of k_{obsd} with [Im]$_{tot}$ for a series of buffer ratios at constant ionic strength indicates (Figure 3) that the free base form of imidazole is catalytically active and that the reaction is first order in imidazole. Plotting these data as $(k_{obsd} - k_{intercept})/[Im]_{tot}$ vs. the mole fraction of buffer present as free base (Figure 4) indicates that there is no contribution to the observed rate from terms in [ImH$^+$] or the kinetic equivalent because at 25 °C and ionic strength 1.0 and in the presence of 10% acetonitrile $k_{Im} = 2.68 \pm 0.49 \times 10^{-3}$ M^{-1} s^{-1} and k_{ImH^+} is calculated to be zero within experimental error.

The value of the intercept on the k_{obsd} axis for 4-nitrophenyl trimethylacetate in 90% free base imidazole buffer [10% (v/v) acetonitrile, ionic strength 0.1] when k_{obsd} is plotted vs. [Im]$_{free}$ is $6.43 \pm 1.32 \times 10^{-4}$ s^{-1}. At this pH (8.00) and under these conditions, this intercept must describe the spontaneous, water-catalyzed rate, as k_{HO^-} is only 0.92 M^{-1} s^{-1} for this ester.

Values of k_{Im} were determined for the series of aryl trimethylacetates from the slopes of plots of k_{obsd} vs. [Im$_{free}$] at 90% base, ionic strength 0.1 (with NaCl as supporting electrolyte) in the presence of 10% (v/v) acetonitrile at 25 °C. Results are collected in Table II and plotted as a Brønsted leaving-group plot in Figure 5. If all the points are fitted to a Brønsted relationship, eq 3 is obtained.

The order of magnitude difference in the value of k_{Im} for 2,5-dinitro and (2-chloro, 4-nitro) esters probably indicates that strong steric factors dominate these imidazole-catalyzed reactions. The kinetic solvent deuterium isotope effects for the imidazole reactions of these latter esters are $(k_{Im})^{H_2O}/(k_{Im})^{D_2O} = 1.17$ and 0.93, respectively.

$$\log k_{Im} = 9.95 - 1.16\ pK_{LG} \qquad (r = 0.982) \qquad (3)$$

The second-order rate constant for the attack of 2,4,6-trimethylpyridine on 2,5-dinitrophenyl trimethylacetate at 25 °C [μ = 0.4, 10% (v/v) acetonitrile] is 3.38×10^{-4} M^{-1} s^{-1}.

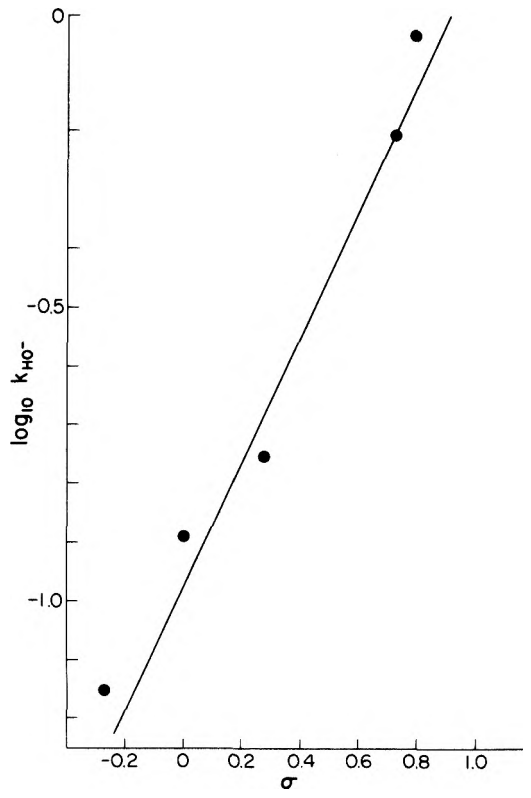


Figure 1. Dependence on σ of the rate constants for the alkaline hydrolysis or aryl-substituted trimethylacetates: values are from G. B. Barlin and D. D. Perrin, *Q. Rev., Chem. Soc.*, **20**, 75 (1966), and rate data are from Table II; line is theoretical (eq 1).

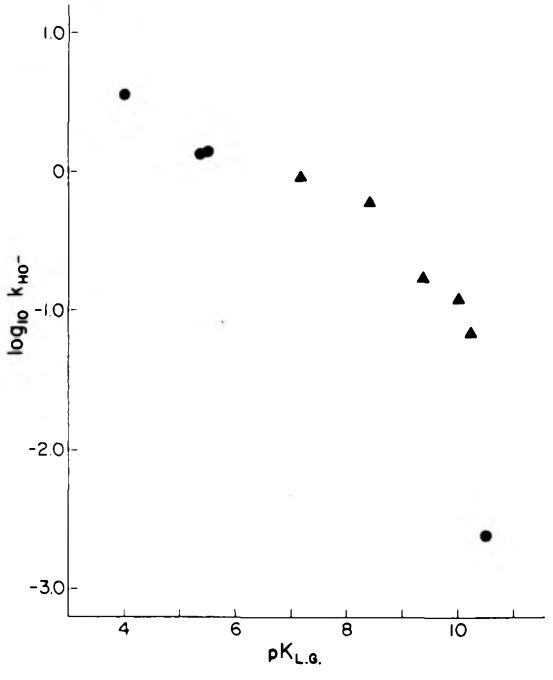


Figure 2. Dependence on the pK_a of the conjugate acid of the leaving group (pK_{LG}) of the rate constants for alkaline hydrolysis of aryl-substituted trimethylacetates: (●) esters with ortho substituents in the leaving group, (▲) esters with only meta or para substitution.

Discussion

Fife[7] has suggested on the basis of a near-unity kinetic solvent isotope effect $(k_{Im})^{H_2O} = 1.15\ (k_{Im})^{D_2O}$ that the imidazole-catalyzed hydrolysis of 4-nitrophenyl trimethylacetate is nucleophilic by analogy with the well-known nucleophilic catalysis observed for 4-nitrophenyl acetate $(k_{Im})^{H_2O} = (k_{Im})^{D_2O}$.[8] However, the best evidence for nucleophilic as opposed to general-base catalysis undoubtedly involves direct detection of the acylimidazole. Thus, the present study in which an intermediate, most likely trimethylacetylimidazole,[9] has been detected by a shift in the apparent isosbestic point during the course of reaction, along with the previous data of Fife,[7] argues strongly for nucleophilic catalysis by imidazole of 4-nitrophenyl trimethylacetate hydrolysis. Indeed, the near-unity kinetic solvent isotope effects observed in imidazole buffers for the ortho-substituted esters 2-chloro-4-nitrophenyl and 2,5-dinitrophenyl trimethylacetates (Table II) imply nucleophilic catalysis even for these "crowded" derivatives. The 1000-fold greater nuceophilic reactivity of imidazole than 2,4,6-trimethylpyridine toward the last-named ester further supports this view.[10] At this point a sharp contrast may be drawn between the steric control of mechanism rife in phosphorus(V) chemistry and the relative insensitivity of mechanistic route to steric influences shown by carboxyl substrates. Diphenyl phosphinates are subject to general base (imidazole) catalyzed attack of water. Steric hindrance by bulky groups in the substrate of direct nucleophilic attack by imidazole, offered as an explanation,[5] seems likely, as imidazole catalyzes the cleavage of the less-hindered aryl dimethylphosphinate analogues by a nucleophilic pathway.[11]

Table I

	W	X	Y	Z
a	NO_2	H	NO_2	H
b	NO_2	H	H	NO_2
c	Cl	H	NO_2	H
d	H	H	NO_2	H
e	H	NO_2	H	H
f	H	H	Br	H
g	H	H	H	H
h	H	H	MeO	H
i	CH_3	CH_3	H	H

Table II. Kinetic Parameters for Hydroxide Ion and Imidazole Catalyzed Hydrolyses of Aryl-Substituted Trimethylacetates[a]

Ester 1	Registry no.	pK_{phenol}	$10^2\ k_{HO^-}$ ($M^{-1}\ s^{-1}$)	$10^5\ k_{Im}$[b] ($M^{-1}\ s^{-1}$)
a	57025-45-3	3.96[f]	359.6 ± 6.0[c]	70 005 ± 389
b	63549-53-1	5.32	133.9 ± 7.5[c]	27 330 ± 510[d]
c	57025-46-4	5.45[g]	137.2 ± 2.0	2820 ± 49.9
d	4195-17-9	7.15	92.3 ± 1.6[e]	304.3 ± 17.9
e	63549-54-2	8.38	62.1 ± 5.3	38.8 ± 0.49
f	63549-55-3	9.34	17.7 ± 0.4	2.45 ± 0.08
g	4920-92-7	9.94	13.0 ± 1.6	
h	19820-47-4	10.20	7.8 ± 0.24	
i	63588-60-3	10.50	0.250 ± 0.012	

[a] Ionic strength 0.1 (NaCl support electrolyte), 10% acetonitrile (v/v) at 25.0 °C. Except where noted, pK values are taken from "Dissociation of Organic Acids", by G. Kortum, W. Vogel, and K. Andrussow, Butterworth, London, 1961. [b] In 90% free-base form imidazole buffer. [c] Checks on the stopped-flow results over periods of several weeks showed reproducibility of 6% or better for **1a** and **1b**. [d] In imidazole-D_2O buffer, k_{Im} was 0.2335 ± 0.00272 $M^{-1}\ s^{-1}$ and $k_{collidine}$ was 3.375 ± 0.485 × 10^{-4} $M^{-1}\ s^{-1}$ at 25 °C, ionic strength 0.4 in 60% free-base collidine buffer (10% (v/v) acetonitrile). [e] The value quoted in the table was measured by conventional spectrophotometry, the value from stopped-flow measurements was 1.20 ± 0.02 $M^{-1}\ s^{-1}$. [f] The pK value for 2,4-dinitrophenol was taken from: "Handbook of Chemistry and Physics", 51st ed, Chemical Rubber Co., Cleveland, Ohio, 1970. [g] The pK value for 2-chloro-4-nitrophenol was taken from: V. E. Bower and R. A. Robinson, *J. Phys. Chem.*, **64**, 1078 (1960).

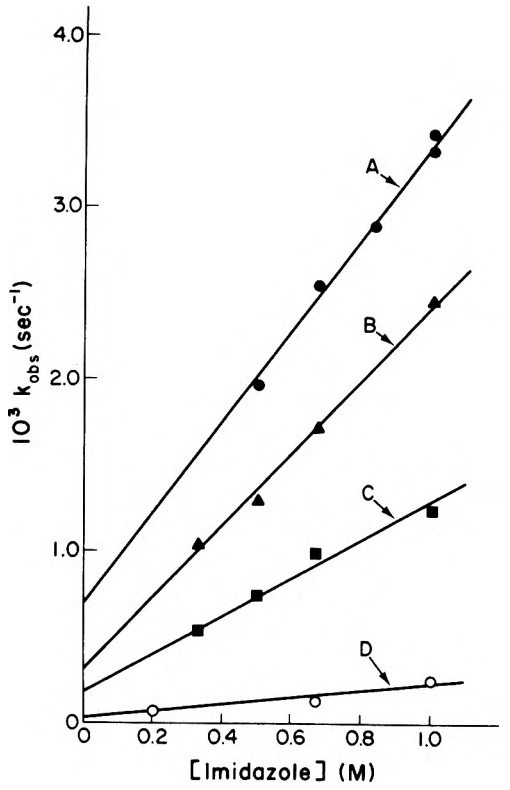


Figure 3. Dependence on imidazole concentration of observed rate constants (k_{obsd}) for imidazole-catalyzed hydrolysis of 4-nitrophenyl trimethylacetates at 25 °C in the presence of 10% (v/v) acetonitrile. Curve A (●) refers to an imidazole buffer series containing 90% free base, pH_{app} 8.06, with an ionic strength of 0.1. Curves B (▲), C (■), and D (○) refer to imidazole buffer series containing 80, 50, and 10% of free base, with pH_{app} values of 7.40, 7.30, and 6.21, respectively. For B, C, and D the ionic strength was 1.0.

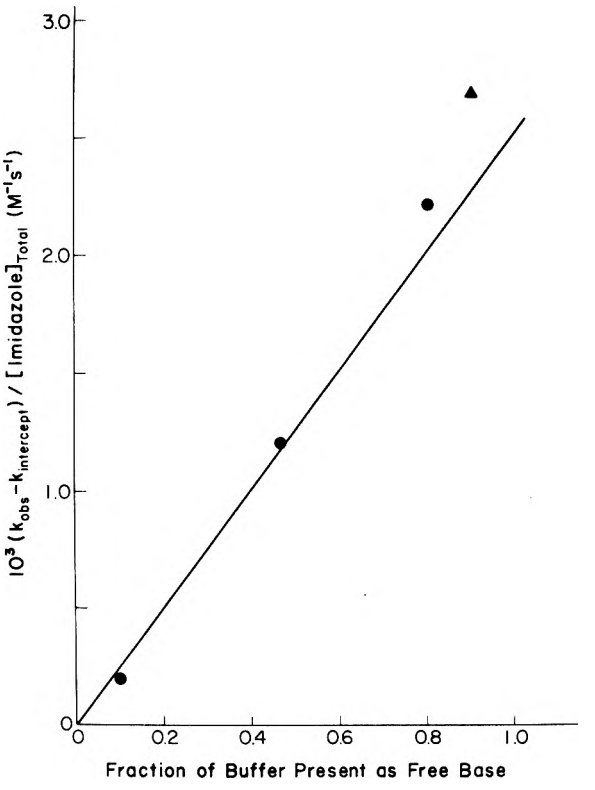
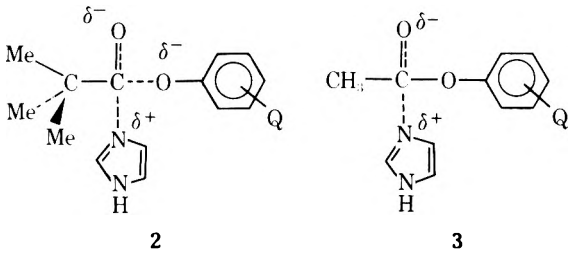


Figure 4. Separation of contributions to imidazole catalysis of 4-nitrophenyl trimethylacetate (25 °C, 10% acetonitrile, v/v) by acidic (imidazolium) and basic (imidazole) forms of the buffer. The values used on the ordinate are the slopes of plots, at a given buffer ratio, of k_{obsd} vs. $[Imidazole]_{total}$. Except for the point (▲) at 0.90 fractional free base, for which the ionic strength was 0.1, the data were obtained at an ionic strength of 1.0.

Further indication of a mechanistic shift from a nucleophilic to a general-base pathway because of steric effects comes from work on the sterically crowded bis(*p*-nitrophenyl) methylphosphonate.[12] The role of steric effects in the nucleophile is well documented for P(V) chemistry.[11-13] However, at the carboxyl level, even the highly hindered trimethylacetic esters with *o*-nitro- or o-chloro-substituted leaving groups react by a nucleophilic mechanism. Presumably the difference lies in the lower coordination number of trigonal carbon compared to tetrahedral phosphorus(V).

The ρ value for hydroxide ion catalysis for trimethylacetates (1.08) is comparable with that for phenyl acetates (0.8)[5,14] and substituted aryl benzoates (1.28).[6,15] However, if we calculate an apparent ρ value for imidazole catalysis of aryl trimethylacetate decomposition from the β_{LG} value of −1.04 using only data for monosubstituted esters (or −1.16 using all data), we obtain a value of $\rho_{Im} \simeq 2.4$ for leaving-group change, a very high value compared to that for imidazole-catalyzed hydrolysis of phenyl acetates (ρ_{Im} = 0.8)[5] or aryl-substituted benzoates (ρ_{Im} = 0.7),[15] presumably indicating some degree of bond cleavage in the transition state in order to relieve the considerable steric demands of such a nucleophilic transition state **2** (cf. **3**).



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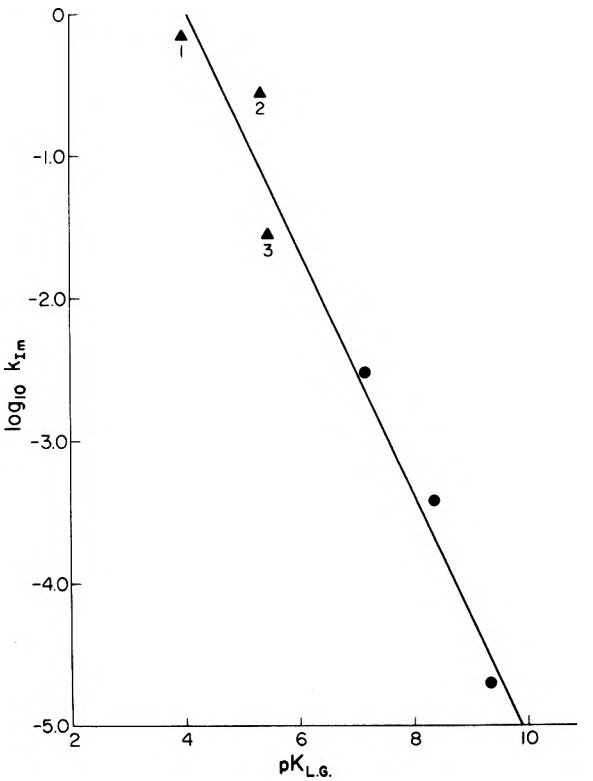


Figure 5. Dependence on the pK_a of the conjugate acid of the leaving group (pK_{LG}) of the rate constants for imidazole catalysis of the hydrolysis of substituted aryl trimethylacetates. Line is theoretical (log k_{Im} = 9.95 − 1.16 pK_{LG}; r = 0.982) for esters with meta or para substitution (●); esters with ortho substituents (▲) are designated as follows: (1) 2,4-dinitro; (2) 2,5-dinitro; and (3) 2-chloro-4-nitro.

Table III. Steric Effects on Hydroxide and Imidazole Catalyzed Hydrolyses of Some Acyl Derivatives

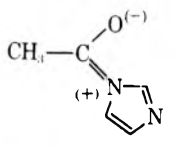
Compound	k_{HO^-} (M^{-1} s^{-1})	$10^3 k_{Im}$ (M^{-1} s^{-1})	Reference
$CH_3CO{\cdot}OC_6H_4$-pNO_2[a]	53.7[a]	590	17
$(CH_3)_3C{\cdot}CO{\cdot}OC_6H_4$-$pNO_2$[b]	0.92	3.04	This work
$CH_3CO{\cdot}Im$[c]	317	2.33	18 (HO^-), 7 (Im)
$(CH_3)_3C{\cdot}COIm$[d]	534	6.50	18 (HO^-), 7 (Im)

[a] At 25 °C, ionic strength 1.0. [b] At 25 °C, ionic strength 0.1. [c] At 25 °C, ionic strength 0.2. [d] At 30 °C, ionic strength 1.0.

Further support for this conclusion lies in the considerably greater rate constant for the imidazole catalysis of 4-nitrophenyl trimethylacetate decomposition than for that of the 3-nitro ester (~80-fold difference), probably implying a correlation with Hammett σ^- rather than σ values[16] ($\Delta\sigma^- = 0.56$, $\Delta\sigma = 0.07$). Such a rate difference indicates extra stabilization of the leaving group, presumably mesomeric, in a phenolate-ion-resembling transition state.

Some values of k_{HO^-} and k_{Im} for esters and acyl imidazoles are collected in Table III. By comparing rate constants in this table it is obvious that for RCOIm, substitution of R = CH_3– by R = $(CH_3)_3C$– causes slight increases in both k_{HO^-} and k_{Im}. The pK_a values for 4-nitrophenol and imidazole are comparable and, other things being equal, one would expect similar rates of hydroxide catalysis for acylimidazoles and the corresponding 4-nitrophenyl esters. This is indeed so for 4-nitrophenyl acetate and acetylimidazole, the difference being only some sixfold. However, trimethylacetylimidazole hydrolyzes 580 times as fast in base as 4-nitrophenyl trimethylacetate. The most likely explanation will lie either in an abnormally high rate of hydrolysis for trimethylacetylimidazole or an abnormally low rate for 4-nitrophenyl trimethylacetate.

Kristol et al.[4] have recently reported that values of k_{HO^-} for a series of trialkylacetate 4-nitrophenyl esters can be correlated well with Charton's constants and a modified Taft equation, showing no unusual behavior for 4-nitrophenyl trimethylacetate.[19] The rate of hydroxide-ion-catalyzed cleavage of trimethylacetylimidazole is *faster* than the corresponding rates for acetyl- and *n*-butyrylimidazole and equal to that for propionylimidazole.[7] Thus, the answer appears to lie in an unexpectedly high reactivity toward hydroxide ion for trimethylacetylimidazole, which is probably caused by steric destruction by the bulky *tert*-butyl group of contributions such as 4 to the ground-state stabilization of trimethylacetylimidazole; little such stabilization is likely for *p*-nitrophenyl esters.



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A comparable explanation (resonance destruction) was advanced by Staab[20] to account for the faster rates of "neutral" hydrolysis of *N*-acylimidazoles as branching in the acyl moiety increased, although he suggested an acylium ion mechanism in that case.

We have demonstrated the abnormal steric effect on substitution of a trimethyl group in the acyl portion of 4-nitrophenyl carboxylic esters and a steric acceleration of the base hydrolysis of trimethylacetylimidazole. Figure 2 shows that ortho groups in the leaving group can also exert a considerable retarding effect, especially on hydroxide catalysis. 2,3-Dimethylphenyl trimethylacetate reacts some 25-fold less readily than predicted, while the effects of 2-nitro or 2-chloro groups are to decrease the rates of hydroxide catalysis some fourfold.

Table IV. Properties and Spectral Characteristics of Substrates

Ester 1	λ_{HO^-}[a] (nm)	λ_{Im}[b] (nm)	mp or bp,[f] °C/Torr
a	410	410	66.5–67.5
b	400	400	117–119
c	410	400	79–80
d	400	400[c]	94.8–96[g]
e	340	340	82–83
f	295	275	58.5–60.5
g	295		240–245/760.2
h	305[d]		270–280/760.3
i	290[e]		*h*

[a] Wavelength at which kinetics were studied in hydroxide ion solution. [b] Wavelength at which kinetics were studied in imidazole buffers. [c] Isosbestic wavelength changes from 249 to 241 nm as reaction proceeds. [d] Isosbestic wavelengths are 282 and 260.5 nm throughout the reaction. [e] Isosbestic wavelength is 309 nm throughout the reaction. [f] Melting points are uncorrected; satisfactory data (±0.3% for C, H,N) were reported for **1a–c** and **1e–i**. [g] Lit. mp 94–95 °C. C. E. McDonald and A. K. Balls, *J. Biol. Chem.*, **227**, 727 (1957). [h] Not recorded.

If one considers the effects of leaving-group substitution on the rates of imidazole catalysis, the situation is much more complex. Equation 3 shows that rate constants for imidazole catalysis obey a Brønsted (leaving-group) relationship with a reasonable correlation coefficient, $r = 0.982$. However, this relationship may well be fortuitous, especially in view of the results for the 2,5-dinitro- and 2-chloro-4-nitro-substituted esters which react with rate constants differing by an order of magnitude, although their pK_{LG} values are closely similar. It is not possible at this point to decide whether the observed difference is caused by the difference in substitution patterns (2,5- as opposed to 2,4-) or by the change from an o-nitro to an o-chloro substituent.

In summary, then, this work presents the interesting situation wherein the reactivity patterns of a given group of compounds may exhibit a steric acceleration caused by increased steric bulk blocking resonance stabilization of the molecular ground state or a steric retardation arising from ortho substitution in the leaving group, noted especially for hydroxide catalysis.

Experimental Section

Materials. Aryl trimethylacetates were prepared from trimethylacetyl chloride (Aldrich Chemical Co.) by the following, nonaqueous, Schotten–Baumann procedure, described for the 2-chloro-4-nitrophenyl ester. To a solution of trimethylacetyl chloride (1.21 g, 0.01 mol) in dry dichloromethane (50 mL) was added a mixture of redistilled triethylamine (1.01 g, 0.01 mol) and 2-chloro-4-nitrophenol (1.74 g, 0.01 mol) in dichloromethane (50 mL). The reaction mixture was stirred at ambient temperature overnight, the solvent was removed and the residue was suspended in dry ether, cooled, and filtered; solvent was removed from the filtrate to give brown crystals which were recrystallized twice from ethanol, yielding white crystals, mp 79–80 °C. Liquid esters were purified by distillation immediately prior to use. Analytical data for the esters are presented in Table IV.

Imidazole perchlorate and sodium perchlorate were each recrystallized twice from methanol before use in buffer solutions. Deuterioimidazole was prepared by dissolving imidazole in deuterium oxide and removing the solvent under vacuum. Imidazole was recrystallized from benzene before use in buffer solutions. Acetonitrile was redistilled, "Gold label" spectroscopic grade from Aldrich, or if Reagent Grade, was fractionally distilled off phosphorus pentoxide for purification. Collidine was freshly distilled before use. Water was distilled

and deionized for these studies. Deuterium oxide was from Columbia Organic Chemicals Co. Inc., and deuterium chloride was supplied by Merck, Sharp and Dohme of Canada, Ltd. as a 38% solution in D_2O and was standardized before use by titration against sodium hydroxide solution.

Methods. Rates of hydrolysis of the esters were determined spectrophotometrically at 25.0 ± 0.1 °C in 10% (v/v) acetonitrile solution containing buffer or sodium hydroxide as appropriate. Ionic strengths were maintained at 1.0 using sodium perchlorate or at 0.1 with sodium chloride as supporting electrolyte.

Spectral scanning experiments on a Cary Model 15 spectrophotometer during the course of reaction indicated the best wavelength for determining kinetic parameters and also provided evidence on the nature of the reaction course. Spectral data are recorded in Table IV. Rates were routinely determined on either a Cary Model 15 or Gilford Model 222 recording spectrophotometer. A typical procedure involved addition of 25 or 50 μL of ester solution in acetonitrile to 3.00 mL of appropriate buffer in a cuvette by plunging in a Teflon rod with a flattened tip. Commencement of recording could be accomplished within 7 s of addition. When velocities were too high for such conventional procedures, reactions were studied usiong a Durrum-Gibson stopped-flow instrument equipped with a logarithmic converter and differential amplifier enabling results to be obtained directly in absorbance units. In typical stopped-flow studies, one syringe was filled with an aqueous acetonitrile solution of the substrate and the other with an acetonitrile–hydroxide ion solution. These solutions were allowed to equilibrate to 25.0 °C. Reaction was initiated by rapid mixing of equal volumes of the contents of these syringes. Experimental traces of phenolate ion production were recorded and retained on the screen of a storage oscilloscope and then photographed, several runs under any given experimental condition being superimposable.

Rate constants were obtained under pseudo-first-order conditions (buffer concentration was also at least 100 times that of the ester), usually from plots of log $(A_\infty - A_t)$ vs. t, where A_∞ and A_t are the changes in absorbance by the end of reaction and by time t, respectively. Final absorbance values (A_∞) were measured directly for sufficiently rapid reactions and calculated in other cases from the exponential time record of the reaction.[21] Random checks showed that measured and calculated final absorbance values were identical. Very slow reactions were studied by the method of initial rates using A_∞ values obtained by allowing specimen runs to proceed to completion.

pH measurements were carried out before and after the reaction using a Beckman Research Model pH meter standardized against appropriate Fisher Sicentific Co. certified buffer solutions. Calculations and least-squares analyses were performed on a Hewlett-Packard Model 9100-A programmable calculator.

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Mechanism of Oxidation of Alkylaromatic Compounds by Metal Ions. 3. A Product Study of the Reaction of Some Polymethylbenzenes with Cerium Ammonium Nitrate in Acetic Acid[1]

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The oxidation of hexamethylbenzene, isodurene, mesitylene, and hemimellitene promoted by cerium ammonium nitrate (CAN) in acetic acid, in the dark and in the absence of oxygen, has been investigated. The reaction requires 2 mol of CAN for 1 mol of hydrocarbon and leads in each case to the formation of benzylic nitrates and acetates. With mesitylene significant ring acetoxylation was also observed. The nitrate/acetate molar ratio appears to depend on the reaction conditions (homogeneous or heterogeneous reaction) but it is unaffected by the presence of NH_4NO_3 as well as by the structure of the substrate. With isodurene and hemimellitene the isomeric distribution of nitrates and acetates indicates that the side-chain substitution occurs predominantly at the 2-CH_3 group. These results can be accounted for by a mechanism involving the formation of a radical cation and its conversion to a benzylic radical which, in turn, can give the final products through an alkyl-Ce^{IV} species or by a ligand-transfer process.

Oxidation reactions of methylbenzenes by cerium ammonium nitrate (CAN) are long known.[2] However, very scanty information is available concerning the mechanism of these reactions.

We have recently studied the kinetic aspects and the structural effects on the reaction rate of the oxidation of polymethylbenzenes by CAN in acetic acid and shown that this reaction occurs by a rate-limiting electron-transfer process.[1] In this paper we wish to report a detailed product study of the oxidation by CAN of hexamethylbenzene, isodurene, mesitylene and hemimellitene.

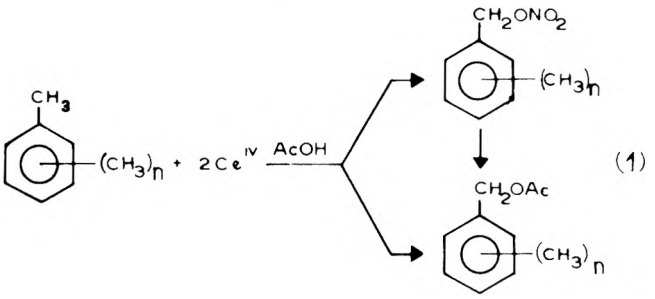
Results

All oxidation reactions were carried out in the dark and under nitrogen atmosphere. Moreover, owing to the low solubility of CAN in acetic acid, ca. 8×10^{-3} M at room temperature, heterogeneous conditions, the only ones suitable for synthetic purposes, were generally used. Some experiments under homogeneous conditions were also brought about for comparison purposes.

The stoichiometry of the reaction was determined using hexamethylbenzene (homogeneous conditions) and isodurene (homogeneous and heterogeneous conditions) as the substrates. In each case it was found that 2 mol of CAN oxidizes 1 mol of hydrocarbon. Interestingly, in the presence of oxygen the stoichiometric ratio CAN/hydrocarbon is significantly less than 2.

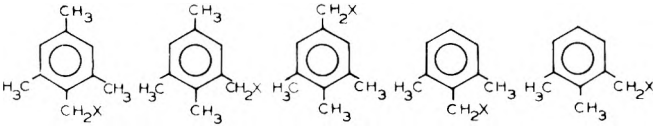
^{1}H NMR analysis of the reaction product indicated that side-chain oxidation is the only one reaction for hexamethylbenzene, isodurene, and hemimellitene. With mesitylene, also ring acetoxylation was observed. At the first stages of the reaction, 2,4,6-trimethylphenyl acetate accounts for about 50% of the reaction product. This figure, however, decreases to 25% as the reaction is complete.[3]

The products of the side-chain oxidation were, in each case, benzylic nitrates and acetates. However, since the former solvolyze in the solvent acetic acid, the nitrate/acetate molar ratio in the reaction product depends upon the reaction time and the solvolysis rate of the nitrate, as nicely illustrated in Figure 1 for the specific case of the oxidation of isodurene. According to these results the side-chain oxidation of polymethylbenzenes by CAN in acetic acid, in the dark and in the absence of oxygen, can be described by eq 1.



(1)

In order to establish the relative yields of benzylic nitrate and acetate actually obtained in the oxidation, the reaction mixtures were analyzed at different reaction times and the molar ratio benzylic nitrate/benzylic acetate was extrapolated to zero time. For isodurene and hemimellitene the ratios have been determined for all isomeric derivatives (I–V) which can be formed. The results are reported in Table I.



a (X = ONO_2)
b (X = OAc)

When the reaction is carried out under heterogeneous conditions, the nitrate/acetate ratio appears to depend upon the amount of solid CAN dispersed in the liquid phase. As the amount of undissolved CAN increases, a significant increase in the nitrate/acetate ratio is observed. Although the error affecting the determination of the nitrate/acetate ratio is rather large because of the low precision of the ^{1}H NMR technique and of the uncertainty in the extrapolation to zero time, there is no doubt that the observed trend is real. Under homogeneous conditions, the nitrate/acetate ratio was determined only for the reaction of mesitylene where the slow solvolysis of the nitrate allows a quite reliable extrapolation of the data in spite of the very small amounts of products obtained. It seems possible to conclude that the nitrate/acetate ratio determined under homogeneous conditions is lower than that obtained under heterogeneous conditions.

Other interesting observations are: (a) the nitrate/acetate ratio, in a given condition, does not significantly depend on the structure of the substrate; for isodurene and hemimellitene, it is the same for each isomer formed; (b) the nitrate/

Table I. Benzylic Nitrate/Benzylic Acetate Molar Ratio, Extrapolated to Zero Time, in the Reaction of Some Polymethylbenzenes with CAN in Acetic Acid at 50 °C

Substrate, M	Registry no.	CAN, solid phase (mmol)[a]	Benzylic nitrate/benzylic acetate, molar ratio
Mesitylene, 0.0251[b]	108-67-8		1.5 ± 0.2
0.220[b]			1.5 ± 0.2
0.119		0.20	3.0 ± 0.5
Isodurene, 0.0252	527-53-7	0.033	2.2 ± 0.2 (Ia/Ib)
			2.1 ± 0.2 (IIa/IIb)
			2.1 ± 0.4 (IIIa/IIIb)
0.0255[c]		0.033	2.2 ± 0.2 (Ia/Ib)
			2.2 ± 0.2 (IIa/IIb)
			2.1 ± 0.4 (IIIa/IIIb)
0.224[c]		0.033	2.1 ± 0.2 (Ia/Ib)
0.112		0.11	2.8 ± 0.4 (Ia/Ib)
			3.2 ± 0.4 (IIa/IIb)
			3.1 ± 0.6 (IIIa/IIIb)
0.224		0.44	>4 (Ia/Ib)
			5.0 ± 0.8 (IIa/IIb)
			5.0 ± 1.2 (IIIa/IIIb)
Hemimellitene, 0.224	526-73-8	0.44	4.8 ± 1.8 (IVa/IVb)
			5.5 ± 1.0 (Va/Vb)
Hexamethylbenzene, 0.0251	87-85-4	0.042	>1.4

[a] Millimoles of undissolved CAN dispersed in 1 mL of liquid phase. [b] [CAN] = 8.05×10^{-3} M, homogeneous condition. [c] In the presence of NH_4NO_3, 2.07×10^{-2} M.

Table II. Distribution of Isomeric Benzylic Acetates and Nitrates, Extrapolated to Zero Time, in the Side-Chain Reaction of Isodurene and Hemimellitene with CAN in Acetic Acid at 50 °C

Substrate	CAN, solid phase[a] (mmol)	Benzylic nitrates, %[b]			Benzylic acetates, %[b]		
		Ia	IIa	IIIa	Ib	IIb	IIIb
Isodurene	0.44	74	16	10	77	14	9
	0.033	72	18	10	72	20	8
	0.033[c]	71	19	10	74	17	9
		IVa	Va		IVb	Vb	
Hemimellitene	0.44	69	31		69	31	

[a] Millimoles of undissolved CAN dispersed in 1 mL of liquid phase. [b] The average error is ±5%. [c] In the presence of NH_4NO_3, 2.07×10^{-2} M.

acetate ratio is not influenced by the presence of ammonium nitrate in the reaction medium.

The distribution of the isomeric nitrates Ia–Va and acetates Ib–Vb in the oxidation of isodurene and hemimellitene, extrapolated to zero time, appears to be the same for the two side-chain derivatives, as expected by the previously observed independence of the nitrate/acetate ratio on the position of the methyl group (see Table II). No appreciable effect of the temperature was noted in the range 30–80 °C; moreover, the positional selectivity is not significantly influenced by the amounts of undissolved CAN dispersed in the solution.

Even though not high, the positional selectivity appears sufficient to allow some synthetic application of the reaction. Thus, 2,4,6-trimethylbenzyl alcohol can be isolated in 40% yield from the oxidation of isodurene followed by reduction with $LiAlH_4$ (see Experimental Section).

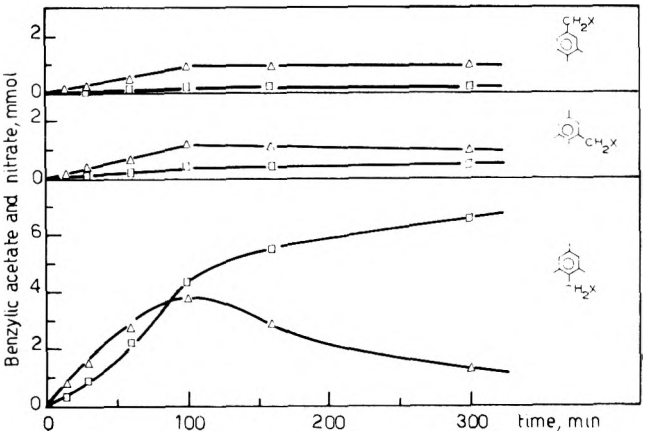


Figure 1. Millimoles of benzylic acetates (□) and nitrates (△) as a function of the reaction time obtained in the oxidation of isodurene (11.2 mmol) by CAN (22.4 mmol) in acetic acid.

Discussion

Side-Chain Oxidation. As stated above, the side-chain oxidation of polymethylbenzenes by CAN in acetic acid probably involves an electron-transfer mechanism leading to the formation of radical cations as reaction intermediates.[1] The suggested mechanism, which is similar to that generally accepted[4] for this type of reaction, is reported in eq 2–4.

$$ArCH_3 + Ce(IV) \rightleftharpoons ArCH_3^{+\cdot} + Ce(III) \quad (2)$$

$$ArCH_3^{+\cdot} \rightarrow ArCH_2^{\cdot} + H^+ \quad (3)$$

$$ArCH_2^{\cdot} + Ce(IV) \rightarrow \text{products} + Ce(III) \quad (4)$$

The results of our product study are in agreement with this mechanism, which indeed predicts the 2:1 stoichiometric ratio CAN/hydrocarbon observed in the oxidation of hexamethylbenzene and isodurene. Moreover, it is also possible to rationalize the observation that the stoichiometric ratio decreases in the presence of oxygen. Accordingly, when oxygen is present it competes with Ce(IV) for the free radical $ArCH_2^{\cdot}$, presumably forming carbonyl derivatives (see Experimental Section), and less Ce(IV) is consumed for the oxidation of 1

mol of hydrocarbon. Also, the isomeric distribution observed for isodurene and hemimellitene is in agreement with this mechanism.[5] The fact that with both these hydrocarbons the side-chain substitution mainly involves the 2-methyl group can be explained by considering that in both cases the initially formed radical cation preferentially loses the proton from the 2-methyl group, since in this way the more stable benzylic free radical can be formed. However, also the amount of positive charge at the substituted ring positions of the radical cation can be of importance.[6] Accordingly, the reactivity order of the three nonequivalent methyl groups of isodurene qualitatively parallels the order of positive charge density calculated[6] for the substituted ring positions of isodurene radical cation.

With regard to the mechanism by which the benzylic free radicals are converted into the final products, the reaction paths reported in eq 5–7, involving the formation of a free

$$ArCH_2^{\cdot} + Ce(IV) \longrightarrow ArCH_2^{+} + Ce(III) \quad (5)$$

$$ArCH_2^{+} \xrightarrow{SOH} ArCH_2OS + H^{+} \quad (6)$$

$$ArCH_2^{+} \xrightarrow{Nu^{-}} ArCH_2Nu \quad (7)$$

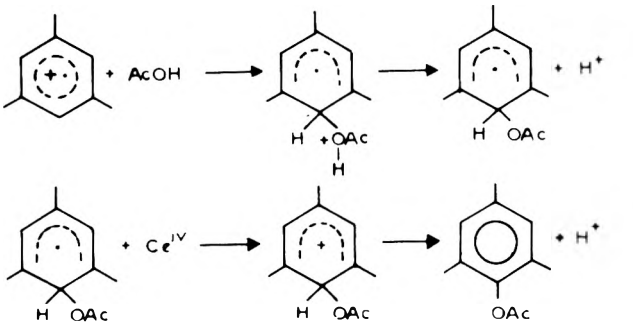
carbocation, appear unlikely, since they do not fit in with the finding that the yield of nitrate is unaffected by the presence of added nitrate ions. A reasonable suggestion could be that, as it has been already proposed for the oxidation of free radicals with Cu^{2+},[7a] the benzylic radical and Ce(IV) form an alkyl-Ce(IV) intermediate[7b] which subsequently undergoes competitive oxidative solvolysis (leading to acetate) and oxidative displacement (leading to nitrate). The two processes should have similar electronic requirements, thus accounting for the finding that the nitrate/acetate ratio, in a given condition, is substantially independent of the structure of the radical being oxidized. Alternatively, a ligand-transfer mechanism might take place.[8] In this respect, it has been reported that when CAN is dissolved in acetic acid it undergoes the exchange of two labile nitrate ions with two solvent molecules.[9] Thus, the ratio of benzyl nitrate to benzyl acetate would be determined by the relative rates of the two ligand-transfer reactions.

The observation that in the reaction carried out under heterogeneous conditions the nitrate/acetate ratio depends on the amount of solid CAN dispersed in the liquid phase suggests that the oxidation of the benzylic radical can also take place at the surface of the undissolved salt. Accordingly, the rate of this oxidation should depend on the surface development of the solid phase which, in turn, should be in some way related to the number of moles of CAN dispersed in the solution. If this interpretation is correct, the observed results indicate also that the reaction occurring at the surface of the undissolved CAN should predominantly lead to the formation of the nitrate, which is quite reasonable since the undissolved Ce(IV) would probably possess nitrate ligands, exclusively.

Finally, the comparison of the results of the oxidation of polymethylbenzenes by CAN in AcOH with those of the oxidation of the same substrates by $Ce(OCOCF_3)_4$ in CF_3COOH[10] is of interest. In the latter reaction, biaryls and diarylmethanes are by far the main reaction products, whereas very small amounts of side-chain trifluoroacetates were observed. Probably the difference between the two reactions lies in the minor basicity and nucleophilicity of CF_3COOH as compared to CH_3COOH. Thus, in CF_3COOH, the reaction of the radical cation with another molecule of aromatic compound (formation of biaryl) can compete with the proton loss to give the benzylic radical. Moreover, even when the radical is formed and is oxidized to carbocation (eq 5), the carbocation reacts with another molecule of aromatic substrate, giving diarylmethanes, rather than with the solvent.

Nuclear Acetoxylation. The formation of 2,4,6-trimethylphenyl acetate in the oxidation of mesitylene is further evidence of the intervention of a radical cation in the oxidation reaction, since such an intermediate can undergo the attack of a nucleophile (in this case the solvent) on the aromatic nucleus, as shown in Scheme I.

Scheme I



With mesitylene radical cation the ring reaction with the solvent competes significantly with the side-chain reaction (eq 3), which is, in contrast, the only one reaction observed with the other investigated hydrocarbons. In other oxidation processes too mesitylene shows a much larger tendency to ring oxidation with respect to other polymethylbenzenes. Thus, in the anodic oxidation of mesitylene and durene ring acetoxylation is observed only with the first substrate;[11] moreover, the relative amounts of biaryls (ring substitution) to diarylmethanes (side-chain substitution) are much higher with mesitylene than with durene in the reactions promoted by $Ce(OCOCF_3)_4$,[10] $FeCl_3$,[12] $Co(OCOCF_3)_3$,[13] and $Mn(OCOCF_3)_3$.[13] Similar results have been also found in the anodic oxidation in nonnucleophilic media,[6] and ring acetoxylation appears to be the major reaction observed in the oxidation of mesitylene by Ag(II).[14]

Thus, it clearly appears that in the competition between side-chain and ring reaction the relative position of the methyl groups plays a very important role, the side-chain reactions being clearly favored in the reaction of substrates having methyl groups ortho or para to each other. The phenomenon has been rationalized[6] by considering that when ortho or para CH_3 groups are present the radical cation carries a much larger amount of positive charge in the methyl-substituted position, thus favoring the loss of a proton in the benzylic position, than when the methyl groups are meta. It is interesting to note in this respect that also in the oxidation of methylnaphthalenes and methoxytoluenes by $Co(OCOCH_3)_3$ in the presence of $KOCOCH_3$ or LiCl the extent of side-chain oxidation was found to be directly related to the degree of positive charge adjacent to the methyl group.[15]

Another factor which could favor ring acetoxylation in the case of mesitylene is that the three methyl groups are in a position very suitable to stabilize the resulting σ complex. However, the role of this factor seems less important than that previously discussed, since no nuclear acetoxylation is observed in the oxidation of isodurene where a similar stabilization of the σ complex is possible.

Experimental Section

Proton magnetic resonance spectra were taken on a Jeol JNM-C60HL spectrometer, using Me_4Si as the internal standard. Infrared spectra were obtained on a Perkin-Elmer 257 from 2% solutions in CCl_4. VPC analyses were performed on a GI Fractovap (C. Erba). Elemental analyses were performed by Alfred Bernhardt, Microanalytisches Laboratorium, Elbach über Engelskirken, West Germany. All melting points are uncorrected.

Materials. Cerium ammonium nitrate $[(NH_4)_2Ce(NO_3)_6]$ (Schuchardt, 99.9% pure) was dried at 85 °C for 1 h. Acetic acid (ERBA

Table III. ^{1}H NMR Chemical Shifts in CCl_4 of Some Polymethylbenzyl Nitrates and Acetates[a]

Registry no.	Compound	Chemical shift, δ			
		Arom	$-CH_2-$	$-CH_3$	$-COCH_3$
51445-98-8	2,6-Dimethylbenzyl nitrate	7.03	5.49	2.38	
63548-89-0	2,3-Dimethylbenzyl nitrate	7.06	5.36	2.25, 2.22	
62346-87-6	2,6-Dimethylbenzyl acetate	6.97	5.11	2.38	2.00
13651-57-5	2,3-Dimethylbenzyl acetate	6.98	5.00	2.26, 2.19	1.98
63548-90-3	2,4,6-Trimethylbenzyl nitrate	6.77	5.43	2.31 (s, 6 H) 2.22 (s, 3 H)	
63548-91-4	2,3,5-Trimethylbenzyl nitrate	7.01	5.30	2.27 (m, 9 H)	
60367-95-5	3,4,5-Trimethylbenzyl nitrate	7.03	5.20	2.29 (s, 6 H) 2.18 (s, 3 H)	
63548-92-5	2,4,6-Trimethylbenzyl acetate	6.70	4.99	2.30 (s, 6 H) 2.22 (s, 3 H)	1.97
63548-93-6	2,3,5-Trimethylbenzyl acetate	6.75	4.87	2.15 (s, 6 H) 2.06 (s, 3 H)	1.89
39126-12-0	3,4,5-Trimethylbenzyl acetate	6.90	4.82	2.26 (s, 6 H) 2.14 (s, 3 H)	1.99
19405-90-4	Pentamethylbenzyl nitrate		5.50	2.26 (s, 6 H) 2.19 (s, 9 H)	
19936-85-7	Pentamethylbenzyl acetate		5.13	2.24 (s, 6 H) 2.19 (s, 9 H)	1.97

[a] Chemical shifts may vary with concentration (δ ±0.08), but in case of isomeric substrates the relative order remains unchanged.

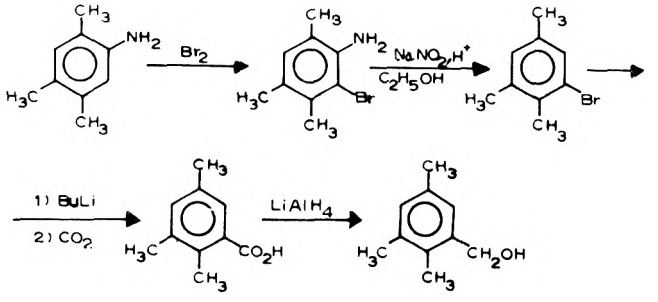
RPE) was thoroughly fluxed with pure nitrogen before use. The purity of hexamethylbenzene (Fluka, 99% pure), isodurene (Schuchardt, 98% pure), hemimellitene (Schuchardt, 98% pure), and mesitylene (ERBA, 99.5% pure) was checked by VPC. 2,6-Dimethylbenzoic acid (Fluka, 98% pure), 2,3-dimethylbenzoic acid (Fluka, 97% pure), and pseudocumidine (Fluka) were commercial samples and were used as received. Bromomesitylene (Aldrich) was distilled before use. 3,4,5-Trimethylbenzoic acid was prepared according to a literature method,[16] mp 218–220 °C, lit.[16] mp 218–220 °C.

Pentamethylbenzyl alcohol was available from a previous investigation.[17]

2,4,6-Trimethylbenzyl alcohol was prepared by the reaction of the Grignard reagent derived from bromomesitylene[18] with gaseous formaldehyde,[19] mp 88.5–89 °C from hexane, lit.[20] mp 88 °C.

2,3,5-Trimethylbenzyl alcohol was synthesized according to the reaction sequence in Scheme II. Any attempt to obtain 6-bromo-

Scheme II



pseudocumene from pseudocumidine according to Smith and Moyle[21] failed, as well as any modification derived therefrom, involving H_3PO_2 as the reducing agent for the diazo compound. In all cases, 2-bromo-3,4,6-trimethylphenol was obtained as the sole product, mp 31–32 °C, lit.[22] mp 32 °C. Better results were achieved following the method of Carpenter and Easter.[23] 6-Bromopseudocumene was obtained as a colorless liquid, n^{22}_D 1.5524, lit.[21] n^{26}_D 1.5516. Treatment of the latter compound with *n*-BuLi in dry ether solution, followed by reaction with excess carbon dioxide, afforded 2,3,5-trimethylbenzoic acid, mp 123–127 °C from aqueous ethanol, lit.[24] mp 124 °C. Reduction of the acid with $LiAlH_4$[25] gave 2,3,5-trimethylbenzyl alcohol in virtually quantitative yield, mp 50–51 °C from hexane.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.97; H, 9.40. Found: C, 79.86. H, 9.33.

The other benzyl alcohols were similarly obtained from the corresponding acids.

3,4,5-Trimethylbenzyl alcohol, mp 72–73 °C from hexane, lit.[26] mp 72–74 °C. Anal. Calcd for $C_{10}H_{14}O$: C, 79.97; H, 9.40. Found: C, 79.83; H, 9.51.

2,6-Dimethylbenzyl alcohol, mp 81–82 °C from ligroine, lit.[27] mp 82–83 °C.

2,3-Dimethylbenzyl alcohol, mp 66–68 °C from ligroine, lit.[28] mp 65–66 °C.

Benzylic Nitrates. These compounds were obtained in 70–90% yield by treatment of the corresponding alcohols with $SOCl_2$, followed by reaction with $AgNO_3$ in CH_3CN. All the compounds showed strong $-ONO_2$ absorption in the IR spectra at 1635 and 1280 cm^{-1}. The ^{1}H NMR spectral data are reported in Table III.

Benzylic Acetates. These compounds were prepared in quantitative yield by acetylation of the appropriate alcohol with acetic anhydride. The ^{1}H NMR spectral data are reported in Table III.

The Oxidation of Polymethylbenzenes with CAN. A mixture of the hydrocarbon (5.0–45 mmol) and CAN (1.6–90 mmol) in 200 mL of acetic acid was stirred at 50 °C in a nitrogen atmosphere in the dark. Aliquots (20–50 mL) were taken at intervals, quenched in cold petroleum ether 30–50 °C, washed with a solution of $FeSO_4$, concentrated, and analyzed by ^{1}H NMR. In all cases, the ^{1}H NMR signal of the oxidation products was compared with those of authentic samples. These were synthesized by independent routes in the cases of hexamethylbenzene, isodurene, and hemimellitene (see above), and obtained by direct isolation in the case of mesitylene (*vide infra*). In each case the relative amounts of nitrates and acetates present in the reaction product and the isomeric distribution were determined by integration of ^{1}H NMR peaks due to the CH_2X groups (Table III).

Stoichiometry of the Reaction. The stoichiometry of the reaction was determined under a variety of conditions using hexamethylbenzene and isodurene as the substrates. A solution of hexamethylbenzene (0.202 mmol) and CAN (0.202 mmol) in 80 mL of acetic acid was heated at 40 °C, in the dark and under nitrogen. When all Ce(IV) was consumed, 0.13 mmol of menthol and 0.14 mmol of 4-nitrobiphenyl (internal standards) were added to the cooled reaction mixture. The solution was diluted with pentane and washed with water. After removing most of the solvent, the residue was analyzed by VPC using a 3-mm i.d. glass column (1.8 m) containing 0.1% FFAP on carbon-coated beads[29] with nitrogen as carrier gas. The column temperature was 90 °C for the analysis of hexamethylbenzene and 150 °C for the analysis of pentamethylbenzyl acetate. It was observed that 0.099 mmol of hexamethylbenzene had reacted and that 0.096 mmol of pentamethylbenzyl acetate had been produced. When the same experiment was carried out in the presence of air, it was found that, starting from 0.260 mmol of hexamethylbenzene and 0.255 mmol of CAN, 0.216 mmol of hexamethylbenzene had been oxidized. IR analysis of the reaction product indicated the presence of significant amounts of carbonyl derivatives.

Isodurene (11.2 mmol), CAN (22.4 mmol, most undissolved), and 1,4-dibromobenzene (standard, 1.13 mmol) in acetic acid (50 mL) were heated with stirring at 50 °C, in the dark under nitrogen. At the end of the reaction the mixture was cooled and worked up as described before. ^{1}H NMR analysis showed that 10.9 mmol of benzylic nitrates and acetates had been formed. Performing the same experiment under

homogeneous conditions it was found that 1.60 mmol of isodurene reacts with 0.80 mmol of CAN to give 0.41 mmol of benzylic acetates and nitrates.

Oxidation of Mesitylene. Isolation of the Reaction Products. A mixture of mesitylene (16.6 mmol) and CAN (33.2 mmol) in acetic acid (200 mL) was treated as above until the red-orange color of CAN faded (45 h). The pale-yellow liquid (2.5 g) obtained after usual workup was chromatographed on silica gel. Elution with $CHCl_3$–light petroleum 1:9 gave 3,5-dimethylbenzyl nitrate (0.93 g, 31% yield) as a colorless liquid: n^{22}_D 1.5172 (lit.[30] 1.5172); IR 2920 and 1640 cm^{-1}; ^1H NMR (CCl_4) δ 6.90 (s, 3 H), 5.22 (s, 2 H), 2.27 (s, 6 H). Recovery was not quantitative, since several fractions containing the product in a less pure form were discarded. Elution with pure $CHCl_3$ gave 0.81 g of a mixture of two products, which were later shown to be 3,5-dimethylbenzyl acetate and 2,4,6-trimethylphenyl acetate. Pure samples of the latter compounds were obtained by resolution of the mixture by preparative VPC, on a 2-m column packed with CWX 20M 10% operating at 140 °C. Structure assignments were based on the following properties. 2,4,6-Trimethylphenyl acetate: IR 2920 and 1760 cm^{-1}; ^1H NMR (C_6D_6) δ 6.73 (s, 2 H), 2.10 (s, 3 H), 2.05 (s, 6 H), 1.90 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 179, M^+ (16), 137 (13), 136 (100), 135 (15), 121 (56), 91 (14), 43 (13). 3,5-Dimethylbenzyl acetate: n^{20}_D 1.5032 (lit.[31] $n^{23.5}_D$ 1.5028); IR 2920 and 1740 cm^{-1}; ^1H NMR (CCl_4) δ 6.88 (s, 3 H), 4.94 (s, 2 H), 2.27 (s, 6 H), 2.00 (s, 3 H).

Oxidation of Isodurene. Isolation of 2,4,6-Trimethylbenzyl Alcohol. Isodurene (7.5 mmol) was made to react with CAN (15.0 mmol) in acetic acid at 80 °C for 10 min, and the crude reaction product was reduced with $LiAlH_4$. The mixture of alcohols was recrystallized from hexane, and 2,4,6-trimethylbenzyl alcohol, mp 83–85 °C, was obtained in 40% yield.

Acknowledgments. The financial support of C.N.R. is gratefully acknowledged for the part of this work which has been carried out at the University of Perugia.

Registry No.—CAN, 16774-21-3; acetic acid, 64-19-7; 3,5-dimethylbenzyl nitrate, 15285-43-5; acetate, 19082-49-6; 2,4,6-trimethylbenzyl alcohol, 4170-90-5; 3,4,5-trimethybenzyl alcohol, 39126-11-9; 2,6-dimethylbenzyl alcohol, 62285-58-9; 2,3-dimethylbenzyl alcohol, 13651-14-4.

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A Study of the Mode of Decomposition of Some Carboxylic *tert*-Alkylcarbonic Anhydrides[1a]

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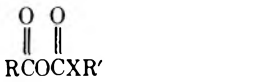
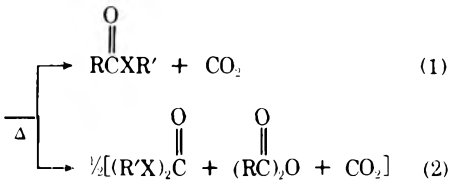
Three hindered carboxylic carbonic anhydrides—pivalic *tert*-butylcarbonic anhydride, pivalic *tert*-butylthiolcarbonic anhydride, and 2,2-dimethylbutyric *tert*-amylthiolcarbonic anhydride—have been prepared and studied with respect to their mode of decomposition and reactivity with a primary amine. While the products from the decomposition of pivalic *tert*-butylcarbonic anhydride are consistent with an ionic chain mechanism, the products from the decomposition of the two pure thiolcarbonic anhydrides are more consistent with an intramolecular decomposition. In addition, results from the decomposition of a mixture of the two thiolcarbonic anhydrides argue strongly against an ionic chain mechanism. Other considerations are discussed briefly.

There have been numerous reports[2] dealing with the synthesis, reactions, and mode of decomposition of carboxylic carbonic anhydrides **1**. In general, this type of compound is thermally unstable, particularly in solution or in the liquid state. Two sets of decomposition products are possible,[3,4] as shown by eq 1 and 2. Usually, mixed anhydrides from alcohols (X = O) tend to give varying ratios of the possible products,[5,6] while anhydrides from thiols (X = S) give primarily thiol ester and carbon dioxide.[7] Although both systems have exhibited first-order or psuedo-first-order decomposition kinetics, the kinetic measurements for thiol-mixed anhydrides were consistent and reproducible, while those for alcohol-mixed anhydrides were erratic and apparently quite succeptible to the influences of trace impurities. It has been proposed that mixed



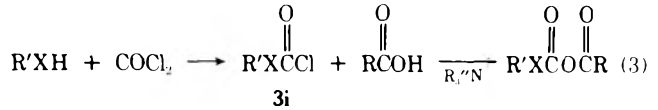
1, R, R′ = alkyl or aryl, X = O or S
2a, R = R′ = $-C(CH_3)_3$, X = O
b, R = R′ = $-C(CH_3)_3$, X = S
c, R = R′ = $-C(CH_3)_2C_2H_5$, X = S

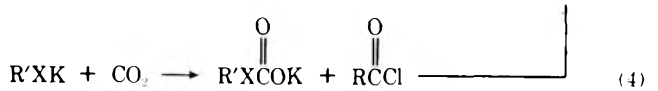


anhydrides derived from alcohols decompose by an ionic chain mechanism, while mixed anhydrides from thiols decompose via an intramolecular route.

In order to further investigate these hypotheses, we have studied a new group of anhydrides which are characterized by a tertiary alkyl group adjacent to both the carboxylic and carbonic carbonyls. First, we have compared pivalic *tert*-butylcarbonic anhydride (**2a**) with pivalic *tert*-butylthiolcarbonic anhydride (**2b**). Secondly, we have compared **2b** with 2,2-dimethylbutyric *tert*-amylthiolcarbonic anhydride (**2c**). Finally, we have decomposed a mixture of **2b** and **2c** and analyzed the resulting product mixture to determine whether the decomposition yielded products expected of an intramolecular reaction or those to be expected from an ionic chain mechanism, i.e., crossover products.[8]

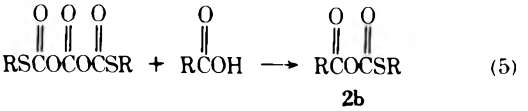
Synthesis of Mixed Anhydrides. The present work with mixed anhydrides indicates that method 3 is preferable for





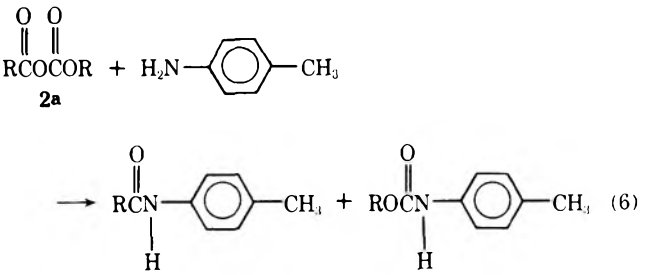
X = O or S

the preparation of anhydrides derived from tertiary thiols and method 4 is preferable for oxygen analogues.[5] The reason for this lies in the stability of the intermediate chlorocarbonate **3**. While tertiary alkyl chlorocarbonates are quite unstable and difficult to work with,[9] the corresponding thiol derivatives are reasonably stable, can be distilled if necessary, and can be stored in the refrigerator for several weeks with no noticeable decomposition. Compound **2b** has been prepared previously[10] in an entirely different fashion (eq 5).



$R = -C(CH_3)_3$

Reactions of 2a–c. Because of the hindered nature of these compounds, their utility as possible selective acylating or nitrogen blocking agents was investigated. Leister and Tarbell[11] had previously demonstrated that the reaction of pivalic ethylcarbonic anhydride and *N*-methylaniline led to the formation of only the corresponding ethyl carbamate and none of the possible pivalamide. We found that **2a** reacted with *p*-toluidine (eq 6) to give isolated yields of 66% of the pivalamide **4a** and 32% of the carbamate **4b**. Subsequently, **2b** and **2c** were found to yield mixtures which consisted of approximately the same ratio of amide vs. carbamate on the basis of



4a, 66% **4b**, 32%

their IR spectrum and TLC.

Next, a product study of the thermal decomposition of these anhydrides was undertaken. Two different approaches were utilized to give the results shown in Table I. First, the amount of carbon dioxide evolved was measured by absorption on Ascarite; and secondly, the residues from these decompositions were subjected to analysis by VPC. Due to the difference in the stoichiometry between reaction 1 and reaction 2, one can predict the amount of carbon dioxide which should be evolved by comparing the ratio of ester formed to symmetrical anhydride or carbonate.

For the decomposition of **2a**, products identified in order of their relative abundance were carbon dioxide, pivalic anhydride, di-*tert*-butyl carbonate, *tert*-butyl pivalate, *tert*-butyl alcohol, and isobutene. The ratio of pivalic anhydride to *tert*-butyl pivalate was 3.7 to 1.0. This ratio is consistent with 88% of the decomposition occurring by reaction 2.

The decompositions of **2b** and **2c** as pure materials led to quite similar product ratios. Both compounds decomposed primarily by reaction 1 to yield 87% of thiol ester and 7% of the symmetrical anhydride in the case of **2b**, and 81% ester to 9% anhydride for **2c**. Products from the decomposition of **2b** were identified as carbon dioxide, *tert*-butyl thiolpivalate (**5**), pivalic anhydride (**6**), and di-*tert*-butyl dithiolcarbonate (**11**). For **2c** the products were carbon dioxide, the *tert*-amylthiol ester from 2,2-dimethylbutyric acid (**9**), 2,2-dimethylbutyric anhydride (**10**), and di-*tert*-amyl thiol carbonate (**12**).

Decomposition of a mixture of **2b** and **2c** led to a mixture which was analyzed by VPC originally to show four major and two minor peaks in addition to carbon dioxide, as noted in Table I. The peaks were identified in order of increasing retention time as *tert*-butyl thiolpivalate (**5**), pivalic anhydride (**6**), *tert*-amyl thiolpivalate (**7**), *tert*-butylthiol 2,2-dimethylbutyrate (**8**), *tert*-amylthiol 2,2-dimethylbutyrate (**9**), and 2,2-dimethylbutyric anhydride (**10**). Since the column temperature was kept below 120 °C during the VPC analysis, it was probable that the symmetrical thiolcarbonates were retained on the column. Subsequent elevation of injection port and column temperature did result indeed in two additional peaks, **11** and **12**, with longer retention times, which were the expected symmetrical thiolcarbonates. The course of the crossover experiment may be summarized by eq 7.

Kinetic Studies of 2a–c. Attempts to measure the rates of decomposition of these compounds were undertaken utilizing IR.[7,12] This method was not possible with **2a** due to the overlap of the carbonyl bands of the starting material and pivalic anhydride, the major product of the decomposition. Further, there was no other IR absorption in **2a** which was suitable to use. However, with the thiolcarbonic anhydrides **2b** and **2c**, carboxylic acid anhydride formation is minor, and through 80% reaction, interference is minimal. A detailed study of **2b** was undertaken to verify kinetic and thermodynamic similarity to previously studied thiolcarbonic anhydrides.[7] The results of this study can be found in Tables II and III.

Although a detailed study of **2c** was not undertaken, a rate determination was carried out at 125 °C, the temperature at

Table I. Measurement of CO_2 Evolution

Compd	Weight decomposed	Weight of CO_2 collected	% of 1 eq.
$(CH_3)_3CCOCOC(CH_3)_3$ (2a)	1.2464	0.1719	63
	0.5604	0.0741	61
			Av 62 (60)[a]
$(CH_3)_3CCOCSC(CH_3)_3$ (2b)	0.1904	0.0319	83
	0.4334[b]	0.0905	103
	0.2313	0.0445	95
	0.1155	0.0207	89
	0.1823	0.0305	83
	0.2049	0.0421	102
			Av 92 (94)[a]
$C_2H_5(CH_3)_2CCOCSC(CH_3)_2C_2H_5$ (2c)	0.3723	0.0600	90 (89)[a]
2b + 2c	0.3235, 0.4172	0.1066	76
	0.9745, 0.2040[b]	0.2850	75
			Av 76 (92)[a]

[a] These numbers represent the predicted amount of CO_2 on the basis of VPC analysis of residue comparing ester to anhydride ratio. [b] These reactions were carried out in chlorobenzene, while all others were carried out without solvent.

$$\mathbf{2b} + \mathbf{2c} \xrightarrow{125\ ^\circ C} (CH_3)_3CCSC(CH_3)_3\ (\mathbf{5},\ 80\%) + [(CH_3)_3CC]_2O\ (\mathbf{6},\ 10\%)$$
$$+ C_2H_5(CH_3)_2CSCC(CH_3)_3\ (\mathbf{7},\ <1\%) + (CH_3)_3CSCC(CH_3)_2C_2H_5\ (\mathbf{8},\ <1\%)$$
$$+ C_2H_5(CH_3)_2CCSC(CH_3)_2C_2H_5\ (\mathbf{9},\ 82\%) + [C_2H_5(CH_3)_2CC]_2O\ (\mathbf{10},\ 9\%)$$
$$+ [(CH_3)_3CS]_2C\ (\mathbf{11},\ \%\ \text{undetermined}) + [C_2H_5(CH_3)_2CS]_2C\ (\mathbf{12},\ \%\ \text{undetermined}) \quad (7)$$

which the crossover experiment was run. At this temperature a 0.4515 M solution of **2c** in chlorobenzene had a first-order rate constant of 4.05×10^{-4} s^{-1} and a 0.3795 M solution had a rate constant of 3.95×10^{-4} s^{-1}. Interpolation of the Arrhenius plot for pivalic *tert*-butylthiolcarbonic anhydride (**2b**) yielded a rate constant of 11.0×10^{-4} s^{-1} at this same temperature.

Table II. Reaction Rates for Pivalic *tert*-Butylthiolcarbonic Anhydride (2b)

Concn, M	Solvent	Temp, °C	First-order $k \times 10^4$ s
0.040 88	Decalin	118.5	2.96
0.121 2		118.5	2.79
0.083 52		125.9	5.25
0.040 09		138.6	14.6
0.040 62	Chlorobenzene	108.2	2.06
0.040 62		118.5	5.33
0.040 62		133.6	17.8

Table III. Activation Parameters for Decomposition of Pivalic *tert*-Butylthiolcarbonic Anhydride

Temp, ±0.1 °C	$k \times 10^4$ s	Concn, M	E_a, kcal/mol	ΔH, kcal/mol	ΔS, eu
		In Decalin			
118.5	2.96	0.040 88	25.5	24.7	−12.0
125.9	5.25	0.083 52			
138.6	14.6	0.040 09			
		In Chlorobenzene			
108.2	2.06	0.04062			
118.5	5.33	0.040 62	26.2	25.4	−9.1
133.6	17.8	0.040 62			

Discussion

In this study we have examined carboxylic carbonic anhydrides, in which the carboxylic portions of the molecules are derived from aliphatic acids with an adjacent tertiary group and not from aromatic acids as in earlier studies.[5-7] Further, we have contrasted the reactivity of two of these mixed anhydrides, which differ only with respect to whether they contain oxygen or sulfur in the carbonic moiety (X = O in **2a** and X = S in **2b**), and we have decomposed two similar mixed anhydrides, **2b** and **2c**, simultaneously in the same reaction vessel to determine if products expected from an ionic chain decomposition are formed.

The reaction of these dually hindered anhydrides with a primary amine led to an interesting observation. Although there is an increased yield of the corresponding carbamate, the reaction was far from being selective, with the major product still the amide for **2a**, **2b**, and **2c**. Whether this change in product ratios is due to steric or electronic effects has not been answered.

Although the aliphatic carboxylic thiolcarbonic anhydrides **2b** and **2c** do decompose more readily than corresponding aromatic carboxylic thiolcarbonic anhydrides, decomposition kinetics are still first order and the product ratios are essentially the same. The oxygen analogue **2a** seems to differ very little both in ease of decomposition and in the range and variability of products formed from the corresponding aromatic system.[5] It seems that **2a** decomposes by one mechanism, while **2b** and **2c** decompose by another. That this may be the case is likely when one considers the much greater propensity for carbon–oxygen cleavage as opposed to carbon–sulfur cleavage in tertiary systems[13,14] and the greater nucleophilicity of sulfur as compared to oxygen.

Since earlier suggestions[5,6] of an ionic chain mechanism for

oxygen anhydrides similar to **2a** seem to explain the results quite well, we decided to carry out a crossover experiment to determine if we could rule out an ionic chain mechanism for the decomposition of the corresponding thiol anhydrides **2b** and **2c** with some degree of certainty. Comparison of the individual decomposition rates of **2b** and **2c** at the temperature at which the crossover study was run showed that **2b** decomposed slightly less than three times as fast as **2c**. On the basis of earlier work,[15] this new rate seems reasonable and one would expect not too much difference in the reactivity of **2b** and **2c**. If the compounds decompose via an ionic chain, reasonably one could expect at least 10–15% of the crossover products **7** and **8**. The results given in eq 7 clearly show that this is not the case. When coupled with the relatively small change in rate constants with a change in polarity of solvents, a result which has been noted previously with the aromatic carboxylic thiolcarbonic anhydrides,[7] this experiment virtually rules out the ionic chain. However, the formation of even trace amounts of these compounds, as well as larger fractions of symmetrical acid anhydrides and thiolcarbonates, is not consistent with a completely intramolecular process. That these compounds might arise from a relatively slow biomolecular process is a possibility, but there is not evidence for this.

Experimental Section

General. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. All melting and boiling points are uncorrected. The IR spectra for qualitative work were recorded on a Beckmann IR-10 or a Perkin-Elmer 727 spectrometer in solution or neat as indicated for each compound. Quantitative IR spectra were recorded in solution on a Perkin-Elmer 621 spectrometer. The NMR spectra were recorded on a Jeol MH-100 instrument under the conditions indicated. For kinetic experiments the temperature was controlled by an E. H. Sargent Co. mercury capillary thermoregulator, which maintained temperatures at ±0.1 °C of the stated values, which have been corrected by calibration against a Dymec Model DY-2801A quartz thermometer (Hewlett-Packard, Dymec Division, Palo Alto, Calif.).

Preparation of Pivalic *tert*-Butylcarbonic Anhydride (2a). A slight modification of the published method[5] was used to prepare the title compound. Potassium *tert*-butoxide (6.0 g, 0.054 mol) was first carbonated in 50 mL of THF, and then treated with freshly distilled pivaloyl chloride (6.2 g, 0.052 mol) in 20 mL of THF over a 3-h period, giving 6.0 g (58%), which appeared to be the desired product from its IR spectrum. Subsequent vacuum distillation at 80–82 °C (12 mm) led to 4.6 g (44%) of a viscous material, which had a neat proton NMR spectrum[16] of equivalent singlets at 1.60 and 1.31 ppm and an IR spectrum (CCl_4) with carbonyl absorption at 1800 and 1745 cm^{-1}. The pure material had mp 21–23 °C.

Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.25; H, 8.96.

Preparation of *tert*-Butyl Pivalate. Equimolar quantities of pivaloyl chloride and triethylamine with a twofold excess of *tert*-butyl alcohol in THF were refluxed for 40 h. After a standard workup on the reaction mixture, distillation gave the ester: bp 134.5–137 °C, NMR spectrum in chlorobenzene of equivalent singlets at 1.39 and 1.12 ppm, and neat IR spectrum with a single carbonyl absorption at 1720 cm^{-1}.

Preparation of Pivalic Anhydride (6). Reaction of equimolar quantities of pivaloyl chloride, pivalic acid, and triethylamine in refluxing THF led to the production of a material whose bp was 192–194 °C and whose IR spectrum (CCl_4) showed carbonyl absorption at 1810 and 1735 cm^{-1}. The NMR spectrum consisted of a singlet at 1.14 ppm in chlorobenzene, and VPC indicated only one compound was present.

Preparation of *tert*-Butylthiol Chlorocarbonate (3b). The following is a modification of the procedure[17] of Tarbell and Parasaran and is due primarily to the unpublished work of Dr. Yutaka Yamamoto. An excess of phosgene (18 g, 0.18 mol) was collected in 50 mL of benzene (an increase in volume of 1 mL is equal to 1.2 g) and then added to an ice–salt cooled 250-mL three-neck round-bottomed flask equipped with nitrogen inlet, mechanical stirrer, and addition funnel. Via the addition funnel a solution of *tert*-butyl mercaptan (14.4 g, 0.16 mol) and pyridine (12.0 g, 0.15 mol) in about 40 mL of benzene was introduced over a period of 30 min and stirred for another hour at ice bath temperature under a nitrogen atmosphere. After the solution was allowed to rise to room temperature over 3 h, insoluble material was removed by suction filtration through a medium-fritted filter while under a dry nitrogen atmosphere, and solvent was removed in vacuo. This provided a crude yield of 17.6 g (75%) of the desired chlorocarbonate as a cloudy solution which exhibited a very characteristic neat IR spectrum with broad absorption centered at 1755 (s) and 1625 cm^{-1} (w). In this case, the thiol chlorocarbonate was used without further purification, although one can readily purify the crude material by distillation at 43 °C (12 mm). The thiol chlorocarbonate appears relatively stable and can be stored in the refrigerator for several weeks without any apparent decomposition.

Preparation of *tert*-Amylthiol Chlorocarbonate (3c). The reaction of *tert*-amyl mercaptan (10.4 g, 0.10 mol) and pyridine (8.0 g, 0.10 mol) with phosgene (6.0 g, 0.60 mol) in benzene, as described previously for **3b**, yielded 11.7 g (70%) of crude product. Subsequent distillation at 30 °C (1 mm) led to 11.2 g (67%) of product with an IR spectrum quite similar to that of **3b**. This material is relatively stable, as evidenced by its unchanged IR spectrum, after storage in the refrigerator for 1 month.

Preparation of 2,2-Dimethylbutyric Acid.[18] The modified procedure[19,20] of Puntambeker and Zollner was used to prepare the title compound from carbon dioxide and *tert*-amyl chloride, which was first prepared from *tert*-amyl alcohol by the procedure[21] of Norris and Olmstead. Distillation at 74 °C (0.5 mm) led to the desired product.

Preparation of Pivalic *tert*-Butylthiolcarbonic Anhydride (2b). The preparation of the title compound was effected by modification of published procedures.[4,17] First, **3b** was prepared as described earlier and was used as the crude product without further purification. A solution of **3b** (17.6 g, 0.12 mol) in 20 mL of benzene was added dropwise to a magnetically stirred solution of pivalic acid (11.8 g, 0.12 mol) and pyridine (9.2 g, 0.12 mol) in 40 mL of benzene at ice bath temperature over a period of 30 min. After the solution was allowed to warm to room temperature over a 3-h period, it was filtered by suction through a medium-fritted funnel under a nitrogen atmosphere. The filtrate was then washed with three 40-mL portions of a 10% sodium carbonate solution, followed by three 40-mL portions of water and dried. Filtration and removal of solvent in vacuo led to **2b** as a white wax which melted from 62.5 to 64.5 °C (lit.[10] mp 57–59 °C). The IR spectrum agreed with the previous report and the NMR spectrum[16] showed equivalent singlets at 1.34 and 1.09 ppm in chlorobenzene.

Preparation of 2,2-Dimethylbutyric *tert*-Amylthiolcarbonic Anhydride (2c). The preparation of the title compound was effected in the same manner in which **2b** was prepared. Reaction of 2,2-dimethylbutyric acid (5.8 g, 0.05 mol) and **3c** (8.3 g, 0.05 mol) in benzene with 1 equiv of pyridine led to 8.0 g (65%) of the title compound. The IR spectrum (CCl_4) showed carbonyl absorptions at 1795 and 1730 cm^{-1}; the NMR (CCl_4) consisted of a multiplet at 1.71 ppm (4 H), a singlet at 1.47 ppm (6 H), a singlet at 1.19 ppm (6 H), and a quartet at 0.95 ppm (6 H); and the compound boiled at 75–76 °C (0.02 mm).

Anal. Calcd for $C_{12}H_{22}O_3S$: C, 58.50; H, 9.00. Found: C, 58.77; H, 9.13.

Preparation of *tert*-Butyl Thiolpivalate (5). Freshly distilled pivaloyl chloride (6.0 g, 0.05 mol) was added dropwise over a 30-min period to a solution of *tert*-butyl mercaptan (6.8 g, 0.075 mol) in 50 mL of dry pyridine and refluxed for 4 h. After the addition of 100 mL of ether, the solution was washed successively with 100 mL in three portions each of water, 5% aqueous hydrochloric acid, and 5% sodium carbonate solution. The resulting ethereal solution was dried, filtered, reduced in vacuo, and distilled in 174–175 °C to yield 4.8 g (55%) of a constant boiling material. Analysis by VPC indicated only one compound was present, and mass spectroscopy showed a parent ion at 174. The IR spectrum (CCl_4) had a strong absorption at 1680 cm^{-1} and the NMR[16] showed two equivalent singlets at 1.19 and 1.47 ppm in chlorobenzene.

Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.25; H, 8.96.

Preparation of Di-*tert*-butyl Dithiolcarbonate (11). The method[7] of Wei and Tarbell was used to prepare the title compound in a crude yield of 61% from sodium *tert*-butyl mercaptide and *tert*-butylthiol chlorocarbonate. Spectra and physical properties were in agreement with the previous report.

Preparation of *tert*-Amyl Thiolpivalate (7). Attempted preparation of *tert*-amyl thiolpivalate in the same manner in which *tert*-butyl thiolpivalate was formed resulted in the formation of a mixture of compounds. From IR and VPC results, the mixture appears to be

primarily the desired compound and pivalic anhydride. Attempts to separate the mixture by distillation and column chromatography on silica gel were unsuccessful. The compound was then isolated by VPC and its identify was confirmed by its mass spectrum, which exhibited a peak at *m/e* 188 that corresponds to the molecular ion, a base peak at *m/e* 85 that corresponds to the acyl ion $(CH_3)_3CC^+{=}O$, and a prominent peak at *m/e* 119 that corresponds to the "McLafferty +1" product[22] $(CH_3)_3CC(=SH^+)OH$. The IR spectrum (CCl_4) contained a carbonyl absorption at 1670 cm^{-1}.

Product Studies. Analysis for carbon dioxide, which was evolved during the thermal decomposition of the various carbonates, was carried out by collecting the carbon dioxide on Ascarite. The apparatus consisted of a two-neck flask equipped with a nitrogen inlet and an upright condenser, which was connected in series to a dry-ice trap containing Drierite, a U-shaped tube filled with Ascarite, and finally a sulfuric acid trap which was placed directly after the condenser. The nitrogen inlet consisted of an adapter, with a stopcock, connected in series to two Ascarite filled tubes, a sulfuric acid trap, and a tank of prepurified nitrogen. The stopcock was open only when the system was under a positive pressure from the tank. The decompositions were usually effected either neat or in solution by placing the two-neck flask in a stirred oil bath heated between 100 and 175 °C. With the adapter stopcock closed, the flask was heated for 3 h, then removed from the bath, and allowed to cool for 5 min. At this time the stopcock was opened and the system was flushed for 15 min with nitrogen before the U-shaped Ascarite tube was weighed. This procedure was repeated at 1-h intervals until a constant weight was obtained for the U-shaped Ascarite tube.

Analysis for other products was usually effected with VPC and IR. The chromatography was carried out on 5 ft × ¼ in. column of 5% SE 30 on Chromosorb W or 5% Ucon on Chromosorb W at injection port temperatures ranging from 170 to 220 °C and column temperatures ranging from 100 to 150 °C. Usually compounds were identified on the basis of their retention times, although in some cases compounds were identified by either coinjection techniques or by collection and analysis of IR and NMR spectra. Samples were usually analyzed at two different column temperatures for comparative purposes. Retention times for the compounds on the Ucon column at an injection port temperature of 210 °C, column temperature of 145 °C, and flow rate of 60 mL/min were 2.64 min for *tert*-butyl thiolpivalate (**5**), 3.06 min for pivalic anhydride (**6**), 3.74 min for *tert*-amyl thiolpivalate (**7**), 4.33 min for what is assumed to be *tert*-butylthiol 2,2-dimethylbutyrate (**8**), 5.81 min for *tert*-amylthiol 2,2-dimethylbutyrate (**9**), and 6.74 min for 2,2-dimethylbutyric anhydride (**10**). It should be noted that the identity of *tert*-amylthiol 2,2-dimethylbutyrate (**9**) was confirmed by collection followed by mass spectral analysis. Th compound gave a peak at *m/e* 202 which corresponds to the molecular ion, a base peak at 99 which corresponds to the acyl ion $C_2H_5(CH_3)_2CC^+{=}O$, and a peak at 133 which corresponds to the "McLafferty +1" ion $C_2H_5(CH_3)_2C(=SH^+)OH$.

Reaction of Mixed Anhydrides 2a–c with *p*-Toluidine. A. Pivalic *tert*-Butylcarbonic Anhydride. To a solution of pivalic *tert*-butylcarbonic anhydride (4.1 g, 0.02 mol) in 25 mL of dry THF was added a solution of *p*-toluidine (2.5 g, 0.023 mol) in 25 mL of THF. After refluxing for 40 m the THF was removed in vacuo to leave a solid mixture with a wide melting range beginning at 65 °C. Addition of 15 mL of anhydrous ether, resulting in partial solution of the mixture, and subsequent filtration yielded a white crystalline substance whose IR ($CHCl_3$) showed a carbonyl absorption at 1670 cm^{-1}; whose NMR ($CHCl_3$) showed a singlet at 1.25 (9 H) and 2.23 ppm (3 H), and multiplet from 6.88 to 7.27 ppm (5 H); and whose melting range was 119–121 °C. All of this information is consistent with this compound being the *N*-pivaloyl derivative of *p*-toluidine, which was reported by Davis and Hickinbottom[23] to have a melting point of 120 °C.

The ethereal solution was then shown to contain two major components. Removal of ether in vacuo was followed by the addition of 10 mL of hexane, which once again led to only partial solution. Filtration gave more of the white crystals. Next the yellowish brown hexane solution was chromatographed on 50 g of silica gel by elution in succession with 550 mL of hexane, 200 mL of 5% ether–hexane, 200 mL of 10% ether–hexane, 200 mL of 20% ether–hexane, 200 mL of 50% ether–hexane, and 200 mL of chloroform to yield two major fractions. The second fraction which came off was more of the *N*-pivaloyl derivative and when added to the previously collected fractions amounted to 2.5 g (66%). The first fraction had an IR spectrum ($CHCl_3$) which showed a carbonyl maximum at 1718 cm^{-1}, and an NMR spectrum ($CDCl_3$) which displayed a singlet at 1.46 ppm (9 H), a singlet at 2.24 ppm (3 H), and a multiplet from 6.28 to 7.00 ppm (5 H). This information coupled with the fact that its melting range was 91–93 °C indicated that this compound was *N*-*tert*-butoxycarbonyl-*p*-toluidine, which was reported by Choppin and Rogers[9] to have a melting range of 92–92.8 °C. The yield of this compound was 1.3 g (32%).

B. Pivalic *tert*-Butylthiolcarbonic Anhydride (2b). Next, **2b** was reacted with *p*-toluidine in the same fashion as its oxygen homologue. Its IR once again indicated the presence of two types of carbonyl absorptions and TLC also indicated two different major components. However, an attempt to purify this mixture by chromatography on silica gel proved unsuccessful. Comparison of the IR spectrum of this mixture with authentically prepared *N*-thiol-BoC derivative of *p*-toluidine and the pivalamide indicated that the thiol derivative was the minor component.

Preparation of *N*-Thiol-Boc of *p*-Toluidine. To a solution of *p*-toluidine (2.4 g) in 10 mL of chloroform was added **3b** (1.75 g) in 15 mL of chloroform over a 20-min period. After stirring overnight the solution was filtered to remove insoluble material and the solvent was removed in vacuo to give 2.1 g (85%) of a crude solid which melted from 99 to 105 °C. Recrystallization from CCl_4 led to a white crystalline solid which melted from 104.5 to 106 °C. The IR spectrum (CCl_4) showed a strong absorption at 1690 cm^{-1} and the NMR spectrum (CCl_4) a singlet at 1.48 ppm (9 H), a singlet at 2.22 ppm (3 H), and a multiplet from 6.62 to 7.11 ppm (5 H).

Anal. Calcd for $C_{12}H_{17}NOS$: C, 64.53; H, 7.67. Found: C, 64.39; H, 7.80.

C. 2,2-Dimethylbutyric *tert*-Amylthiolcarbonic Anhydride. Reaction once again led to the production of two major components by TLC and two different carbonyl absorptions in the IR. No attempt was made to purify these products.

Kinetic Studies. The kinetic studies were performed using the procedure[12] of Dean, Tarbell, and Friederang with one major exception. Rate constants were determined by computer utilizing a program[24] which yielded a least-squares fit for the data. Also, the activation parameters were determined by computer in order to obtain a least-squares fit.

Acknowledgment. We are indebted to Grant GP-7874 from the National Science Foundation for support of this work.

Registry No.—**2a**, 39982-01-9; **2b**, 28058-95-9; **2c**, 63528-31-4; **3b**, 13889-95-7; **3c**, 63528-32-5; **4a** [R = $C(CH_3)_3$], 21354-40-5; **4b** [R = $C(CH_3)_3$], 14618-59-8; **5**, 28058-96-0; **6**, 1538-75-6; **7**, 63528-33-6; **9**, 63528-34-7; **11**, 16118-32-4; potassium *tert*-butoxide, 865-74-4; pivaloyl chloride, 3282-30-2; *tert*-butyl pivalate, 16474-43-4; pivalic acid, 75-98-9; phosgene, 75-44-5; *tert*-butyl mercaptan, 75-66-1; *tert*-amyl mercaptan, 1679-09-0; *tert*-amyl chloride, 594-36-5; 2,2-dimethylbutyric acid, 595-37-9; *p*-toluidine, 106-49-0; *p*-toluidine *N*-thiol-BoC derivative, 63528-35-8.

References and Notes

(1) (a) Taken from the Ph.D. Thesis of R. L. Stanley, Vanderbilt University, 1976. (b) Present address: School of Pharmacy, Ferris State College, Big Rapids, Michigan 49307.
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Thermal Rearrangement of α-Oxo-α,β-unsaturated Azines to N-Substituted Pyrazoles

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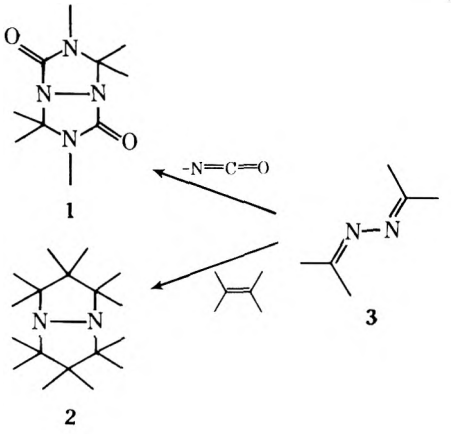
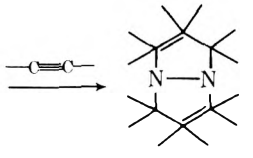
Thermolysis of α-oxo-α,β-unsaturated azines (**9**) was found to be an efficient and general route to α-pyrazolyl esters (**12**, R_1 = OEt) or ketones (**12**, R_1 = alkyl or aryl). The azines were readily synthesized by either the condensation of α-diketone monohydrazones (**22, 25**) with α,β-unsaturated aldehydes and ketones (**26**) or the Wittig olefination of the stabilized phosphoranes (**17, 18**) with aryl adehydes.

We would like to report a simple, general synthesis of the pyrazole ring system based on the thermolysis of α-oxo-α,β-unsaturated azines **9** (Scheme I). Although azines (e.g., **3**) are dienes, the 1,3 relationship of an eletrophillic C–N double bond and a relatively electron-rich nitrogen greatly alters the cycloaddition behavior of these compounds. Attempted



1 **2** **3**



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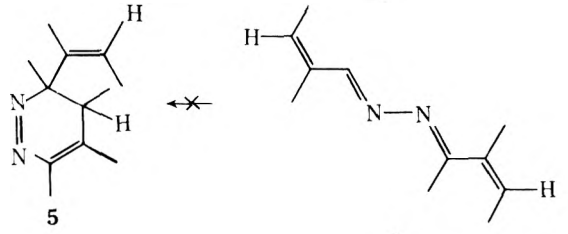
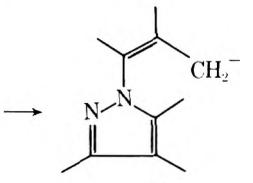


5 **6**



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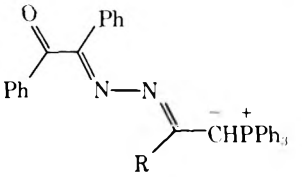
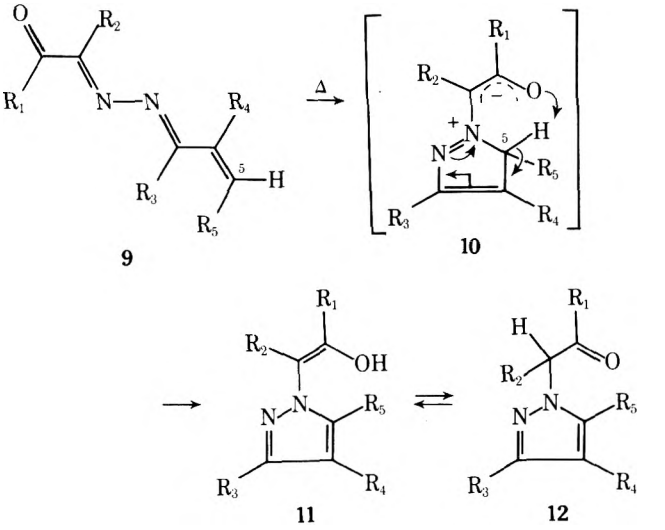


8a, R = CH_3

b, R = $Ph_3\overset{+}{P}\overset{-}{C}H$-

Scheme I

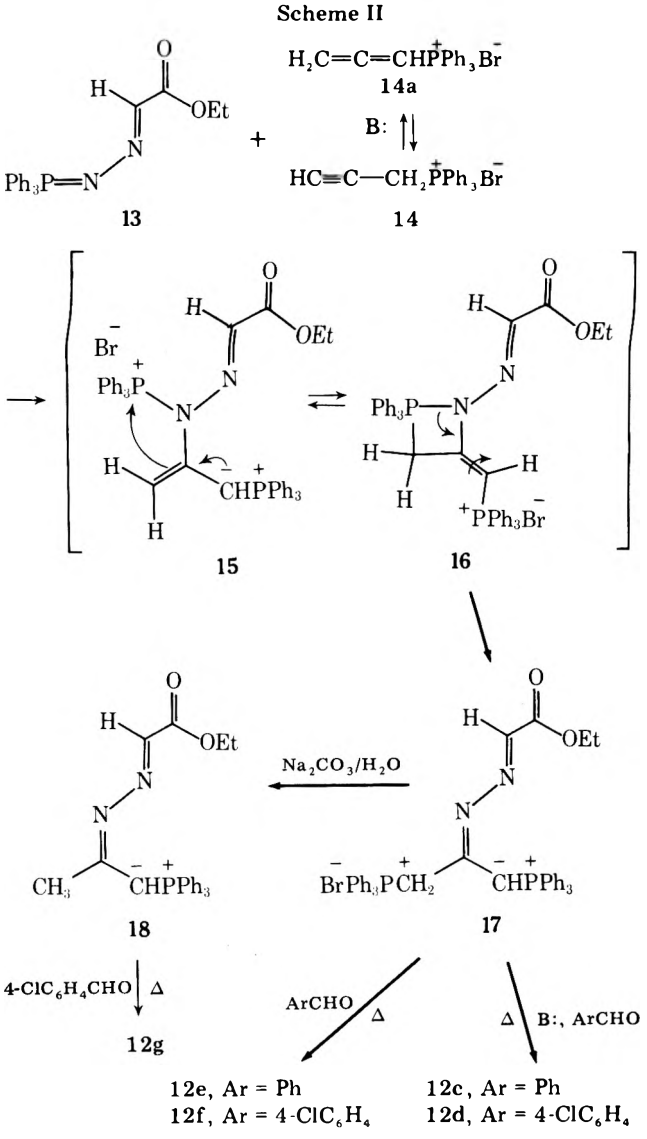


9 **10** **11** **12**

	R_1	R_2	R_3	R_4	R_5
9–12a,	Ph	H	4-ClC_6H_4CH=CH–	H	4-ClC_6H_4
b,	Ph	H	CH_3	H	4-ClC_6H_4
c,	EtO	H	PhCH=CH–	H	Ph
d,	EtO	H	4-ClC_6H_4CH=CH–	H	4-ClC_6H_4
e,	EtO	H	$BrPh_3\overset{+}{P}\overset{-}{C}H_2$–	H	Ph
f,	EtO	H	$BrPh_3\overset{+}{P}\overset{-}{C}H_2$–	H	4-ClC_6H_4
g,	EtO	H	CH_3	H	4-ClC_6H_4
h,	Ph	Ph	CH_3	H	4-ClC_6H_4
i,	CH_3	CH_3	H	H	Ph
j,	Ph	Ph	H	H	Ph
k,	Ph	Ph	H	H	
l,	Ph	Ph	H	H	CH_3
m,	Ph	Ph	H	CH_3	Ph
n,	Ph	Ph	CH_3	H	Ph
o,	Ph	Ph	CH_3	H	
p,	Ph	Ph	Ph	H	Ph
q,	Ph	Ph	Ph	H	–COPh
r,	Ph	Ph	H	Br	Ph
s,	Ph	Ph	H	$-CH_2CH_2CH_2CH_2-$	
t,	Ph	Ph	H	$-CH_2CH_2CH_2O-$	
u,	Ph	Ph	H	$-CH_2OCH_2CH_2-$	
v,	Ph	Ph	H	$-CH_2CH_2CH_2-$	
w,	Ph	Ph	$-CH_2CH_2CH_2CH_2-$		Ph
x,	Ph	Ph	$-CH_2CH_2CH_2-$		Ph

Diels–Alder reaction of azines with olefins, isocyanates, or acetylenes leads[2,3] to bicyclic 2:1 (dienophile/azine) adducts **1**, **2**, or **4** (or products of further thermal rearrangements[2,3]), respectively, rather than the expected 1:1 adducts associated with butadienes. This type of reactivity is unique to azine chemistry and has been termed[2] "criss-cross" cycloaddition.

Scheme II

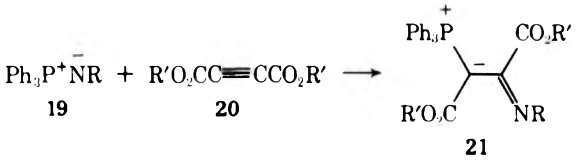


Azines (6) derived from α,β-unsaturated aldehydes and ketones exhibited[4,5] similar intramolecular cycloaddition reactivity, yielding *N-cis*-propenylpyrazoles **7**, rather than cyclic azo compounds **5**, on thermolysis.

Recently we reported[6] that stabilized phosphoranes **8a** and **8b** yielded phenacyl pyrazoles, **12a** and **12b** (Scheme I), when allowed to react with benzaldehyde. Presumably, the origin of these products was a thermal rearrangement of azines **9a** and **9b** (the expected Wittig olefination products) similar to that observed for **6**. Scheme I outlines a proposed mechanism for this rearrangement based on the work of Stern and Krause.[4,5] Initial attack of the imine nitrogen on the terminal olefinic carbon of **9** would generate the azomethine imine **10**. A prior isomerization of one or both of the C–N double bonds in **9** may be necessary in order to attain the correct geometry for the cyclization (**9** → **10**). If the original azine **9** was mono- or unsubstituted at C-5, aromatization by intramolecular hydrogen transfer could occur, leading to the observed products. Any azine of the type **9**, bearing at least one hydrogen substituent on C-5, should serve as a precursor for pyrazoles **12** (and/or **11**), making the overall sequence an attractive new route to N-substituted pyrazoles. We now wish to report our investigations into the synthetic utility of these transformations.

Results and Discussion

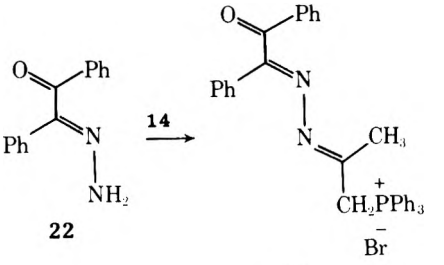
Syntheses of Azines and Pyrazoles Based on Phosphonium Ylide Intermediates. Ylide salt **17** may be readily synthesized by the reaction of carboethoxyphophazine (**13**) with propargyltriphenylphosphonium bromide (**14**) (Scheme II). Brown[7] has reported an analogous reaction, yielding phosphoranes (**21**) from phosphinimines (**19**) and acetylenic

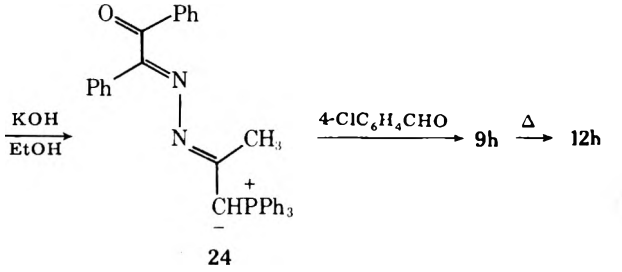


esters (**20**). The formation of **17** probably involved the series of steps outlined in Scheme II. Initial reaction of **13** with the allenyl isomer (**14a**) of **14**[8] would yield zwitterion **15**, presumably in equilibrium with azaphosphetidine **16**. Decomposition of **16** in the indicated manner would then generate **17**.

After treatment with a strong base (NaH or NaOEt, forming a bisylide) **17** could be converted in good yield to pyrazoles **12c** or **12d** by reaction with benzaldehyde or 4-chlorobenzaldehyde, respectively. Simply heating **17** in the prescence of the same aldehydes led to **12e** or **12f**, which retain the methylenetriphenylphosphonium moiety. Mild alkaline hydrolysis (Na_2CO_3, H_2O) of **17** selectively cleaved one of the triphenylphosphonium substituents, yielding ylide **18**, which could in turn be converted to pyrazole **12g** by heating with 4-chlorobenzaldehyde. Elemental and spectral analysis of the colorless crystalline products **12c–g** supports the structural assignments (see Tables III and IV). The configuration of the 3-styryl groups in **12a**, **12c**, and **12d** could not be determined since, in the ^1H NMR, the vinyl protons were obscured by aromatic resonances.

Azines **9a–g** were presumably intermediates in these reactions, although they were not isolable under the reaction conditions. The intermediacy of **9** in a related system was confirmed. Azine phosphonium salt **23** could be readily prepared by employing the reaction of benzil monohydrazone (**22**)

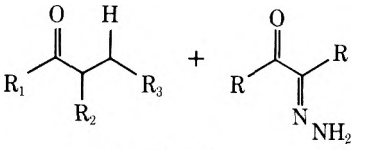




with propargylphosphonium salt **14**. When the corresponding ylide (**24**) was allowed to react with 4-chlorobenzaldehyde, an orange solid resulted which could be converted to colorless pyrazole **12h** by distillation at 260 °C (0.5 mm). This sequence, coupled with an analysis of its spectral data, allows us to assign the structure of the orange solid as azine **9h**.

Syntheses of Azines and Pyrazoles From α-Diketone Monohydrazones and α,β-Unsaturated Carbonyl Compounds. Intermediates based on phosphonium salt **14** were useful synthons for a number of pyrazole systems (i.e., **12a–h**), but limited the substituents which could be introduced into

Table I. Reactions of α-Diketone Monohydrazones with α,β-Unsaturated Aldehydes and Ketones



22, R = Ph
25, R = CH_3

	R_1	R_2	R_3	Hydrazone	Product	Yield,[a] %	Method[b]
26a	H	H	Ph	25	9i	68	B, 4 h
a	H	H	Ph	22	9j	86	A, 24 h
b	H	H	2-Furyl	22	9k	52	A, 4 h, *p*-TSA[c]
c	H	H	CH_3	22	12l	50	A, 12 h
d	H	CH_3	Ph	22	12m	91	A, 25 h, HOAc
e	CH_3	H	Ph	22	12n	75	A, 24 h, *p*-TSA
f	CH_3	H	2-Furyl	22	12o	48	A, 5 h, *p*-TSA
g	Ph	H	Ph	22	12p	57	A, 8 h, *p*-TSA
h	Ph	H	COPh	22	12q	54	A, 8 h, *p*-TSA
i	H	Br	Ph	22	9r	82	A, 3.5 h
j	H	$-CH_2CH_2CH_2CH_2-$		22	9s	79	A, 5 h, HOAc
k	H	$-CH_2CH_2CH_2O-$		22	9t	38	B, 7 h
l	H	$-CH_2OCH_2CH_2-$		22	9u	82	A, 5 h, HOAc
m	H	$-CH_2CH_2CH_2-$		22	9v	83	A, 5 h, HOAc
n	$-CH_2CH_2CH_2CH_2-$		Ph	22	12w	62	A, 19 h, *p*-TSA
o	$-CH_2CH_2CH_2-$		Ph	22	9x	75	A, 36 h, *p*-TSA

[a] Isolated yield based on hydrazone. [b] See Experimental Section. [c] *p*-Toluenesulfonic acid.

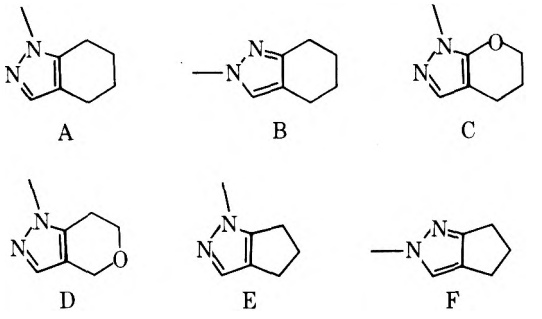
Table II. Thermolysis of Azines

Azine	Conditions (T, °C/time, h)	Product(s)	% yield
9i	180/1	**12i**	90
9j	175/2	**12j**	88
9k	130/2.5	**12k**	64
9r	175/2.5	**12r**	67
9s	150/4	**12s**	72
9t	175/3	**11t**	74
9u	150/5	**12u**	85
9v	150/4	**12v**	73
9x	160/4	**11x**	25
		12x	50

the heterocyclic ring. Thus, we sought a more general route to α-oxo-α,β-unsaturated azines **9** utilizing readily available starting materials. We reasoned that the reactions of α-diketone monohydrazones (**22** or **25**) with α,β-unsaturated aldehydes or ketones (**26**) would provide a flexible and straightforward route to azines **9** and/or their rearrangement products (**11/12**) (see Table I).

In fact, when cinnamaldehyde (**26a**) was allowed to react with either diacetyl (**25**) or benzil (**22**) monohydrazone, azines **9i** and **9j** could be isolated in good yield. We have extended this sequence to include the reactions of **22** with a variety of other α,β-unsaturated aldehydes and ketones (**26b–p**), summarized in Table I. Azines (**9**) were isolable in approximately half of the reactions, pyrazoles, **11**, and/or **12**, being formed directly in the remainder. The α-oxo-α,β-unsaturated azines, ranging in color from yellow to orange, could be converted to the colorless pyrazoles **11/12** in good yield by thermolysis (Table II). Although no attempts at optimization were made, the yields were generally good (38–91%), establishing this reaction sequence (**22/25** + **26** → **9** → **11/12**) as a viable route to α-pyrazolyl ketones.

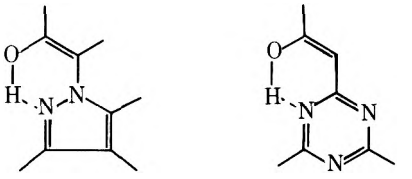
In addition to monocyclic pyrazoles (**12i–r**), this sequence permitted the synthesis of bicyclic systems when the carbonyl or olefinic portion of **26** was incorporated into a carbo- or heterocyclic ring. By proper choice of the α,β-unsaturated aldehyde or ketone (**26**) we were able to prepare examples of the 1*H*- (**A**) and 2*H*-tetrahydroindazole (B) (**12s** and **12w**),



A B C D E F

pyrazolo[5,4-*b*]-(C) and pyrazolo[4,5-c]pyran (D) (**11t** and **12u**), and 1*H*- (E) and 2-*H*-cyclopentapyrazole (F) (**12y** and **11x/12x**) systems.

Interestingly, in two cases, enol tautomers (**11t** and **11x**) of the α-pyrazolyl ketones were isolable. The infrared spectra were particularly distinctive, showing bands for OH (~3450 cm^{-1}) and C=C (~1570 cm^{-1}), while lacking a carbonyl stretching absorption. Additional support was provided by the conversion of pure **11x** to a mixture (as determined by thin-layer chromatography) of **11x** and **12x** upon heating at 170 °C for 2 h. Presumably stabilization of the enol form in these cases is provided by intramolecular hydrogen bonding with N-2 of the pyrazole ring as in **27**. Similar enol stabilization is seen in α-triazinyl ketones (e.g., **28**).[9] We can offer no explanation as to why these two systems were the only ones in which the enol was isolable.



27 28

Spectral Characteristics. Table III lists the physical properties and characteristic IR absorption frequencies of the azines and pyrazoles described above. Azines **9** exhibit bands at 1665–1685 (conjugated C=O) and 1570–1625 cm^{-1} (C=N, C=C) in their infrared spectra. The α-pyrazolyl esters **12c–g** show strong bands at ~1750 (ester C=O) and ~1590 cm^{-1}

Table III. Physical Properties and Characteristic Infrared Bands of Azines (9) and Pyrazoles (11/12)

Compd	Mp[a] (bp/mm), °C	IR[b] cm^{-1}
9h	117–118	1685, 1595, 1575
9i	67.5–69	1680, 1625, 1545
9j	133.5–135	1675, 1620, 1580
9k	106–108	1665, 1615, 1580
9r	145–146	1660, 1595, 1565
9s	100–101	1675, 1630, 1590
9t	89–91	1665, 1620, 1590
9u	134.5–136	1675, 1640, 1595
9v	81–82	1680, 1620, 1590
9x	157–158	1675, 1595, 1575
11t	126–128	3450, 1560, 1525
11x	165.5–167	3460, 1560, 1530
12c	87–89	1750, 1580
12d	139–140	1750, 1600
12e	208–209	1740, 1570
12f	175–176	1740, 1580
12g	64–65	1750, 1600
12h	151–152	1700, 1600
12i	(100/1.1)	1730, 1610
12j	129–130	1705, 1600
12k	145	1690, 1600
12l	151.5–152.5	1690, 1595
12m	137.5–138.5	1700, 1600
12n	105–106.5	1690, 1595
12o	138–139	1665, 1615, 1570
12p	110	1690, 1600, 1580
12q	119–121	1680, 1630, 1575
12r	140–141	1665, 1590
12s	123–124	1695, 1600
12u	139.5–140.5	1695, 1600
12v	146–147	1680, 1600
12w	120–122	1700, 1600
12x	133–134.5	1690, 1595

[a] Melting (boiling) points are uncorrected. [b] Standarized by reference to polystyrene film.

(pyrazole C=N/C=C).[10] Infrared spectra of α-pyrazolyl ketones **12h–s** and **12u–x** are characterized by peaks at 1690–1730 (C=O) and ~1600 cm^{-1} (pyrazole C=N/C=C).

Proton NMR data for all compounds are collected in Table IV and are completely consistent with the assigned structures. A few general observations may be made. The aldimine (HC=N–) protons in those azines derived from aldehydes (**9i,j,k** and **9r–y**) resonate at 7.8–8.2 ppm. In the pyrazole derivatives, systems unsubstituted at carbon 3 and/or 4 exhibit signals at 7.0–7.8 [C(3)–H] and/or 5.9–6.3 ppm [C(4)–H], consistent with reported[11] NMR data. In addition, the α-pyrazolyl α-phenyl ketones derived from benzil monohydrazone (**22**) and **26** show a characteristic peak at 6.4–7.0 ppm for the proton α to the carbonyl [C(2)–H].

Table V lists selected ^{13}C NMR parameters for the azines and pyrazoles synthesized by the α-diketone hydrazone–unsaturated aldehyde/ketone route. Peaks at 197–199 (C=O) and 160–170 ppm (C=N) as well as the lack of any saturated carbon resonances other than expected for aliphatic substituents characterize the spectra of the azines **9**. Enols **11t** and **11x**, as expected, show no peaks attributable to a carbonyl carbon, but the spectra do show a very deshielded (170–176 ppm) and a very shielded (~80 ppm) vinyl carbon, consistent with other reports[12] of the ^{13}C spectra of enols and enol ethers. The α-phenyl α-pyrazolyl ketones **12j–s** and **12u–x** show peaks at 104–117 [C(4)],[13] 192–194 [C(1)], and 67–69 ppm [C(2)]. The remainder of the resonances are consistent with the proposed structures and assignments are based on model compounds when available (e.g., ref 13).

We have demonstrated that the thermal rearrangement of α-oxo-α,β-unsaturated azines **9** is a facile and general route to N-substituted pyrazoles **11** and/or **12**, and should prove to be a valuable addition to current methods of pyrazole synthesis.

Experimental Section

All chemicals, except as noted below, were purchased from the Aldrich or Eastman Organic Chemical Companies and used as is. Solvents used in the phosphonium ylide reactions were dried by standard techniques and distilled prior to use. A dry nitrogen atmosphere was employed in all reactions. Melting points were obtained with a Thomas-Hoover apparatus and are uncorrected. Proton NMR spectra were recorded with either a Varian A-60A or Perkin-Elmer R12-b instrument on ~10% $CDCl_3$ solutions. A Bruker HFX-90 NMR spectrometer equipped for Fourier transform pulsed NMR with a Nicolet 1085 data system operating at 22.63 MHz was used to collect the ^{13}C NMR data. All NMR chemical shifts are reported as parts per million δ vs. Me_4Si as internal standard. All new compounds gave elemental (C, H) analyses consistent with the proposed empirical formulas.

Cyclcohexene-1-carboxyaldehyde (26j) was prepared by the method of Heilbron et al.[20] with the modification that triethylamine at 110–120 °C (pressure bottle) was used to effect the dehydrobromination. The following compounds were prepared by known methods: **propargyltriphenylphosphonium bromide (14),**[14] **ethyl (triphenylphosphoranylidenehydrazono)acetate (13),**[15] ***2H*-3,4-dihydropyran-5-carboxyaldehyde (26k),**[16] **cyclopentene-1-carboxyaldehyde (26m),**[17] **2-benzylidenecyclohexanone (26n),**[18] **2-benzylidenecyclopentanone (26o),**[18] and **diacetyl monhydrazone (25).**[19]

Preparation of 3-(Triphenylphosphoranylidene)-2-(carboethoxymethylidenehydrazonopropyl)triphenylphosphonium Bromide (17). A solution of 10.2 g (0.0266 mol) of propargyltriphenylphosphonium bromide (**14**) and 10.0 g (0.0266 mol) of phosphazine **13** in 200 mL of cold (0 °C), dry CH_2Cl_2 was stirred under nitrogen for 3 days at 0 °C and 2 days at room temperature. Addition of the reaction mixture to 1200 mL of EtOAc yielded **17** as a yellow powder. Recrystallization from CH_2Cl_2/EtOAc afforded 13.5 g (67%) of analytically pure material, mp 224.5–225.0 °C: IR (cm^{-1}) 1680 (C=O), 1580 (C=N), 1440, 1105 (C–P); ^1H NMR δ 0.6–1.5 (m, 3 H, CH_3CH_2O–), 3.50–4.50 (m, 3 H, CH_3CH_2O– + Ph_3P=CH–), 5.12 (d, J_{PH} = 15.0 Hz, $Ph_3{}^+CH_2$), 7.0–8.1 (m, 30 H, aromatic).

Anal. Calcd for $C_{43}H_{39}BrN_2O_2$: C, 68.16; H, 5.19. Found: C, 68.11; H, 5.15.

Preparation of Ethyl 1-(3-Styryl-5-phenylpyrazolyl)acetate (12c). In 60 mL of dry CH_3CN was dissolved 4.0 g (5.2 mmol) of ylide salt **17** and 1.4 g (14.4 mmol) of benzaldehyde. To this solution was added 0.24 g (0.05 mol) of sodium hydride (57% oil dispersion), and the reaction mixture was heated at reflux for 18 h. After cooling to room temperature, the reaction mixture was poured into water (500 mL) and extracted with two 150-mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to an oily solid. Column chromatography (silica gel; 1:1 hexane–ether as eluent) yielded 1.0 g (87%) of **12c** as a pale yellow solid. An analytical sample was prepared by crystallization from hexane–ether.

Preparation of Ethyl-1-[3-(4-chlorostyryl)-5-(4-chlorophenyl)pyrazolyl]acetate (12d). In 80 mL of freshly distilled ethanol was dissolved 0.46 g (0.02 mol) of sodium metal. Then 5.6 g (0.04 mol) of 4-chlorobenzaldehyde and 15.0 g (0.02 mol) of ylide salt **17** were added, and the reaction mixture was stirred at ambient temperatures for 5 h and at reflux for 72 h. The reaction was then poured into water (500 mL) and extracted with two 250-mL portions of ether; the ether extracts were dried ($MgSO_4$) and concentrated in vacuo to ~100 mL, at which point a solid precipitated. The solid (presumably Ph_3PO) was removed by filtration, the filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel (1:1 ether–pentane as eluent), yielding 5.0 g (61%) of **12d** as a colorless solid. Recrystallization from ether–hexane afforded an analytical sample.

Preparation of Triphenyl-1-carboethoxymethyl-5-phenylpyrazol-3-ylmethylphosphonium Bromide (12e). A solution of 2.5 g (0.0033 mol) of ylide salt **17** and 0.70 g (0.0066 mol) of benzaldehyde in 200 mL of acetonitrile was heated at reflux for 29 h. After concentration in vacuo to 20 mL, the reaction mixture was precipitated into 700 mL of anhydrous ether, yielding 3.4 g (88%) of **12e** as a cream colored solid. An analytical sample was prepared by recrystallization from CH_2Cl_2–EtOAc.

Preparation of Triphenyl-1-carboethoxymethyl-5-(4-chlorophenyl)pyrazol-3-ylmethylphosphonium Bromide (12f). A solution of 5.0 g (0.066 mol) of ylide salt **17** and 1.86 g (0.0132 mol) of 4-chlorobenzaldehyde in 200 mL of acetonitrile was heated at reflux

Table IV. ^{1}H NMR Parameters for Azines (9) and Pyrazoles (11/12)[a]

9h 2.22 (s, 3 H, C(3)-CH_3), 6.62 ("d", $J \cong 6$ Hz, 2 H, C(4)-H + C(5)-H), 7.03 (s, 4 H, C_6H_4Cl), 7.2 (m, 6 H, aromatic), 7.70 (m, 4 H, aromatic ortho to C=O/C=N)

9i 2.01 (s, 3 H, C(2)-CH_3), 2.39 (s, 3 H, C(1)-CH_3), 6.90 ("d", $J \cong 5$ Hz, 2 H, C(4)-H + C(5)-H), 7.25 (m, 5 H, aromatic), 7.85 ("t", $J \cong 4$ Hz, 1 H, C(3)-H)

9j 6.73 (d, $J \cong 8.0$ Hz, 2 H, C(4)-H + C(5)-H), 6.93–7.46 (m, 11 H, aromatic), 7.75 (m, 4 H, aromatic ortho to C=O/C=N), 8.20 (dd, J = 8.0, 1.5 Hz, 1 H, C(3)-H)

9k 6.29–6.38 (m, 2 H, furan C(3)-H + C(4)-H), 6.63–6.75 (m, 2 H, C(4)-H + C(5)-H), 7.25–7.48 (m, 7 H, aromatic + furan C(5)-H), 7.72–7.98 (m, 4 H, aromatic ortho to C=O/C=N), 8.36 (dd, J = 6.0, 3.3 Hz, 1 H, C(3)-H)

9r 7.35–7.60 (m, 12 H, aromatic + C(5)-H), 7.75–8.07 (m, 4 H, aromatic ortho to C=O/C=N), 8.28 (s, 1 H, C(3)-H)

9s 1.44 (br m, 4 H, -$CH_2\mathbf{CH_2}CH_2CH_2$-), 1.95 (br m, 4 H, -$CH_2CH_2CH_2\mathbf{CH_2}$-), 6.12 (m, 1 H, C(5)-H), 7.3 (m, 6 H, aromatic), 7.7 (m, 4 H, aromatic ortho to C=O/C=N), 7.96 (s, 1 H, C(3)-H)

9t 1.66 (m, 4 H, -$\mathbf{CH_2}CH_2CH_2O$-), 4.26 (br t, $J \cong 5$ Hz, 2 H, -$CH_2CH_2\mathbf{CH_2}O$-), 6.79 (br s, 1 H, C(5)-H), 7.2 (m, 6 H, aromatic), 7.7 (m, 4 H, aromatic ortho to C=O/C=N), 7.92 (s, 1 H, C(3)-H)

9u 2.16 (m, 2 H, -$\mathbf{CH_2}CH_2O$-), 3.06 (br t, $J \cong 6$ Hz, 2 H, -$CH_2\mathbf{CH_2}O$), 3.85 (br s, 2 H, C=C$\mathbf{CH_2}O$-), 6.28 (m, 1 H, C(5)-H), 7.2 (m, 6 H, aromatic), 7.7 (m, 4 H, aromatic ortho to C=O/C=N), 7.85 (s, 1 H, C(3)-H)

9v 1.66 (br q, $J \cong 7$ Hz, 2 H, -$CH_2\mathbf{CH_2}CH_2$-), 2.12 (m, 4 H, -$\mathbf{CH_2}CH_2\mathbf{CH_2}$-), 6.12 (m, 1 H, C(5)-H), 7.22 (m, 6 H, aromatic), 7.68 (m, 4 H, aromatic ortho to C=O/C=N), 8.22 (s, 1 H, C(3)-H)

9x 1.73 (m, 2 H, -$CH_2\mathbf{CH_2}CH_2$-), 2.67 (m, 4 H, -$\mathbf{CH_2}CH_2\mathbf{CH_2}$-), 6.87 (t, J = 2.5 Hz, 1 H, C(5)-H), 7.1 (m, 11 H, aromatic), 7.7 (m, 4 H, aromatic ortho to C=O/C=N)

11t 1.76 (m, 2 H, -$CH_2\mathbf{CH_2}CH_2O$-), 2.44 (br t, $J \cong 6$ Hz, 2 H, -$\mathbf{CH_2}CH_2CH_2O$-), 4.06 (br t, $J \cong 5$ Hz, 2 H, -$CH_2CH_2\mathbf{CH_2}O$-), 5.96 (br s, 1 H, -OH), 7.2 (m, 10 H, aromatic), 8.01 (s, 1 H, C(3)-H)

11x 1.96 (br, p,[b] $J \cong 7$ Hz, 2 H, -$CH_2\mathbf{CH_2}CH_2$-), 2.95 (br q, $J \cong 7$ Hz, 4 H, -$\mathbf{CH_2}CH_2\mathbf{CH_2}$-), 6.36 (s, 1 H, -OH), 6.9–7.8 (m, 15 H, aromatic)

12c 1.20 (t, J = 6.0 Hz, 3 H, $\mathbf{CH_3}CH_2O$-), 4.20 (q, J = 6.0 Hz, 2 H, $CH_3\mathbf{CH_2}O$-), 4.80 (s, 2 H, C(2)-H_2), 6.50 (s, 1 H, C(4)-H), 7.1–7.5 (m, 12 H, aromatic + vinyl)

12d 1.20 (t, J = 6.0 Hz, 3 H, $\mathbf{CH_3}CH_2O$-), 4.17 (q, J = 6.0 Hz, 2 H, $CH_3\mathbf{CH_2}O$-), 4.80 (s, 2 H, C(2)-H_2), 6.46 (s, 1 H, C(4)-H), 7.02–7.50 (m, 10 H, aromatic + vinyl)

12e 1.20 (t, J = 6.7 Hz, 3 H, $\mathbf{CH_3}CH_2O$-), 4.12 (q, J = 6.7 Hz, 2 H, $CH_3\mathbf{CH_2}O$-). 4.68 (s, 2 H, C(2)-H_2), 5.28 (d, J_{PH} = 14.6 Hz, 2 H, -$\mathbf{CH_2}P^+Ph_3Br^-$), 6.39 (d, J_{PH} = 1.3 Hz, 1 H, C(4)-H), 7.08–8.10 (m, 20 H, aromatic)

12f 1.20 (t, J = 7.3 Hz, 3 H, $\mathbf{CH_3}CH_2O$-), 4.16 (q, J = 7.3 Hz, 2 H, $CH_3\mathbf{CH_2}O$-), 4.70 (s, 2 H, C(2)-H_2), 5.34 (d, J_{PH} = 14.0 Hz, 2 H, -$\mathbf{CH_2}P^+Ph_3Br^-$), 6.39 (d, J_{PH} = 1.3 Hz, 1 H, C(4)-H), 7.1–8.2 (m, 19 H, aromatic)

12g 1.17 (t, J = 7.0 Hz, 3 H, $\mathbf{CH_3}CH_2O$-), 2.20 (s, 3 H, C(3)-CH_3), 4.10 (q, J = 7.0 Hz, 2 H, $CH_3\mathbf{CH_2}O$-), 4.63 (s, 2 H, C(2)-H_2), 6.00 (s, 1 H, C(4)-H), 7.3 (m, 4 H, aromatic)

12h 2.15 (s, 3 H, C(3)-CH_3), 6.02 (s, 1 H, C(4)-H), 6.50 (s, 1 H, C(2)-H), 7.1–7.3 (m, 12 H, aromatic), 7.5 (m, 2 H aromatic ortho to C=O)

12i 1.64 (d, J = 7.0 Hz, 3 H, C(2)-CH_3), 1.69 (s, 3 H, C(1)-CH_3), 4.77 (q, J = 7.0 Hz, 1 H, C(2)-H), 6.25 (d, J = 1.5 Hz, 1 H, C(4)-H), 7.31 (s, 5 H, aromatic), 7.46 (d, J = 1.5 Hz, 1 H, C(3)-H)

12j 6.16 (d, J = 1.5 Hz, 1 H, C(4)-H), 6.58 (s, 1 H, C(2)-H), 7.18 (br s, 13 H, aromatic), 7.4 (m, 3 H, C(3)-H + aromatic ortho to C=O)

12k 6.45–6.58 (m, 3 H, C(2)-H + furan C(3)-H, C(4)-H), 7.25 (s, 1 H, C(4)-H), 7.35–7.56 (m, 9 H, aromatic + furan C(5)-H), 7.78–7.93 (m, 3 H, aromatic ortho to C=O and C(3)-H)

12l 2.06 (s, 3 H, C(5)-CH_3), 5.93 (d, J = 1.5 Hz, 1 H, C(4)-H), 6.86 (s, 1 H, C(2)-H), 7.2 (m, 8 H, aromatic), 7.76 (d, J = 1.5 Hz, 1 H, C(3)-H), 7.6–8.0 (m, 2 H, aromatic ortho to C=O)

12m 1.89 (s, 3 H, C(4)-CH_3), 6.47 (s, 1 H, C(2)-H), 7.13 (br s, 13 H, aromatic), 7.24 (s, 1 H, C(3)-H), 7.5 (m, 2 H, aromatic ortho to C=O)

12n 2.09 (s, 3 H, C(3)-CH_3), 5.99 (s, 1 H, C(4)-H), 6.50 (s, 1 H, C(2)-H), 7.16 (br s, 13 H, aromatic), 7.45 (m, 2 H, aromatic ortho to C=O)

12o 2.22 (s, 3 H, C(3)-CH_3), 6.35 (s, 1 H, C(2)-H), 6.43 (d, J = 1.3 Hz, 2 H, furan C(3)-H, C(4)-H), 7.15 (s, 1 H, C(4)-H), 7.25–7.70 (m, 9 H, aromatic and furan C(5)-H), 7.75–7.93 (m, 2 H, aromatic ortho to C=O)

12p 6.63 (s, 1 H, C(4)-H[c]), 6.68 (s, 1 H, C(2)-H), 7.2–7.75 (m, 20 H, aromatic)

12q 6.94 (s, 1 H, C(4)-H[c]), 7.05–7.95 (m, 21 H, aromatic + C(2)-H)

12r 6.67 (s, 1 H, C(2)-H), 7.31–7.46 (m, 13 H, aromatic), 7.56–7.81 (m, aromatic ortho to C=O) + 7.59 (s, C(3)-H) – total 3 H

12s 1.6 (m, 4 H, -$CH_2\mathbf{CH_2}\mathbf{CH_2}CH_2$-), 2.3 (m, 4 H, -$\mathbf{CH_2}CH_2CH_2\mathbf{CH_2}$-), 6.78 (s, 1 H, C(2)-H), 7.15 (br s, 8 H, aromatic), 7.30 (s, 1 H, C(3)-H), 7.75 (m, 2 H, aromatic ortho to C=O)

12u 2.34 (m, 2 H, -$\mathbf{CH_2}CH_2OCH_2$-), 3.64 (br t, $J \cong 5.5$ Hz, 2 H, -$CH_2\mathbf{CH_2}OCH_2$-), 4.48 (br s, 2 H, -$CH_2CH_2OCH_2$-), 6.95 (s, 1 H, C(2)-H), 7.11 (s, 8 H, aromatic), 7.27 (s, 1 H, C(3)-H), 7.76 (m, 2 H, aromatic ortho to C=O)

12v 2.36 (m, 6 H, -$CH_2CH_2CH_2$-), 7.02 (s, 1 H, C(2)-H), 7.08 (s, 1 H, C(3)-H), 7.16 (s, 8 H, aromatic), 7.8 (m, 2 H, aromatic ortho to C=O)

12w 1.67 (m, 4 H, -$CH_2\mathbf{CH_2}\mathbf{CH_2}CH_2$-), 2.5 (m, 4 H, -$\mathbf{CH_2}CH_2CH_2\mathbf{CH_2}$-), 6.54 (s, 1 H, C(2)-H), 7.2 (br s, 13 H, aromatic), 7.5 (m, 2 H, aromatic ortho to C=O)

12x 2.5 (m, 6 H, -$CH_2CH_2CH_2$-), 6.54 (s, 1 H, C(2)-H), 7.22 (br s, 13 H, aromatic), 7.5 (m, 2 H, aromatic ortho to C=O)

[a] Chemical shifts reported as parts per million δ vs. Me_4Si in $CDCl_3$ solution. [b] Numbering as in Table V; pentet. [c] Assignments for C(2)-H and C(4)-H may be reversed.

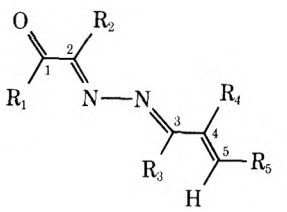
for 29 h. After concentration in vacuo to ~20 mL, precipitation into 500 mL of anhydrous ether yielded 3.7 g (90%) of **12f** as a colorless solid. Recrystallization from CH_2Cl_2–EtOAc afforded an analytical sample.

Hydrolysis of 17. Preparation of Triphenyl-2-carboethoxymethylidenehydrazonopropylidenephosphorane (18). A solution of 7.6 g (0.01 mol) of ylide salt **17** in 50 mL of methylene chloride was stirred for 8 h with 100 mL of 10% Na_2CO_3. After drying ($MgSO_4$) and removal of most of the solvent in vacuo, the methylene chloride layer was added dropwise to 300 mL of ethyl acetate. The orange solid which precipitated was shown (TLC, NMR) to be a mixture of ylide **18** and triphenylphosphine oxide. We were unable to completely separate **18** from Ph_3PO, and the mixture was used as is in further reactions: ^{1}H NMR δ 0.7–1.3 (br m, $\mathbf{CH_3}CH_2O$), 2.30 (s, $CH_3C{=}N$), 3.0–4.3 (br m, $CH_3\mathbf{CH_2}O$ + $\mathbf{CH}{=}PPh_3$), 7.05 (s, -N=$\mathbf{CH}$-), 7.15–7.0 (m, aromatic **18** + Ph_3PO).

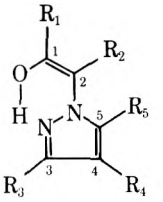
Preparation of Ethyl 1-[3-methyl-5-(4-chlorophenyl)pyrazolyl]acetate (12g). To 40 mL of benzyl alcohol was added the mixture of **18** and Ph_3PO prepared as above from 3.8 g (0.005 mol) of ylide salt **17** and 0.8 g (0.0057 mol) of 4-chlorobenzaldehyde. The solution was refluxed for 12 h, poured into water, and extracted with two 100-mL portions of ether. After drying ($MgSO_4$) and concentration in vacuo, the ether extracts afforded a thick oil, which was chromatographed [silica gel, pentane–ether (2:1) as eluent] to yield 1.0 g (74%) of **12g** as a pale yellow oil. Distillation at 220 °C (10 mm) yielded a colorless analytical sample which solidified on standing.

Preparation of Triphenyl-2-(phenylphenacylidenehydrazono)propylphosphium Bromide (23). A slurry of 9.2 g (0.041 mol) of benzil monohydrazone (**22**) and 15.2 g (0.04 mol) of porpargyltriphenylphosphonium bromide (**14**) in 40 mL of chloroform was heated at reflux for 2 h. The clear solution was then added dropwise to 600 mL of boiling benzene, stirred at ambient temperatures for 1 h, and filtered. The filter cake was recrystallized from methylene chloride–ethyl acetate to yield 19.6 g (83%) of **23** as a pale yellow solid: mp 224–225 °C; ^{1}H NMR δ 2.50 (d, J_{PH} = 1.3 Hz, 3 H, CH_3), 5.41 (d, J_{PH} = 13.3 Hz, 2 H, CH_2), 7.02–8.00 (m, 25 H, aromatic).

Table V. Selected ^{13}C NMR Parameters for Azines (9) and Pyrazoles (11/12) Prepared from α-Diketone Monohydrazones and α,β-Unsaturated Aldehydes and Ketones



9



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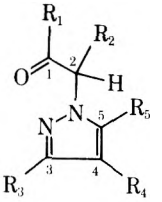

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Compd	C(1)	C(2)	C(3)	C(4)	C(5)	Other
9i	199.0[a]	161.7[b]	159.5	*d*	143.6	11.4; C(2)–CH_3 24.9; C(1)–CH_3
9j	197.3	166.4[b]	164.0	*d*	143.7	
9k	197.4	166.3[b]	163.5	*d*	144.1	112.2, 112.7; β-furyl 152.0; α-furyl
9r	197.2	167.4	160.9	119.2	140.9	
9s	197.6	166.5[b]	164.6	*d*	141.8	21.7, 22.1, 23.2, 26.4; $-(CH_2)_4-$
9t	198.1	164.5[b]	162.5	113.8	155.5	18.5, 21.0, 67.5; $-(CH_2)_2O-$
9u	197.0	167.2	160.7	*d*	137.4	26.1, 63.5, 64.0; $-CH_2O(CH_2)_2-$
9v	197.5	166.6	158.9	*d*	143.5	22.8, 30.3, 33.6; $-(CH_2)_3-$
9x	198.1	163.1	173.9	*d*	137.8	22.5, 29.6, 30.8; $-(CH_2)_3-$
11t	170.2	80.4	156.6[c]	113.2	166.8	20.9, 21.5, 68.1; $-(CH_2)_2O-$
11x	176.4	80.7	169.7[c]	*e*	158.4	22.8, 30.8, 34.3; $-(CH_2)_3-$
12i	204.0	62.6	139.9	106.6	144.6	16.2; C(2)–CH_3 26.0; C(1)–CH_3
12j	192.5	67.0	139.8	106.9	144.2	
12k	192.5	68.4	139.6	106.2	144.4	109.4, 111.6; β-furyl 142.7; α-furyl
12l	193.0	67.9	135.6	106.8	139.1	11.5; C(5)–CH_3
12m	193.1	67.3	140.5	115.4	141.3	9.0; C(4)–CH_3
12n	192.7	66.9	149.0	106.8	145.0	13.6; C(3)–CH_3
12p	192.5	67.4	151.4	104.1	145.6	
12o	192.5	68.0	148.7	106.0	144.4	13.5; C(3)–CH_3 109.2, 111.5; β-furyl 142.7; α-furyl
12q	193.0	69.1	*d*	111.3	*d*	197.8; C(5)–COPh
12r	192.4	68.3	140.5	94.9	141.7	
12s	193.2	68.1	135.6	117.2	137.4	20.7, 22.0, 22.8(2); $-(CH_2)_4-$
12u	193.3	68.7	135.2	115.8	136.4	23.5, 63.6, 68.6; $-(CH_2)_2OCH_2-$
12v	194.0	69.6	135.1	*e*	150.8	22.6, 25.0, 30.7; $-(CH_2)_3-$
12w	192.8	66.6	149.5	115.5	139.8	21.0, 23.2(2), 23.4; $-(CH_2)_4-$
12x	192.9	67.3	161.8	*e*	136.6	23.4, 25.0, 29.7; $-(CH_2)_3-$

[a] Parts per million δ vs. Me_4Si as internal standard in $CDCl_3$. [b] The assignments for C(2) and C(3) may be reversed. [c] The assignments for C(3) and C(5) may be reversed. [d] Unable to assign unambiguously. [e] Obscured by phenyl resonances.

Anal. Calcd for $C_{35}H_{30}BrN_2OP$: C, 69.43; H, 4.99. Found C, 69.26; H, 4.88.

Preparation of Triphenyl-2-(phenylphenacylidenehydrazono)propylidenephosphorane (24). In a 100-mL round-bottom flask was dissolved 2 g (~0.0358 mol) of potassium hydroxide in 40 mL of absolute ethanol. This solution was cooled to −15 °C (ice–methanol) and 9.7 g (0.0161 mol) of **23** was added with stirring. The deep red solution was then stirred at ambient temperatures for 30 min, during which an orange solid precipitates. Filtration and recrystallization from CH_2Cl_2–heptane afforded 8.0 g (93%) of **24** as yellow-orange crystals: mp 181–182 °C; ^1H NMR δ 2.42 (d, J_{PH} = 1.3 Hz, 3 H, CH_3), 2.98 (d, J_{PH} = 24.0 Hz, 1 H, $Ph_3P{=}CH$), 6.90–7.90 (m, 25 H, aromatic).

Anal. Calcd for $C_{35}H_{29}N_2OP$: C, 80.14; H, 5.55. Found: C, 79.81; H, 5.77.

Preparation of 3-Phenylphenacylidenehydrazono-1-(4-chlorophenyl)but-1-ene (9h). A solution of 2.0 g (3.8 mmol) of ylide **24** and 0.8 g (5.7 mmol) of 4-chlorobenzaldehyde in 20 mL of dry acetonitrile was heated at reflux for 2 h. Removal of solvent in vacuo afforded a yellow oil from which 0.7 g (52%) of **9h** was isolated by dry-column chromatography [Florisil (2 × 30 cm), 2.5:1 hexane–ether as eluent]. An analytical sample was prepared by crystallization from CH_2Cl_2–petroleum ether.

Preparation of 1-Phenyl-1-[3-methyl-5-(4-chlorophenyl)-pyrazolyl]acetophenone (12h). In a microstill was placed 1.0 g (3.75 mmol) of azine **9h**. Distillation at 260 °C (0.5 mm) yielded a pale yellow oil, which crystallized from methylene chloride–hexane to afford 0.5 g (50%) of pyrazole **12h** as a colorless solid.

Reactions of α-Diketone Monohydrazones (22 or 25) with α,β-Unsaturated Aldehydes and Ketones (26). General Method A. A solution of the hydrazone and carbonyl compound (5% excess) in absolute ethanol (50 mL/0.01 mol) was heated at reflux for the amount of time indicated in Table I. Small (10–15 mg) amounts of acetic or *p*-toluenesulfonic (*p*-TSA) acids were sometimes employed as catalysts and this is also noted in Table i. Cooling the reaction mixture or concentration/cooling initiated the crystallization of the listed products. Recrystallization from ethanol afforded analytically pure samples.

General Method B. A slurry of the hydrazone and carbonyl compound (5% excess) in benzene (50 mL/0.01 mol scale) was heated at reflux in a round-bottom flask fitted with a Dean–Stark water separater for the time indicated in Table I. After removal of the benzene in vacuo, crystallization of the residue from ethanol afforded the products listed in Table I.

Thermolysis of α-Oxo-α,β-unsaturated Azines. General Method. A sample (0.5–2.0 g) of the azine **9** was placed in a thick-walled glass tube, capped, and heated in an oil bath under the conditions listed in Table II. After cooling to room temperature, the crude product was dissolved in a minimal amount of CH_2Cl_2, diluted with ethanol (15 mL/g of azine), and treated with Darco G-60 activated carbon. The solution was filtered and the methylene chloride removed by gentle boiling for several minutes. Cooling led to the crystallization of the pyrazole products. The thermolysis of **9x** yielded a mixture of **11x** and **12x** which could only be separated by column chromatography (silica gel; CH_2Cl_2 as eluent).

Acknowledgment. Financial support for one of us (S.E.) by the National Science Foundation is gratefully acknowl-

edged. We would like to thank Drs. David L. Dalrymple and Roger Crecely for obtaining and helping to interpret the ^{13}C NMR data.

Registry No.—**9h,** 63569-86-8; **9i,** 63569-87-9; **9j,** 63569-88-0; **9k,** 63569-89-1; **9r,** 63569-90-4; **9s,** 63569-91-5; **9t,** 63569-92-6; **9u,** 63569-93-7; **9v,** 53569-94-8; **9x,** 63569-95-9; **11t,** 63569-96-0; **11x,** 63569-97-1; **12c,** 63569-98-2; **12d,** 63569-99-3; **12e,** 63570-00-3; **12f,** 63570-01-4; **12g,** 63570-02-5; **12h,** 63570-03-6; **12i,** 63570-04-7; **12j,** 63570-05-8; **12k,** 63570-06-9; **12l,** 63570-07-0; **12m,** 63570-08-1; **12n,** 63570-09-2; **12o,** 63570-10-5; **12p,** 63570-11-6; **12q,** 63570-12-7; **12r,** 63570-13-8; **12s,** 63570-14-9; **12u,** 63570-15-0; **12v,** 63570-16-1; **12w,** 63570-17-2; **12x,** 63570-18-3; **13,** 22610-15-7; **14,** 2091-46-5; **17** charged form, 63570-19-4; **17** uncharged form, 63570-20-7; **18** charged form, 63570-21-8; **18** charged form, 63570-22-9; **22,** 5344-88-7; **23,** 63570-23-0; **24** charged form, 63570-24-1; **24** unchanged form, 63570-25-2; **25,** 33487-48-8; **26a,** 104-55-2; **26b,** 623-30-3; **26c,** 4170-30-3; **26d,** 101-39-3; **26e,** 122-57-6; **26f,** 623-15-4; **26g,** 94-41-7; **26h,** 4070-75-1; **26i,** 5443-49-2; **26j,** 1192-88-7; **26k,** 25090-33-9; **26l,** 13417-49-7; **26m,** 6140-65-4; **26n,** 5682-83-7; **26o,** 5679-13-0; benzaldehyde, 100-52-7; 4-chlorobenzaldehyde, 104-88-1.

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Estimation of Allene Optical Purities by Nuclear Magnetic Resonance

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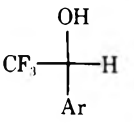
Methoxymercuration of chiral allenes affords chiral ethers, the enantiomeric purity and absolute configuration of which are related to those of the allenic precursor. Enantiomeric purity and absolute configuration of these allene derivatives can be determined by NMR using (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**1a**) as a chiral solvating agent. A solvation model is advanced to account for the origin and sense of the observed NMR nonequivalence of the enantiomeric derivatives in the presence of **1a**.

Despite considerable interest in the chemistry of chiral allenes, there is no general experimental method for the determination of enantiomeric purity of allenes lacking additional functionality. However, Brewster has calculated the rotational values expected for several chiral allenes including those without additional functional groups.[1] Chemical transformation of a chiral allene to a known chiral reference compound can provide enantiomeric purity data, although this approach is seldom used since most reactions that might be employed to modify the allenic functionality do not proceed stereospecifically. Thus far, the use of chiral solvating agents (CSA) as a direct method for determining enantiomeric purities of chiral allenes has been unsuccessful unless an additional "handle" is present.[2] An alternate indirect approach in which the chiral allene is stereospecifically converted to a chiral compound, the enantiomeric purity of which is then determined by NMR using a CSA, is the subject of the present paper.

Prior work with chiral type 1 fluoro alcohols has shown that these CSA render nonequivalent the NMR spectra of enantiomeric benzylic, allylic, or propargylic alcohols and their ethers. The oxymercuration of allenes in H_2O or methanol, believed to be a highly stereospecific reaction, affords mercury-containing allylic alcohols or methyl ethers. Owing to the sharp singlets arising from methoxyl groups, methoxymercuration is well suited to the overall process for NMR determination of enantiomeric purity. We have methoxymercurated several partially resolved simple allenes and used a type



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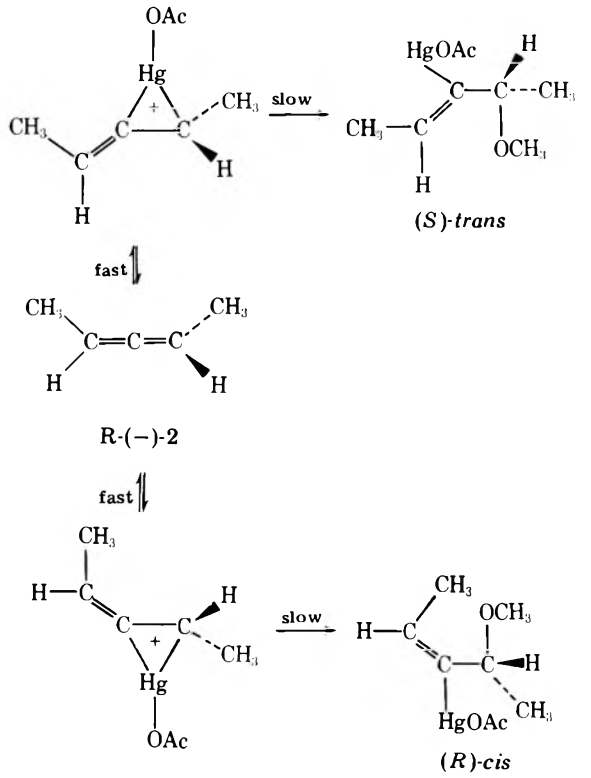
1 CSA to determine enantiomeric composition of the product ethers.

Methoxymercuration of allenes with mercuric acetate in methanol usually affords both cis and trans adducts and is considered to occur by the mechanistic pathway shown in Scheme I.[3] This scheme predicts that the two adducts will be of opposite chirality.[3]

Reaction of (*R*)-(−)-2,3-pentadiene (**2**), $[\alpha]^{25}_D$ −14.5° (1, Et_2O), with $Hg(OAc)_2$ in dry methanol at 25 °C followed by exchange of acetate for chloride affords a 6:1 ratio of trans:cis 3-chloromercuri-4-methoxy-2-pentenes, **3t** and **3c**, respectively. In CCl_4 solution with 3 equiv of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**1a**) the mixture of **3t** and **3c** shows NMR nonequivalence of the enantiotopic methoxyl resonances for each isomer. Although the sense of nonequivalence and enantiomeric purity of **3c** in the mixture could not be reliably determined due to the proximity of other signals, the enantiomeric purity of (*S*)-**3t**, the major isomer, was ascertained to be 9.2%, with the methoxyl signal of the major enantiomer occurring at a higher field than that of the minor enantiomer (high field "sense" of nonequivalence). This value represents the *minimum* enantiomeric enrichment for **2**,

Scheme I



which hence has a *maximum* specific rotation value of −158°. After separation of **3c** and **3t** by preparative GLPC (4 ft × 0.25 in., 20% SE-30 on Chromosorb W, 115 °C), **3c** showed a low-field sense of methoxyl nonequivalence and 6% enantiomeric excess.

Although too little of the cis isomer was obtained to establish its configurational stability during GLPC, the major trans isomer **3t** does undergo partial racemization during gas chromatography. The observation of opposite senses of methoxyl nonequivalence for **3c** and **3t** strongly suggests that these isomers are formed with opposite absolute configurations. This point will be elaborated further during the discussion of the mode of solvation of allyl ethers by CSA **1a.**

Methoxymercuration of (*S*)-(+)-3,4-heptadiene (**4**), $[\alpha]^{25}_{D}$ +33.8° (2 $CHCl_3$), at −78 °C affords a 19:1 mixture of the trans and cis chloromercurals **5t** and **5c.** Again using CSA **1a, 5t** was found to be 33% enantiomerically enriched. Reduction of the amount of **5c** present through use of low-reaction temperatures simplifies the NMR analysis of enantiomeric purity. The results of similar experiments on other allenes are reported in Table I. In each instance, enantiomeric purity and absolute configuration of the chloromercurals could be established by NMR, thus also establishing the absolute configuration and minimum enantiomeric purity of the initial allene.

The accuracy of these determinations of enantiomeric purities of chiral allenes is dependent on the stereospecificity of the methoxymerucration reaction. Different allenes might well undergo methoxymercuration with different degrees of stereospecificity. Presently, it is our view that simple acyclic allenes, such as those in Table I, undergo methoxymercuration at −78 °C with high and perhaps complete stereospecificity. Cyclic allenes may show lessened stereospecificity. For example, Bach[4] has suggested that, for 1,2-cyclononadiene, the stereospecificity of ethoxymercuration is a function of the mercurating agent. In Bach's hands, mercuric acetate, the most commonly used reagent for oxymercuration, led, after demercuration, to allyl ether **7** that had but 81% of the rotatory power of the same adduct obtained directly from **6** using ethylmercuric acetate and boron trifluoride (Scheme II).[5]

Scheme II

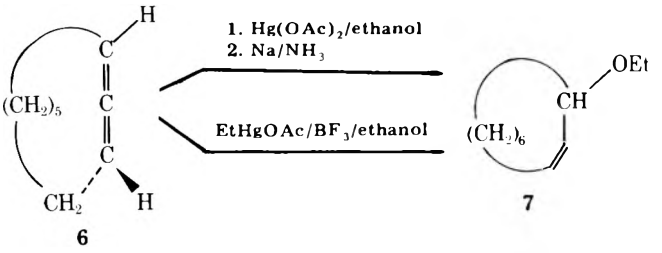
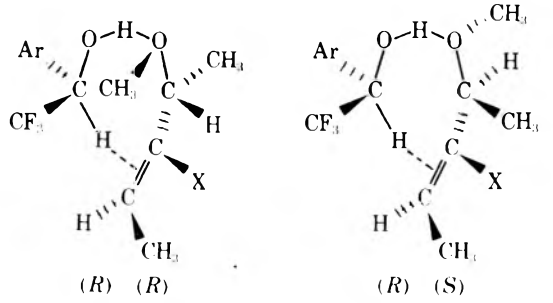


Chart I



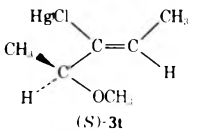
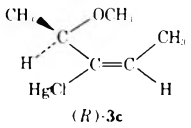
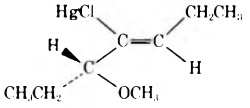
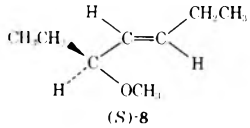
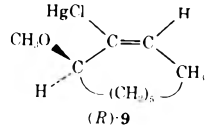
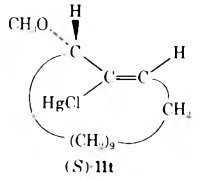
X = HgCl or H

However, methoxymercuration of partially resolved (*R*)-**4**, $[\alpha]^{25}_{D}$ −26.4°, using ethylmercuric acetate/BF_3 at 0 °C leads to *trans*-**8** of an enantiomeric purity (25%) such that the maximum absolute rotation calculated for allene **4** by this method is not significantly different from that calculated by the alternate methoxymercuration procedure (Table I). Thus, the two methoxymercuration reactions proceed with the same degree of stereospecificity. Note also (Table I) that methoxymercuration of **2** proceeds with the same stereospecificity at 25 °C as it does at −78 °C. These results are consistent with (but do not require) essentially complete stereospecificity during methoxymercuration of acyclic allenes.

Solvation Model. The NMR nonequivalence shown by the enantiomers of a variety of solute types in the presence of chiral fluoro alcohols such as **1a** appears to fit a uniform model.[7] Chart I shows the application of this type of solvation model to the allyl ethers arising from methoxymercuration of allenes. The carbinol hydrogen bonds to a primary basic site, the methoxyl oxygen, and a weaker secondary interaction between the carbinyl hydrogen and the second basic site, the π electrons in the double bond, serves to populate chelate-like conformations of the two diastereomeric solvates. The diastereomeric solvates show NMR nonequivalence due to the stereochemically dependant shielding exerted by the aryl substituent of the carbinol. For steric reasons, a significantly populated rotomer in these solvates is one in which the methoxyl group is approximately eclipsed with the carbinyl hydrogen of the ether, the smaller of the three remaining substituents upon the chiral center. In this rotomer, the anthryl substituent of **1a** causes the methoxyl signal of (*S*)-**3t** to occur at a higher field than does the methoxyl signal of (*R*)-**3t.** The model takes no cognizance of whether the ether has cis or trans geometry about the double bond or whether or not it contains mercury. Neither structural variation appears to perturb the correlation between sense of nonequivalence and absolute configuration.

Summary. Reaction of chiral allenes with mercuric acetate–methanol or with ethylmercuric acetate–BF_3–methanol leads to chiral methyl allyl ethers, the enantiomeric purity and absolute configuration of which can be determined by NMR using a chiral solvating agent. This approach is most easily applied to allenes having identical substituents on the termini of the allenic group. Dissimilarly substituted allenes may af-

Table I. Methoxymercuration of Optically Enriched Chiral Allenes

Allene, $[\alpha]^{25}_D$	Registry no.	Product	Registry no.	ee[b] / yield[a]	Max absolute rotation[c]	Sense of nonequivalence in 1a[e,f]
(*R*)-(−)-2,3-Pentadiene (2), −14.5° (1, Et_2O)	20431-56-5	 (*S*)-3t	63597-50-2	9.2% / (86%)	(−)158°	Hg (1.6)[h]
		 (*R*)-3c	63597-51-3	– / (14%)		L (1.5)
(*R*)-(−)-2, −29.6° (2.6, Et_2O)		(*S*)-3t		19.0% / (95%)[d]	(−)156°	H (1.6)
(*S*)-(+)-3,4-Heptadiene (4), +33.8° (2, $CHCl_3$)	20431-62-3	 (*R*)-5t	63534-25-8	33.1% / (94%)[d]	(+)102°	L (1.6)
(*R*)-(−)-4, −22.7° (2.5, $CHCl_3$)	34862-66-3	(*S*)-5t	63534-26-9	21.6% / (96%)[d]	(−)105°	H (1.6)
(*R*)-(−)-4, −26.4° (1, $CHCl_3$)		 (*S*)-8	63534-27-0	25.0% / (>90%)	(−)106°	Hg (1.7)
(*R*)-(+)-1,2-Cyclononadiene (6), +18.8° (2.8, $CHCl_3$)	26114-92-1	 (*R*)-9	63597-52-4	8.4% / (100%)	(+)223°	Lg (1.8)
(*R*)-(+)-1,2-Cyclotridecadiene (10), +15.2° (3.4, $CHCl_3$)	18526-51-7	 (*S*)-11t	63597-53-5	7.8% / (86%)	(+)195°	H (1.8)

[a] Number in parenthesis is percent of product in product mixture. [b] Calculated from areas under methoxyl resonances in the presence of 1a. [c] Calculated from enantiomeric excess of mercural as *minimum* enantiomeric excess of allene. [d] Methoxymercurated at −78 °C. [e] A 3:1 1a:substrate ratio in CCl_4. [f] Nonequivalence of methoxyl resonances. [g] NMR data was obtained using (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Senses of nonequivalence have been inverted here for uniformity and clarity. [h] Magnitude of nonequivalence in Hz at 100 MHz. H and L refer to high- or low-field sense of nonequivalence.

ford regioisomers, and the additional resonances may complicate spectral interpretation. Liquid chromatographic separation of the regioisomers would obviate this difficulty.

Experimental Section

Mercuric acetate methoxymercuration products (except **5t**) were characterized from previously reported data. Carbinol **1a** was prepared as previously reported.[7] Optically enriched allenes were prepared by asymmetric hydroboration[8] or by a modification of Crabbé's method[9] that will be reported elsewhere.

Methoxymercuration of Allenes with $Hg(OAc)_2$ in Methanol. Methoxymercuration was carried out at 25 °C according to the method of Caserio.[3] The following procedure is typical for methoxymercurations at −78 °C. To a stirred solution of $Hg(OAc)_2$ (66 mg, 0.21 mmol) in dry methanol (15 mL) cooled in a dry ice/isopropyl alcohol bath was added 4 (20 mg, 0.21 mmol) in 1 mL of diethyl ether. The reaction was stirred at −78 °C for 9 h after which Na_2CO_3 (28 mg, 0.26 mmol) was added. The reaction mixture was warmed to room temperature, methanol was removed under reduced pressure, and an aqueous solution of NaCl (12 mg, 0.21 mmol) was added to the remaining oil. Extraction of the chloromercural into $CHCl_3$ (four 5-mL portions), drying of the organic layer ($MgSO_4$), filtration, and evaporation of the $CHCl_3$ afforded a colorless oil, **5t** and **5c** (19:1 by NMR): NMR (**5t**) (CCl_4) δ 0.8 (t, 3, J = 7 Hz, $CHOCH_3CH_2\mathbf{CH_3}$), 1.05 (t, 3, J = 7 Hz, $C{=}CHCH_2\mathbf{CH_3}$) 1.2–1.7 (m, 2, $CHOCH_3\text{–}\mathbf{CH_2}\text{–}CH_3$), 2.2 (quintet, 2, $C{=}CH\mathbf{CH_2}CH_3$), 3.2 (s, 3, $\mathbf{OCH_3}$), 3.5 (t, 1, J = 6 Hz, $CHOCH_3$), 6.15 (t, 1, J = 8 Hz, C=C**H**).

Methoxymercuration of (*R*)-(−)-3,4-Heptadiene with $EtHgOAc/BF_3{\cdot}Et_2O$ in Methanol. The procedure described by Bach[4] was followed using (*R*)-(−)-4, $[\alpha]^{25}_D$ −22.6° (1, $CHCl_3$) and methanol except that the reaction was conducted for 24 h at 0 °C. Control experiments using 5,6-undecadiene and GLPC analysis showed that this reaction proceeds at a negligable rate at −78 or −30 °C. Allylic ether 8 (>90% trans)[10] was isolated by preparative GLPC (4.5 ft × 0.25 in., SE-30 on Chromosorb W, 60°C): NMR (CCl_4) δ 0.85 (t, 3, J = 7 Hz, $CHOCH_3CH_2\mathbf{CH_3}$), 1.01 (t, 3, J = 7 Hz, $C{=}CHCH_2\mathbf{CH_3}$), 1.45 (m, 2, $CHOCH_3\mathbf{CH_2}CH_3$), 2.1 (quintet, 2, $C{=}CH\mathbf{CH_2}CH_3$), 3.15 (s, 3, $\mathbf{OCH_3}$) 3.3 (m, 1, **CH**OCH_3), 5.0–5.7 (m, 2, **HC=CH**). Ether 8 was stable to racemization under GLPC conditions.

Acknowledgment. This work has been partially funded by grants from the National Science Foundation and the National Institutes of Health.

Registry No.—(*R*)-**5c**, 63534-28-1; $Hg(OAc)_2$, 1600-27-7.

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Dynamic Stereochemistry of Imines and Derivatives. 12. Bis(*N*-alkylimines) Derived from Tetramethylcyclobutane-1,3-dione[1]

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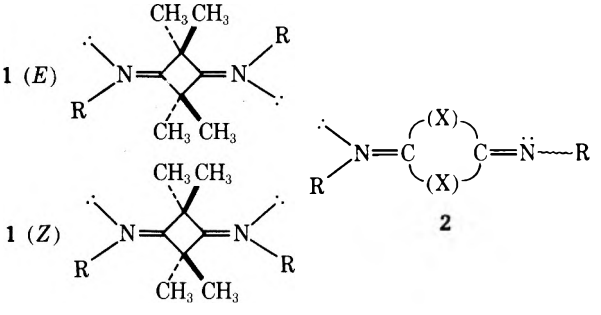
A series of bisimines **1** where R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, and C_6H_{11} has been prepared in high yield using $TiCl_4$ as catalyst. The *tert*-butyl compound exists exclusively in the *E* configuration, but the other less hindered compounds showed 20–30% *Z* isomer at equilibrium in solution. It is proposed that the *Z* isomer is destabilized by a buttressing interaction between the ring methyl groups and the flanking *N*-alkyl substituents, though dipolar interactions were also evaluated. The rates of *E*–*Z* isomerization were determined, where appropriate, by direct equilibration at 35 °C and by dynamic NMR spectroscopy at higher temperatures. The $\Delta G^{\ddagger}$ values lie in the range 24.8–21.8 kcal mol^{-1} and decrease with increasing bulk of the *N*-alkyl group. The mono(*tert*-butylimine) **4** shows a markedly lower $\Delta G^{\ddagger}$ value of 19.2 kcal mol^{-1}. Some $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ data were also determined, and the results are consistent with a lateral shift pathway for isomerization. ^1H and ^{13}C chemical shift data for both isomers are tablulated and discussed.

Tetramethylcyclobutane-1,3-dione should, in principle, condense with primary amines, RNH_2, to form bisimines of structure **1**. These compounds are capable of exhibiting an interesting type of *E*–*Z* isomerism, and are examples of the more general representation depicted in **2**. Other bisimines



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a, R = CH_3
b, R = CH_2CH_3
c, R = $CH(CH_3)_2$
d, R = $C(CH_3)_3$
e, R = cyclohexyl

within the scope of this general structure are 1,4-diazabutatriene[3] (**2**, X = –) and the 1,4-benzoquinone bisimines (**2**, X = CH=CH).[4]

The ring methyl groups in **1** provide a useful handle for assigning the stereochemistry by NMR spectroscopy. Tetramethylcyclobutane-1,3-dione has been reported to form bisimines with aromatic amines in the presence of an acid catalyst, but alkylamines were found to give 2,2,4-trimethyl-3-oxopentanamides by ring cleavage.[5] Only in the case where R = cyclohexyl was the bis(*N*-alkylimine) **1** isolated in low yield (ca. 15%). Worman and Schmidt[6] have shown by ^1H NMR spectroscopy that these bisimines were formed as an *E*–*Z* isomeric mixture. The ring methyl signals from both isomers were reported to coalesce on raising the sample temperature above 100 °C, but no kinetic data were reported.

We now report the preparation of a series of *N*-alkyl compounds with structure **1** in good yield, including the very hindered compound where R = *tert*-butyl. The isomer distribution has been investigated and the rates of isomerization have been determined by direct thermal stereomutation and dynamic NMR spectroscopy.

Results and Discussion

Synthesis and Stereochemistry. Titanium(IV) chloride has proven to be a remarkably effective catalyst for the condensation of amines with a wide range of aldehydes and ketones, including relatively unreactive diaryl ketones.[7-9] This method also enabled the new bisimines **1a–d** to be prepared from tetramethylcyclobutane-1,3-dione in high yield. Prolonged reaction in boiling toluene was required, presumably due to steric hindrance around the carbonyl groups. The biscyclohexyl compound **1e**, which had been prepared previously in low yield,[5] was obtained in 65% yield by the above method.

^1H and ^{13}C NMR spectra showed that the bisimines **1a–c** (R = CH_3, CH_2CH_3, and $CH(CH_3)_2$) were present as an *E*/*Z* isomer mixture in solution. Stereochemical assignment was straightforward as the ring carbons C-2 and C-4 and their *gem*-dimethyl groups are nonequivalent in the *Z* form but isochronous in the *E* isomer (as noted previously for other compounds of this type[6]).

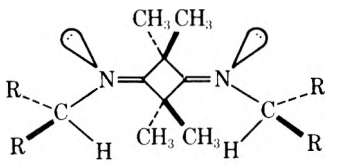
The position of equilibrium markedly favors the *E* configuration (Table I), hence the configuration at one nitrogen

Table I. ^{1}H NMR Data and Equilibrium Isomer Distribution for Bisimines 1[a]

Compd	R	δ (ring CH_3) E	Registry no.	δ (ring CH_3) Z	Registry no.	δ (N-alkyl) E	δ (N-alkyl) Z	% Z[b]
1a	CH_3	1.41	63196-47-4	1.27, 1.60	63297-69-6	3.29[c]	3.30[c]	26
1b	CH_2CH_3	1.40	63268-40-6	1.29, 1.55	63196-48-5	1.23[c]	1.24[c]	24
						3.50[d]	3.51[d]	
1c	$CH(CH_3)_2$	1.40	63196-49-6	1.30, 1.56	63267-70-9	1.17[c]	1.17[c]	21
						3.79[e]	3.79[e]	
1d	$C(CH_3)_3$	1.30	63196-50-9	*f*		1.25[c]	*f*	<0.5
1e	C_6H_{11}[g]	1.39	24627-18-7	1.29, 1.52	24627-17-6	3.41[e]	3.41[e]	~25[h]

[a] Measured in $CDCl_3$ solution (0.5 M) at 35 °C. [b] Precision ±1%. [c] CH_3 group. [d] CH_2 group. [e] CH group. [f] No signals due to the Z isomer were detected. [g] Saturated solution <0.5 M. [h] Overlap of the ring methyl and cyclohexyl methylene signals precluded an accurate determination of the isomer ratio.

atom is sensitive to the configuration of the other nitrogen, even though they are fairly remote. A buttress effect between the *gem*-dimethyl moiety and the flanking N-alkyl groups may account for the reduced stability of 1 (Z) compared with 1 (E). Molecular models indicate that these interactions are particulary severe in the N-*tert*-butyl compound **1d** which showed no detectable concentration of the E isomer. The inability to detect signals from the Z isomer of **1d** at 35 °C cannot result from unusually fast E–Z isomerization (i.e., fast on the NMR time scale), since no additional signals were detected in the NMR spectra even at −50 °C.[10] The N-ethyl, N-isopropyl, and N-cyclohexyl compounds **1b**, **1c**, and **1e** can minimize the interactions with the ring methyl groups by adopting preferred conformations as shown in 3. Thus, the



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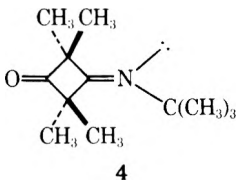

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equilibrium concentration of the Z isomer in these compounds is much closer to that in the N-methyl analogue **1a** than in the N-*tert*-butyl compound **1d**.

Further evidence for steric congestion in **1d** comes from the observation that tetramethylcyclobutane-1,3-dione gave only the monoimine **4** with *tert*-butylamine under conditions where less bulky amines gave bisimines (see Experimental Section).

Polar effects should also be considered. Thus, the E isomer has no net resultant dipole moment, whereas the Z isomer will have a dipole moment in the plane of the ring. However, the dipole–dipole repulsive interaction between the two N–R bonds in 1 (Z) was estimated[11] to be only ca. 17 cal mol^{-1} using the accepted value[12] of 0.45 D for the N–C bond moment in imines. This interaction is therefore too small to cause any significant perturbation of the E:Z ratio, and would in any case be mediated by the dielectric of the solvent and the intervening molecular structure.

The isomer ratio in the representative bisimine **1b** was investigated in a number of solvents and the results are given in Table II. It can be seen that the relative proportion of the Z isomer, which possesses a dipole moment, increases with increasing solvent dielectric constant. Hydrogen bonding effects may also play a role in methanol solution, as the proportion of the Z isomer is larger than would be indicated by the dielectric constant. Previous investigations of other imine systems have shown that alcohols can hydrogen bond to the nitrogen lone-pair electrons.[13,14] Although the bisimines have been depicted with planar rings, the molecule could be oscillating between puckered conformations. X-ray studies[15] on tetramethylcyclobutane-1,3-dione indicate that the ring is

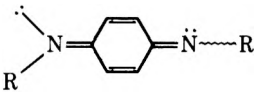
Table II. Equilibrium Isomer Composition of 1b as a Function of Solvent[a]

Solvent	ε[b]	% Z[c]
Carbon tetrachloride	2.24	22
Benzene-d_6	2.27	23
Chloroform-*d*	4.80	26
Dichloromethane	9.08	27
Acetone-d_6	20.7	25
Methanol-d_4	32.63	29
Acetonitrile-d_3	38.82	27
Dimethyl-d_6 sulfoxide	48.9	27
Formamide	109	31

[a] Determined at 35 °C on 0.5 M solutions. [b] Solvent dielectric constant as given in "Handbook of Chemistry and Physics", 53rd ed, The Chemical Rubber Co., Cleveland, Ohio, 1972. [c] Considered to be ±1%.

coplanar in the solid state, but other data favor rapid oscillation between puckered forms.[16]

Interestingly, the quinone bisimine **5** (R = 2,6-diethylphenyl), where steric buttressing effects between the N–R groups should be minimal, shows a 50:50 E:Z ratio.[4]



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NMR Spectra. ^{1}H and ^{13}C chemical shifts are given in Tables I and III. Assignment of signals to the E and Z isomers was straightforward due to the large difference in abundance. The ^{13}C spectra were recorded using long pulse intervals, and the nuclear Overhauser effect was suppressed using gated decoupling. The two sets of ring methyl signals in the Z isomer were well separated in both the ^{1}H and ^{13}C spectra (by 0.33–0.26 and 1.69–0.33 ppm, respectively). However, assignment to the groups cis or trans to the N-alkyl substituents is uncertain, though the former may be at higher field in the ^{13}C spectrum due to a steric compression effect.[17] Assuming that the anisotropic effects of the N–R groups and the imino lone pairs are additive and that the bond lengths and angles are equal in both isomers, the ring methyl groups in the E isomer should resonate approximately midway between the two signals for the Z form. This was indeed the case in the ^{1}H spectra as the ring methyl signal of the E isomer was only 0.02–0.03 ppm from the mean position of the signals from the Z isomer (Table I). However, this prediction breaks down for the ^{13}C spectra (Table III).

Carbons C-2 and C-4 are markedly anisochronous in the Z isomer (δ = 3.71–5.20 ppm, see Table III). A similar effect has been observed previously in ^{13}C spectra of other imino compounds, and the upfield signal generally arises from the more hindered α carbon which is cis to the substituent on nitrogen.[18,19] Interestingly, in this case, the signal from the E iso-

Table III. ^{13}C NMR Data for Bisimines 1[a]

	R	δ (ring CH_3)		δ (C-2, C-4)		δ (C=N)		δ (N-alkyl)	
		E	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*
1a	CH_3	22.55	21.44, 23.13	57.70	56.07, 59.78	180.82	180.30	39.50[b]	38.59[b]
1b	CH_2CH_3	23.15	22.55, 23.13	57.63	55.62, 60.10	179.33	178.74	16.44[b]	16.44[b]
								46.91[c]	45.87[c]
1c	$CH(CH_3)_2$	123.39	23.06, 23.39	57.44	55.03, 60.23	177.25	176.66	24.04[b]	24.04[b]
								52.43[d]	51.26[d]
1d	$C(CH_3)_3$	25.34		54.84		174.00		31.25[b]	
								60.82[e]	

[a] Measured in $CDCl_3$ solution (0.5 M) at 25 °C (digital resolution 0.065 ppm). [b] CH_3 group. [c] CH_2 group. [d] CH group. [e] Quaternary carbon.

Table IV. Kinetic Data and Free Energies of Activation for Imine Isomerization[a]

Compd	Temp, °C	Method	k_{E-Z}, s^{-1}	k_{Z-E}, s^{-1}	$\Delta G^{\ddagger}_{E-Z}$,[b] kcal mol^{-1}	$\Delta G^{\ddagger}_{Z-E}$[b] kcal mol^{-1}
1a	35.0	Equilibration	1.62×10^{-5}	5.35×10^{-5}	24.8	24.1
	176.5	DNMR	11.7	28.9	24.5	23.7
1b	160.5	DNMR	11.2	32.0	23.6	22.7
1c	35.0	Equilibration	0.781×10^{-4}	3.17×10^{-4}	23.9	23.0
	144.8	DNMR	9.44	33.0	22.9	21.8
4	84.5	DNMR	14.3[c]	14.3[c]	19.2[c]	19.2[c]

[a] In 1,2,4-trichlorobenzene solution. [b] Calculated from the Eyring equation: $\Delta G^{\ddagger} = 1.987\ T\ (\ln\ (T/k) + 23.75994)$; error limits ±0.1 kcal mol^{-1}. [c] No *E*–*Z* isomerism is possible for this monoimine; data refer to topomerization.

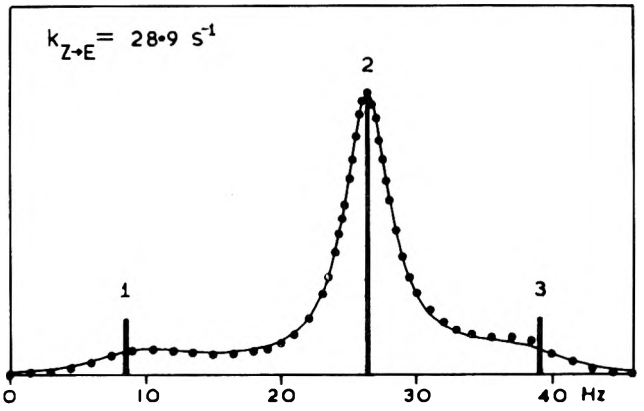


Figure 1. Experimental (●) and "best fit" computed (solid line) dynamic ^1H NMR spectra of the ring methyl groups of **1a** at 176.5 °C in 1,2,4-trichlorobenzene. The preexchange signal positions are also indicated; signals 1 and 3 = *Z* isomer; signal 2 = *E* isomer.

mer is indeed reasonably close to the midpoint of the two signals from the *Z* form.

The imino carbon shifts for both isomers are only slightly different, but the signals move significantly upfield on increasing the bulk of the *N*-alkyl group. Similar effects have been observed in acyclic imines of the type $C_6H_5CH{=}CHCH{=}NR$.[19] The effect of changing the N–R substituent along the series methyl, isopropyl, *tert*-butyl is to shift the imino carbon signal upfield by 4.3 and 7.0 ppm in the latter compounds, compared with shifts of 3.6 and 6.8 ppm in the bisimines **1**. The various *N*-alkyl group hydrogens and carbons exhibit very similar shifts in both isomers, though the N–C signals were detectably anisochronous in the *E* and *Z* forms.

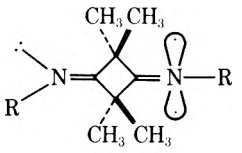
Isomerization Studies. Careful sublimation or recrystallization of **1a** and **1c** afforded crystals of the pure *E* isomer (as shown by ^1H NMR analysis immediately after dissolution of the sample). The stereomutation was monitored at 35 °C in 1,2,4-trichlorobenzene solution by following the appearance of the *gem*-dimethyl signals of the *Z* isomer as a function of time. Imine **1b** was a liquid and not amenable to thermal stereomutation studies.

The degenerate isomerization of **1a**, **1b**, and **1c** was also investigated at high temperature in 1,2,4-trichlorobenzene solution by dynamic ^1H NMR spectroscopy. On raising the probe temperature to between 140 and 180 °C (depending on the compound), both *gem*-dimethyl signals of the *Z* isomer broadened and coalesced with the larger single $C(CH_3)_2$ resonance of the *E* isomer. The site exchange process therefore involves three signals of unequal intensity and two interdependent rate constants (k_{E-Z} and k_{Z-E}). The band shape near the "coalescence temperature" was analyzed using methods described elsewhere.[20] On numbering the ring methyl signals in order of increasing field (i.e., signals 1 and 3 = *Z* isomer; signal 2 = *E* isomer) the elements of the exchange matrix $\mathbf{R}_{ij}$ (see ref 20) were as follows: $\mathbf{R}_{12} = \mathbf{R}_{32} = k_{Z-E}$, $\mathbf{R}_{21} = \mathbf{R}_{23} = k_{Z-E}/2K$, all other $\mathbf{R}_{jk} = 0$ (where $K = k_{Z-E}/k_{E-Z}$). A representative band shape at coalescence in depicted in Figure 1. Rate constants and free energies of activation for **1a–c** determined by dynamic NMR and by direct equilibration are given in Table IV. Kinetic data could not be obtained for the bis(*N-tert*-butyl) compound (**1d**), as this imine existed exclusively in the *E* configuration. However, the topomerization of the monoimine **4** was investigated by observing the coalescence of the two sets of ring methyl signals at 84.5 °C. In this case, the exchange is a simple two-site process, though the overlapping *tert*-butyl signal was included in the band shape analysis as an additional nonexchanging site. The results are given in Table IV.

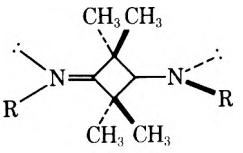
The free-energy barriers to isomerization of **1a–c** decrease with increasing branching of the *N*-alkyl group. The markedly lower barrier in the monoimine **4** is almost certainly due to the large bulk of the *N-tert*-butyl group rather than any transannular effect from the carbonyl group. The difference in $\Delta G^{\ddagger}_{E-Z}$ for **1a** and **4** (ca. 5.5 kcal mol^{-1}) closely parallels the situation in imines derived from 4-nitrobenzophenone where the interconversion barrier is lowered by ca. 5.7 kcal mol^{-1} on replacing *N*-methyl with *N-tert*-butyl.[9]

In the case of imines **1a** and **1c**, combination of the equilibration and dynamic NMR data for the same solution allowed the activation enthalpy and entropy to be determined. Activation entropies for intramolecular stereodynamic processes are usually very small, since solvation effects are commonly minimal and there are often only small differences in rota-

tional and vibrational contributions between the ground and transition states.[9,21] The $\Delta S^{\ddagger}$ value for **1a** is indeed small (Table V). The transition state **6** for *E–Z* isomerization, assuming a lateral-shift mechanism (see below), lacks the twofold rotational axis present in the ground states **1** (*E*) and **1** (*Z*). Accordingly, there should be a statistical contribution to $\Delta S^{\ddagger}_{E-Z}$ and $\Delta S^{\ddagger}_{Z-E}$ of $\mathbf{R} \ln 2 = 1.4$ cal mol^{-1} K^{-1}. Therefore, the intrinsic contribution to $\Delta S^{\ddagger}$ is indeed close to zero for imine **1a**. The larger (positive) entropy term for **1c** might be due to severe steric hindrance to libration of the isopropyl groups in the ground state. These restrictions are removed for one isopropyl group in the transition state **6**, R = $CH(CH_3)_2$, which should therefore have higher entropy.



6



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The mechanism of imine isomerization is of considerable interest, since at least four possibilities have been considered in the literature, viz: (1) simple rotation around the C=N bond,[21,22] (2) planar nitrogen inversion (lateral shift),[21,22] (3) reversible tautomerization coupled with rapid rotation around the CN single bond in the enamine,[23] and (4) reversible addition of traces of acidic impurity across the double bond, coupled with fast rotation around the CN single bond in the adduct.[24] Isomerization pathways intermediate between pure rotation (1) and planar nitrogen inversion (2) are also possible.[25] Pathway (3) can be excluded for the imines in this investigation, since they have no α-hydrogen atoms. Furthermore, the relatively small positive $\Delta S^{\ddagger}$ values (Table V) are inconsistent with the addition route (4), since this involves a large negative activation entropy.[24] In any case, the samples were carefully purified in order to minimize the possibility of catalysis by trace impurity. Experimental data for other imines generally support the lateral-shift mechanism rather than C=N rotation.[9,22] The close similarity between the barriers in the bisimines **1a–c** and those reported for acyclic *N*-alkylimines, e.g., $(CH_3CH_2)_2C{=}NCH_2C_6H_5$ ($\Delta G^{\ddagger}$ = 24.5 kcal mol^{-1})[23] and 4-$NO_2C_6H_4(C_6H_5)C{=}NCH_3$ ($\Delta G^{\ddagger}_{E-Z}$ = 26.1 kcal mol^{-1})[9], supports a common pathway (nitrogen inversion). The slightly lower $\Delta G^{\ddagger}$ values for **1a–c** may be ascribed to greater steric hindrance in the ground state. Were bond rotation operative, one might have expected that the incorporation of the imino carbon into a four-membered ring would have had a more marked effect on the C=N torsional potential, as this carbon atom is directly involved in the dynamic process. The observed lowering of $\Delta G^{\ddagger}$ with increasing steric bulk of the *N*-alkyl substituents also supports an inversion mechanism. Thus, an inspection of molecular models indicated that the transition state **6** for nitrogen inversion is much less hindered than the ground states, whereas the transition state **7** for C=N rotation still suffers from considerable interactions between the *N*-alkyl substituent and the ring methyl groups. However, it should be emphasized that the present results do not rigorously exclude a rotational or an intermediate pathway for isomerization.

Worman and Schmidt previously invoked a steric effect to account for the higher coalescence temperature (165 °C) of the biscyclohexyl compound **1**, R = C_6H_{11}, compared with the bisphenyl analogue **1**, R = C_6H_5 (T_c ca. 100 °C). This postulate is at variance with our observations that the barrier (and coalescence temperature) *decreases* with increasing bulk of the nitrogen substitutents. The low barrier in the phenyl compound is almost certainly a consequence of conjugation between the aryl group and the nitrogen lone-pair electrons. It is well established in other systems that an *N*-phenyl group stabilizes the transition state for nitrogen inversion.[21,22]

Table V. Enthalpies and Entropies of Activation for Isomerization of Bisimines 1a and 1c

Compd	$\Delta H^{\ddagger}_{E-Z}$,[a] kcal mol^{-1}	$\Delta H^{\ddagger}_{Z-E}$,[a] kcal mol^{-1}	$\Delta S^{\ddagger}_{E-Z}$,[b] cal mol^{-1} K^{-1}	$\Delta S^{\ddagger}_{Z-E}$,[b] cal mol^{-1} K^{-1}
1a	25.5	25.0	+2.3	+ 2.8
1c	26.6	26.2	+8.8	+10.5

[a] $\Delta H^{\ddagger}$ values are ±0.5 kcal mol^{-1}. [b] $\Delta S^{\ddagger}$ values are ±1.5 cal mol^{-1} K^{-1}.

Experimental Section

^{1}H NMR spectra were recorded on a Varian XL-100 or Perkin-Elmer R-14 or R-12B spectrometers in CW mode; ^{13}C spectra were obtained on a Jeol FX-60 Fourier instrument.

Bisimines (1) from Tetramethylcyclobutane-1,3-dione. The titanium(IV) chloride procedure described previously[7,8] proved to be satisfactory, though more vigorous conditions were necessary (particularly for the highly hindered *tert*-butyl compound **1d**). Typically, titanium(IV) chloride (0.05 M) in dry toluene (50 cm^3) was added slowly to tetramethylcyclobutane-1,3-dione (0.05 M) and excess amine (0.50 M) in dry toluene (100 cm^3) at ca. −10 °C under nitrogen. The mixture was then allowed to assume ambient temperature and refluxed for ca. 20 h. The cooled solution was then filtered and the residual solid washed thoroughly with dry benzene. Concentration of the filtrate and sublimation in vacuo (or distillation in the case of **1b**) gave the bisimine in ca. 50% yield. Further purification was achieved by recrystallization from hexane. In the case of *tert*-butylamine, the above procedure afforded the *mono*(*tert*-butylimine) **4**. However, the bisimine **1d** was obtained by employing an excess of titanium(IV) chloride (0.10 M) and continuing reflux for 4 days until infrared spectra indicated that the monoimine has been completely converted to the bisimine. Physical properties and microanalytical data for the bisimines are given below:

Bis(methylimine) (1a): mp 72 °C. Anal. Calcd for $C_{10}H_{18}N_2$: C, 72.2; H, 10.9; N, 16.85. Found: C, 72.1; H, 10.9; N, 16.85.

Bis(ethylimine) (1b): bp 54–56 °C/2.0 mm. Anal. Calcd for $C_{12}H_{22}N_2$: C, 74.2; H, 11.4; N, 14.4. Found C, 74.0; H, 11.1; N, 14.4.

Bis(isopropylimine) (1c): mp 113–115 °C. Anal. Calcd for $C_{14}H_{26}N_2$: C, 75.6; H, 11.8; N, 12.6. Found: C, 75.6; H, 11.7; N, 12.4.

Bis(*tert*-butylimine) (1d): mp 83–84 °C. Anal Calcd for $C_{16}H_{30}N_2$: C, 76.7; H, 12.1; N, 11.15. Found: C, 76.7; H, 12.1; N, 11.2.

Bis(cyclohexylimine) (1e): mp 149–151 °C (lit.[5] mp 152 °C).

Mono(*tert*-butylimine) (4): mp 60–62 °C. Anal. Calcd for $C_{12}H_{21}NO$: C, 73.8; H, 10.8; N, 7.2. Found: C, 73.6; H, 10.6; N, 7.0.

Kinetic Studies. Thermal equilibrations were performed in the probe of the Perkin-Elmer (permanent magnet) spectrometer which is constantly maintained at 35.0 °C. The 1,2,4-trichlorobenzene used as solvent was washed with base and stored over anhydrous potassium carbonate to remove traces of acidic material. The solvent was preheated to 35 °C and the isomerization was followed on a freshly dissolved sample of the pure *E* isomer by integration and peak-height measurements. Rate constants were determined from the usual plot of ln $(x_e/x_e - x)$ vs. time for a reversible first-order approach to equilibrium.

Dynamic NMR studies were performed on the XL-100 using the same sample that had been previously studied by direct equilibration. Probe temperature was measured using a digital readout temperature indicator attached to a copper–constantan thermocouple which was inserted into the sample at the level of the receiver coil. Exchange rates for the three-site collapse were determined by computer analysis of the digitized experimental band shape.[20] Signal positions and the isomer distribution were measured at a series of temperatures in the slow-exchange region and extrapolated to the coalescence temperature.

Registry No., 63196-51-0; tetramethylcyclobutane-1,3-dione, 933-52-8.

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Rearrangement of α-Chloroaldimines: Synthesis of 2-Imidazolidinethiones[1]

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1-Substituted 4-methoxy-5,5-dimethyl-2-imidazolidinethiones have been prepared by reaction of *N*-1-(2-chloro-2-methylpropylidene)amines with potassium thiocyanate in methanol under reflux. The 1-substituted 4-methoxy-5,5-dimethyl-2-imidazolidinethiones were conveniently converted into the corresponding 1-substituted 5,5-dimethyl-2-imidazolidinethiones by lithium aluminum hydride treatment in ethereal medium. The structure elucidation was based on NMR, IR, and mass spectrometry next to x-ray crystallographic analysis. The formation of the heterocyclic five-membered rings was explained by a mechanism involving an aziridine intermediate, which underwent competitive opening.

N-1-(2-Chloro-2-methylpropylidene)amines (1), easily obtained from isobutyraldimines and *N*-chlorosuccinimide, are a new class of simple bifunctional compounds which have been used recently as synthetic blocks in organic synthesis.[3,4] An entry into the heterocyclic chemistry is presented here.

Results and Discussion

In continuation of work on the reactivity of α-halogenated imino compounds, the reaction of α-chloroaldimines **1** with KSCN in methanol has been found to provide a convenient preparation of 1-substituted 4-methoxy-5,5-dimethyl-2-imidazolidinethiones (**2**) (Table I).

Treatment of compounds **2** with methyl iodide in dry acetone afforded imidazoline hydriodides **4**, which were converted into the 2-methylthioimidazolines **6** by alkali treatment (Scheme I). The structure of these products, which involved rearrangement of the imino nitrogen, was established by x-ray crystallographic analysis of 1-cyclohexyl-4-methoxy-5,5-dimethyl-2-methylthioimidazoline hydriodide (**4b**).

The molecular structure of compound **4b** as determined by the x-ray analysis is shown in Figure 1 together with the atom labeling system used. The final coordinates, standard deviations, and bond distances are listed in Tables II and III, included in the microfilm edition of this journal. The experimental conditions for the x-ray crystallographic analysis are further given in the Experimental Section.

A further support of the presence of a CH_3OCHN moiety in the heterocycles described here was provided by the conversion of **2** into the nonmethoxylated compounds **3**, i.e., 1-substituted 5,5-dimethyl-2-imidazolidinethiones, by reaction

Scheme I

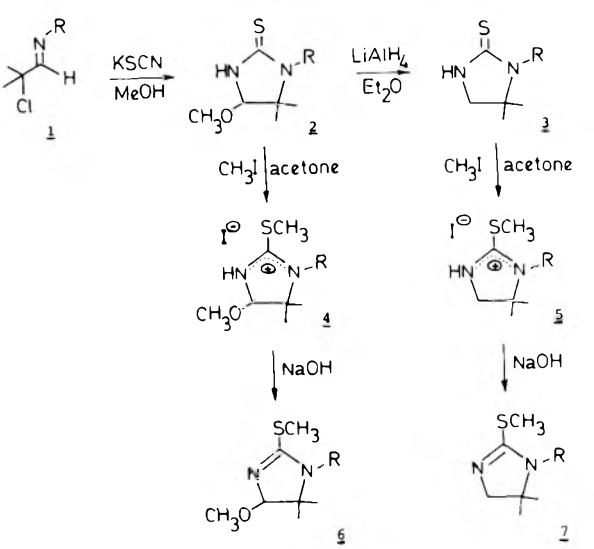


Table I. Synthesis and Spectrometric Properties of 1-Substituted 4-Methoxy-5,5-dimethyl-2-imidazolidinethiones 2, 1-Substituted 5,5-Dimethyl-2-imidazolidinethiones 3, and 1-Substituted 4-Alkoxy-5,5-dimethyl-2-imidazolidinethiones 24

Compd[a]	R	Yield, %	Mp, °C	NMR, δ ($CDCl_3$) $\delta_{(CH_3)_2}$	δ_{NCHO}	δ_{NCH_2}	δ_{OCH_3}	δ_{NH}[b]	δ_R	IR (KBr),[c] cm^{-1}	Mass spectrum,[d,e] m/e (rel intensity)
2a	*t*-Bu	50	176	1.44 (s, 3) 1.51 (s, 3)	4.25 (d, J = 1.0 Hz)		3.40 (s)	7.50	1.76 (s, 9, *t*-Bu)	3220 (ν_{NH})	216 (M^+, 24); 184 (M^+ − MeOH, 48); 60 (100)
2b	Cyclohexyl	78	184	1.30 (s, 3) 1.36 (s, 3	4.38 (d, J = 1.0 Hz)		3.38 (s)	7.65	1–2 [m, 10, $(CH_2)_5$];2.5 (m, 1, NCH)	3220 (ν_{NH})	242 (M^+, 27); 210 (M^+ − MeOH, 60); 86 (100)
2c	*n*-Bu	22	110	1.22 (s, 3) 1.30 (s, 3)	4.41 (d, J = 1.0 Hz)		3.36 (s)	7.78	0.94 (t, 3, CH_3) 1.1–2 [m, 4, $(CH_2)_2$]; 3.4 (m, 2, NCH_2)	3220 (ν_{NH})	216 (M^+, 27); 184 (M^+ − MeOH, 53); 86 (100)
2d	*i*-Pr	73	126	1.30 (s, 3) 1.35 (s, 3)	4.36 (d, J = 1.0 Hz)		3.36 (s)	7.69	1.52 [d, J = 7 Hz, 6, $(CH_3)_2$]; 4.13 (septet, J = 7 Hz, 1, $CHMe_2$)	3220 (ν_{NH})	202 (M^+, 19); 170 (M^+ − MeOH, 15); 86 (100)
2e	CH_2-C_6H_5	64	126	1.08 (s, 3) 1.17 (s, 3)	4.46 (d, J = 0.8 Hz)		3.35 (s)	7.97	4.77 and 4.87 (AB, J = 15.6 Hz, NCH_2); 7.1–7.6 (m, 5, C_6H_5)	3220 (ν_{NH})	250 (M^+, 26); 218 (M^+ − MeOH, 20); 86 (100)
3a	*t*-Bu	75	180	1.50 (s, 6)		3.23 (d, 1.0 Hz)		6.65	1.76 (s, 9, *t*-Bu)	3180 (ν_{NH})	186 (M^+, 3); 41 (100)
3b	Cyclohexyl	89	164	1.37 (s, 6)		3.35 (d, 0.8 Hz)		7.08	1–2 [m, 10, $(CH_2)_5$]; 2.6 (m, 1, NCH)	3100–3220 (ν_{NH})	212 (M^+, 78); 55 (100)
3c	*n*-Bu	85	70	1.30 (s, 6)		3.35 (d, 1.0 Hz)		7.23	0.95 (t, 3, CH_3); 1.2–1.9 [m, 4, $(CH_2)_2$]; 3.4 (covered, NCH_2)	3260 (ν_{NH})	186 (M^+, 100)
3d	*i*-Pr	91	181	1.37 (s,6)		3.33 (d, 1.0 Hz)		6.85	1.56 [d, J = 7 Hz, 6, $(CH_3)_2$]; 4.04 (1, H, septet, 1, $CHMe_2$)	3180 (ν_{NH})	172 (M^+, 100)
3e	CH_2-C_6H_5	86	128	1.16 (s, 6)		3.33 (d, 1.0 Hz)		see δ_R	4.77 (s br, 2, NCH_2); 6.9 (m, 6, C_6H_5 + NH)	3100–3200 (ν_{NH})	220 (M^+, 96); 91 (100)
24b (R′ = Et)	Cyclohexyl	85	124	1.30 (s, 3) 1.34 (s,3)	4.46 (d, J = 1 Hz)		δ_{OEt} (see δ_R entry)	7.86	1–2 [m, 10, $(CH_2)_5$]; ~2.5 (m, 1, NCH); 1.19 (t, J = 7 Hz, 3 CH_3CO); 3.2–4 (m, 2, OCH_2)	3200 (ν_{NH})	
24a (R′ = Et)	*t*-Bu	34		1.40 (s, 3) 1.47 (s, 3)	4.26 (d, J = 1 Hz)		δ_{OEt} (see δ_R entry)	7.50	1.75 (s, 9, *t*-Bu); 1.19 (t, J = 7 Hz, 3, CH_3CO); 3.5 (m, 2, OCH_2)	3200 (ν_{NH})	no M^+; 184 (M^+ − EtOH, 70); 57 (100)
24a (R′ = *i*-Pr)	*t*-Bu	50		1.40 (s, 6)	4.33 (d, J = 1 Hz)		$\delta_{O\text{-}i\text{-}Pr}$ (see δ_R entry)	7.80	1.71 (s, 9, *t*-Bu); 1.15 and 1.22 (2 d, J = 6 Hz, 6 H, Me_2CO); 3.80 (m, 1, CHO)	3200 (ν_{NH})	244 (M^+, 33); 184 (M^+ − *i*-PrOH, 20); 91 (100)

[a] Elemental analyses of compounds **2** and **3** are tabulated in the microfilm edition (Tables IV and V). [b] Broad signal. [c] Full IR data will appear in the microfilm edition of this journal (Table VI). [d] Mass spectra of compounds **2** were recorded with a A.E.I. MS 30 mass spectrometer, while mass spectra of compounds **3** were measured with a A.E.I. MS 20 mass spectrometer coupled with a gas chromatograph (GC–MS). [e] Full mass spectral data will appear in the microfilm edition of this journal (Table VI).

with mixed metal hydrides, such as lithium aluminum hydride in diethyl ether (for R = *t*-Bu, cyclohexyl, *n*-Bu, *i*-Pr, benzyl), and sodium bis(2-methoxyethoxy)aluminum hydride in benzene (for R = cyclohexyl). Sodium borohydride in methanol did not react. Physical and spectrometrical data of compounds **3** are given in Table I.

This nucleophilic substitution by hydride is analogous to the reactions of mixed metal hydrides with *N*-(α-alkoxy-

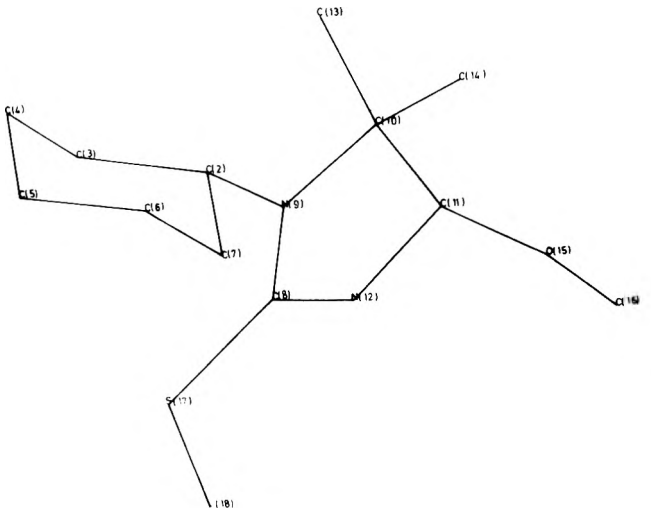


Figure 1. Structure of compound **4b**, showing the crystallographic numbering system.

benzyl)acetanilide, 2,3-diphenyl-2-ethoxyaziridine, and 2-methoxy-3,4,5,6-tetrahydropyridine, which gave respectively *N*-ethyl-*N*-phenylbenzylamine,[5] 2,3-diphenylaziridine,[6] and piperidine.[7]

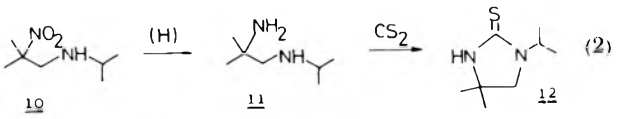
Treatment of 2-imidazolidinethiones **3** with methyl iodide in dry acetone gave rise to hydriodides **5**, from which the free bases **7** were liberated on alkali treatment (Scheme I). A survey of the synthesis and spectrometric data of imidazoline hydriodides **5** and imidazolines **7** is given in Tables VII and VIII, included in the microfilm edition of this journal.

Our attempts to synthesize 1-alkyl-5,5-dimethyl-2-imidazolidinethiones **3** were unsuccessful because no appropriate 1,2-diamine, i.e., 1-amino-2-alkylamino-2-methylpropane (**9**), could be prepared. The preparation of these diamines was necessary in order to be condensed with carbon disulfide.[8,9,10]

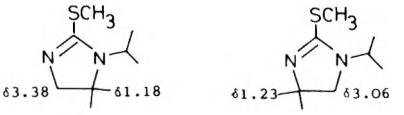
$$\underset{\mathbf{8}}{RNHCMe_2CN} \not\rightarrow \underset{\mathbf{9}}{RNHCMe_2CH_2NH_2} \qquad (1)$$

The reduction of 2-(*N*-alkylamino)-2-methylpropionitrile (**8**) with various reducing agents such as $LiAlH_4$ in diethyl ether, $NaBH_4$ in ethanol and catalytic hydrogenation on a palladium–carbon catalyst in methanol or acetic acid (both at 60 psi) did not give rise to diamines **9** (eq 1). Only decomposition products, e.g., primary alkylamines RNH_2, were detected in the reaction mixture. These results are in accordance with earlier reports concerning the preparation of 1,2-diamines with general structure $RNHCMe_2CH_2NH_2$. These diamines were not accessible by the reductive methods schedules above.[11,12]

However, the isomeric 1,2-diamines **11**, with the geminal dimethyl function in the α position of the unsubstituted nitrogen atom, were readily available by condensation of 2-nitropropane with formaldehyde and an appropriate primary amine (here described for isopropylamine), the resulting *N*-isopropyl-2-methyl-2-nitropropylamine (**10**) being reduced by catalytic hydrogenation to 2-amino-1-isopropylamino-2-methylpropane (**11**).[13] The 1,2-diamine **11** was then subjected to condensation with carbon disulfide, after which the intermediate dithiocarbamate was cyclized by pyrolysis to 1-isopropyl-4,4-dimethyl-2-imidazolidinethione (**12**) (eq 2). Compound **12** was found to be unidentical with the product (**3d**) obtained from α-chloroaldimine **1d** (R = *i*-Pr), a conclusion which was drawn on the basis of spectrometric data (NMR, IR, MS) and the melting point. Analogously, compound **12** (R = *i*-Pr) was derivatized to 1-isopropyl-4,4-dimethyl-2-methylthioimidazoline (**13**) according to the reaction sequence outlined in Scheme I. A comparison between the NMR spectra ($CDCl_3$) of the 5,5-dimethylimidazoline **7d** (R = *i*-Pr) and the 4,4-dimethylimidazoline **13** indicated again



(2)



the correct structural assignments. As expected, the chemical shifts of the methylene function and the geminal dimethyl protons, both in the α position of the sp^2-hybridized nitrogen atom, were higher than those for similar protons in the β position.

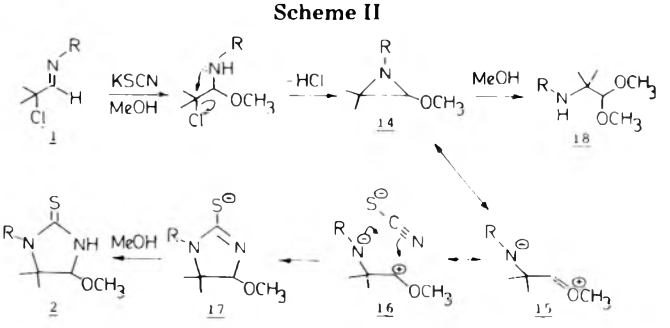
Discussion of the Mechanism. From the mechanistic point of view the formation of 1-substituted 4-methoxy-5,5-dimethyl-2-imidazolidinethiones **2** from α-chloroaldimines **1** and KSCN in methanol can be interpreted in terms of the initial attack of methanol at the carbon–nitrogen double bond, followed by intramolecular nucleophilic attack of the chlorinated carbon atom, producing an intermediate 1-alkyl-2-methoxy-3,3-dimethylaziridine **14**. The extreme form of the polarization of this functionalized aziridine is represented as the zwitterionic species **15** ↔ **16** (Scheme II). The energy barrier for opening the three-membered ring at the $N–C_2$ bond is lowered by the methoxy substitutent, which enables delocalization (see **15**). The dipolarophilic thiocyanate anion approaches now the dipole and forms the five-membered heterocycle.

That indeed α-haloimines are apt to undergo nucleophilic addition at the C=N bond and subsequent ring closure to aziridines has been shown recently.[1,3,14,15,16] For instance, *N*-1-(2-chloro-2-methylpropylidene)amines **1** reacted with methanol to produce α-amino acetal (under hydrochloride form) **18**, which was explained via the methoxyaziridine **14**.[3]

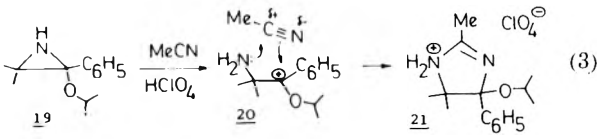
The methoxyaziridine **14**, when attacked by methanol, produced rearranged compound **18**, while with the dipolarophilic thiocyanate anion the 2-imidazolidinethiones **2** were formed. It is noteworthy that compounds **2** are practically always accompanied by small amounts of rearranged products **18**, which can be easily separated from heterocycles **2** (see Experimental Section).

The proposed mechanism described above is comparable to the reaction of 2-isopropoxy-2-phenyl-3,3-dimethylaziridine (**19**) with acetonitrile in the presence of anhydrous perchloric acid.[17] In this case, the opening of the alkoxyaziridine is facilitated by protonation and concordant S_N1-type opening of the ring, but the dipolarophilic cyanide moiety behaves

Scheme II



analogously, as was proposed for the thiocyanate anion. As shown in eq 3 aziridine **19** and $CH_3CN/HClO_4$ gave rise to

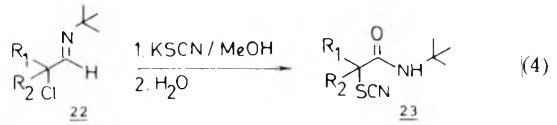


(3)

imidazolinium perchlorate **21**. Less activated aziridines such as 1,1,2,2-tetramethylaziridinium perchlorate reacted in similar manner to imidazolinium salts,[18] while the corresponding oxygen analogues, i.e., epoxides, showed comparable ring expansions to oxazolinium salts with nitriles.[19,20]

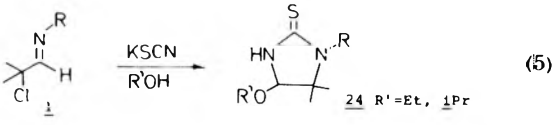
Therefore we carried out the reaction of **1a** with KSCN/CH_3OH in the presence of acetonitrile in order to trap the intermediate methoxyaziridine **14**. The exclusive product, however, was 1-*tert*-butyl-4-methoxy-5,5-dimethyl-2-imidazolidinethione (**2a**).

The scope of the reaction of α-chloroaldimines with KSCN is limited to the α-chloroisobutyraldimines **1** (or **22**; $R_1 = R_2 = CH_3$), since higher substituted derivatives **22** (R_1, $R_2 \neq CH_3$) yielded no heterocyclic compounds. In this manner, *N*-1-(2-chloro-2-ethylbutylidene)-*tert*-butylamine (**22**, $R_1 = R_2$ = Et) reacted with KSCN in methanol for 48 h under reflux to afford a reaction mixture from which only 19% *N*-*tert*-butyl-2-ethyl-2-thiocyanobutanamide (**23**; $R_1 = R_2$ = Et) was isolated by crystallization (mp 126–127 °C) (eq 4). Ac-



(4)

cordingly, no 2-imidazolidinethione was formed by reaction of *N*-(1′-chlorocyclohexylmethylidene)-*tert*-butylamine [**22**; R_1, R_2 = $(CH_2)_5$] with KSCN in methanol. Even carefully dried and purified reagents did not afford any five-membered ring. These limitations are in accordance with the observation that the reaction of higher substituted compounds **22** (R_1, $R_2 \neq CH_3$) with methanol produced only a minor amount of the rearranged β-amino acetals besides the corresponding *N*-alkyl-α-chloroamides. However, an extension of the reaction outlined in Scheme I was the use of other alcohols than methanol. It was possible to obtain 1-alkyl-4-alkoxy-5,5-dimethyl-2-imidazolidinethiones **24** by carrying out the reaction of **1** with KSCN in ethanol or 2-propanol (eq 5).



(5)

The reaction with ethanol proceeded readily, while several days of reflux were required for the reactions with 2-propanol. The reaction in 2-methyl-2-propanol did not give heterocycles at all. In conclusion, the reaction of α-chloroisobutyraldimines **1** with KSCN in alcoholic medium presents a versatile one-step synthesis of functionalized and otherwise not accessible 2-imidazolidinethiones **2**. The final products were formed by a rearrangement of the α-chloroaldimines **1** involving an aziridine intermediate.

Experimental Section

Nuclear magnetic resonance spectra were recorded with a Varian T-60 NMR spectrometer. Infrared spectra were measured with a Perkin-Elmer Model 257 spectrophotometer. Mass spectra were obtained from A.E.I. MS 20 or A.E.I. MS 30 mass spectrometers (70 eV). Melting points were measured with a Kofler hot stage and are uncorrected.

N-1-(2-chloro-2-methylpropylidene)amines **1** were prepared by condensing isobutyraldehyde with a primary amine, followed by chlorination of the resulting aldimine with *N*-chlorosuccinimide according to a method described previously.[3]

Preparation of 1-Substituted 4-Methoxy-5,5-dimethyl-2-imidazolidinethiones (2). In a typical experiment, 15.0 g (0.080 mol) of *N*-1-(2-chloro-2-methylpropylidene)cyclohexylamine (**1b**) was dissolved in 150 mL of dry methanol and treated with 23.3 g (0.24 mol) of KSCN. The mixture was refluxed overnight, half evaporated, and poured into 500 mL of vigorously stirred distilled water. The resulting precipitate was collected by filtration and washed with cold methanol/water, 25/75. 1-Cyclohexyl-4-methoxy-5,5-dimethyl-2-imidazolidinethione (**2b**) was dried in the desiccator, yield 15.1 g (78%), mp 184 °C. The product could be recrystallized from diethyl ether. Physical and spectral data of compounds **2** are given in Table I.

When other alcohols than methanol and ethanol were used, the following isolation procedure was applied as illustrated for 1-*tert*-butyl-4-isopropoxy-5,5-dimethyl-2-imidazolidinethione (**24a**; R′ = *i*-Pr). The reaction mixture, obtained as above, was poured into distilled water. The liquid which separated was taken up in ether, and the water layer was extracted twice with ether. After drying ($MgSO_4$), evaporation of the solvent left an oil which was purified by passing it through a silica gel column (elution with ether). Compound **24a** (R′ = *i*-Pr) was sufficiently pure (>95% as revealed by NMR), but the purity could not be checked by gas chromatography due to decomposition, probably in the injector (see data in Table I).

Synthesis of 1-Substituted 5,5-Dimethyl-2-imidazolidinethiones 3. (A) Reaction of 2 with $LiAlH_4$ in Diethyl Ether. In a typical experiment, a suspension of 380 mg (0.01 mol) of lithium aluminum hydride and 10 mL of dry diethyl ether (distilled over lithium aluminum hydride) was cooled in an ice bath. A solution of 1.21 g (0.005 mol) of 1-cyclohexyl-4-methoxy-5,5-dimethyl-2-imidazolidinethione (**2b**) in 30 mL of dry diethyl ether was added dropwise over a period of 15 min. The suspension was further stirred for 1 h and then poured into a vigorously stirred mixture of ether and water. The ether layer was separated and the water layer was extracted twice with ether. The combined extracts were dried ($MgSO_4$), and evaporation of the solvent in vacuo yielded 890 mg of pure 1-cyclohexyl-4,4-dimethyl-2-imidazolidinethione (**3b**) as white crystals, yield 80%. Recrystallization was performed with ether/pentane.

(B) Reaction of $Na(CH_3OCH_2CH_2O)_2AlH_2$ in Benzene. To a solution of 1.0 g (0.0041 mol) of 1-cyclohexyl-4-methoxy-5,5-dimethyl-2-imidazolidinethione (**2b**) in 20 cm^3 of dry benzene was added dropwise with stirring 2.37 mL of a 70% solution of sodium bis(2-methoxyethoxy)aluminium hydride in benzene (= Red-Al, purchased from the Aldrich Chemical Co.). After stirring for 2 h at ambient temperature, the homogenous yellow benzene solution was treated with moistened ether and poured into a mixture of ether and water. The ether layer was separated and the water layer twice extracted with ether. After drying the combined extracts ($MgSO_4$), evaporation of the solvent yielded 780 mg of pure 1-cyclohexyl-5,5-dimethyl-2-imidazolidinethione (**3b**), yield 89%. Physical and spectral data of compounds **3** are given in Table I.

The structural assignment of compounds 3 was also supported by the ^{13}C NMR spectrum (Varian XL-100). The δ values (ppm) of 1-isopropyl-5,5-dimethyl-2-imidazolidinethione (**3d**) in $CDCl_3$ solution are given below (noise decoupled): 21.1 (q), 26.3 (q), 47.1 (d), 56.5 (t), 65.5 (s). The signal corresponding with the thione function was not visible. The multiplicities are derived from the partially decoupled spectrum.

Synthesis of 2-Amino-1-isopropylamino-2-methylpropane (11). Condensation of isopropylamine, formaldehyde, and 2-nitropropane afforded *N*-isopropyl-2-methyl-2-nitropropylamine (**10**), which was reduced by catalytic hydrogenation to 2-amino-1-isopropylamino-2-methylpropane (**11**) as previously described.[13]

Preparation of 1-Isopropyl-4,4-dimethyl-2-imidazolidinethione (12). A solution of 13.0 g (0.1 mol) of 2-amino-1-isopropylamino-2-methylpropane (**11**) in 20 mL of H_2O and 20 mL of 95% ethanol was thoroughly stirred and treated dropwise with 8.4 g (0.11 mol) of carbon disulfide over a period of 15 min. The reaction mixture was then heated under reflux in an oil bath (110 °C). After cooling in the refrigerator for 1 h, the solid material was collected by filtration, washed with a little cold acetone and dried, yielding 11.2 g of 1-isopropyl-4,4-dimethyl-2-imidazolidinethione (**12**): mp 192 °C; yield, 73%; NMR ($CDCl_3$) δ 1.17 [d, J = 7 Hz, 6, $(CH_3)_2CH$], 1.33 [s, 6, $(CH_3)_2$], 3.31 (s, 2, CH_2N), 4.83 (septet, J = 7 Hz, 1, $NCHMe_2$), 6.80 (s br, 1, NH); IR (KBr) 3200 (ν_{NH}), 1510–1450 (br, strong), 1370, 1320, 1286, 1235, 1195, 1165, 1129, 1063 cm^{-1}; mass spectrum *m/e* (rel abundance) 172 (M, 78), 171 (12), 157 (12), 139 (4), 130 (4), 129 (4), 115 (18), 112 (7), 100 (8), 98 (12), 83 (41), 72 (30), 58 (100), 57 (26), 56 (12), 55 (17), 43 (15), 42 (25), 41 (21).

Reaction of 2-Imidazolidinethiones 2 and 3 with Methyl Iodide.[21,22,23] In a typical experiment, 1.21 g (0.005 mol) of 1-cyclohexyl-4-methoxy-5,5-dimethyl-2-imidazolidinethione (**2b**), dissolved

in a minimum of dry acetone, was treated with 750 mg (1.05 equiv) of methyl iodide. After standing overnight at ambient temperature 1.8 g of colorless well-formed crystals of **4b** were separated by filtration, yield 93%. If little or no crystals were formed, the acetone was treated with dry diethyl ether, after which evaporation yielded hydriodides **4** or **5** in pure form. The crystals were isolated by filtration and washed with ether (see data in the microfilm edition).

Conversion of Hydriodides 4 and 5 into Imidazolines 6 and 7. To a mixture of 60 mL of 1 N NaOH and 50 mL of ether was added 1.0 g of hydriodide **4b**. After shaking for 2 min the ether layer was separated and the water layer twice extracted with ether. Drying of the ether ($MgSO_4$) and evaporation in vacuo left 550 mg of a colorless oil. The purity of 1-cyclohexyl-4-methoxy-5,5-dimethyl-2-methylthioimidazoline (**6b**) was higher than 98% as revealed by NMR and VPC (see data in the microfilm edition).

Reaction of *N*-1-(2-Chloro-2-ethylbutylidene)-*tert*-butylamine (22; $R_1 = R_2 =$ Et) and KSCN/CH_3OH. Compound **22** ($R_1 = R_2$ = Et) was treated with KSCN in methanol, as described for α-chloroisobutyraldimines **1**. After pouring the reaction mixture in water, extraction with ether, drying ($MgSO_4$), and evaporation yielded a residue from which N-*tert*-butyl-2-ethyl-2-thiocyanobutanamide (**23**; $R_1 = R_2$ = Et) was isolated as a solid compound by trituration with ether/hexane: mp 126–127 °C; yield 19%; NMR ($CDCl_3$) δ 0.87 (t, J = 6.2 Hz, 6, 2 CH_3), 1.34 (s, 9, *t*-Bu), 1.56 (m, 4, 2 CH_2), 5.49 (s br, 1, NH); IR (KBr) 3305 (ν_{NH}), 2065 (SCN), 1650 cm^{-1} ($\nu_{C=O}$); mass spectrum m/e (rel abundance) no M^+, 170 (29), 156 (6), 143 (53), 142 (10), 128 (9), 116 (55), 100 (8), 99 (15), 87 (10), 86 (13), 72 (12), 71 (26), 58 (100), 57 (86), 56 (17), 55 (9), 43 (21), 41 (15).

Anal. Calcd: C, 57.86; H, 8.83; N, 12.27. Found: C, 57.99; H, 8.95; N, 12.16.

X-Ray Crystallographic Analysis. Well-formed colorless crystals of **4b**, obtained by recrystallization from acetone, were used for the x-ray work. Crystal data: $C_{13}H_{26}N_2OSI$, monoclinic, $P2_1/n$, a = 20.462 (10), b = 8.659 (4), c = 9.847 (3) Å, β = 99.20 (3)°, Z = 4. Experimental conditions: source $CuK\bar{\alpha}$; λ 1.5418 Å; w–2θ scan; θ_{max} = 55°; confidence level 2.5; total number of independent reflections, 2167; total observed, 1892.

The data were collected on a Syntex $P2_1$ diffractometer. The experimental conditions during the measurement of the intensities were given above. The structure was determined by direct methods using the MULTAN 74 program[24] and refined by block-diagonal least-squares calculations with the programs written by Ahmed et al.[25] A structure-factor calculation resulted in $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.078$ for all observed reflections. The scattering factors used are those given in the international Tables for X-Ray Crystallography.[26]

Acknowledgments. We are indebted to the Belgian "Nationaal Fonds voor Wetenschappelijk Onderzoek" and the "Instituut tot Aanmoediging van het Wetenschappelijk Onderzoek in Nijverheid en Landbouw" for financial support to the laboratory.

Supplementary Material Available: positional and thermal parameters of compound **4b** (x-ray) (Table II); intramolecular bond distances and angles of compound **4b** (x-ray) (Table III); elemental analyses of 2-imidazolidinethiones **2** (Table IV); elemental analyses of 2-imidazolidinethiones **3** (Table V); full IR and MS data of 2-imidazolidinethiones **2, 3,** and **24** (Table VI); synthesis and spectrometric properties (IR and NMR) of compounds **4** and **5** (Table VII); synthesis and spectrometric properties (IR, NMR, and MS) of compounds **6** and **7** (Table VIII) (10 pages). Ordering information is given on any current masthead page.

Registry No.—**1a**, 56990-50-2; **1b**, 63364-31-8; **1c**, 63547-66-0; **1d**, 63364-30-7; **1e**, 63547-67-1; **2a**, 63547-68-2; **2b**, 63547-69-3; **2c**, 63547-70-6; **2d**, 63547-71-7; **2e**, 63547-72-8; **3a**, 63547-73-9; **3b**, 63547-74-0; **3c**, 63547-75-1; **3d**, 63547-76-2; **3e**, 63547-77-3; **4b**, 63547-78-4; **4c**, 63547-79-5; **4e**, 63547-80-8; **5d**, 63547-81-9; **5e**, 63547-82-0; **6b**, 63588-59-0; **6c**, 63547-83-1; **6e**, 63547-84-2; **7d**, 63547-85-3; **7e**, 63547-86-4; **11**, 5448-29-3; **12**, 31596-21-1; **22** ($R_1 = R_2$ = Et), 63364-33-0; **23** ($R_1 = R_2$ = Et), 63547-87-5; **24a** (R_1 = Et), 63547-88-6; **24a** (R_1 = i-Pr), 63547-89-7; **24b** (R_1 = Et), 63547-90-0; KSCN, 333-20-0; ethanol, 64-17-5; isopropyl alcohol, 67-63-0; methyl iodide, 74-88-4.

References and Notes

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Reaction of Di- and Trisubstituted Chloroiminium Chlorides with Azide Ion. A New "Curtius Type" Rearrangement[1]

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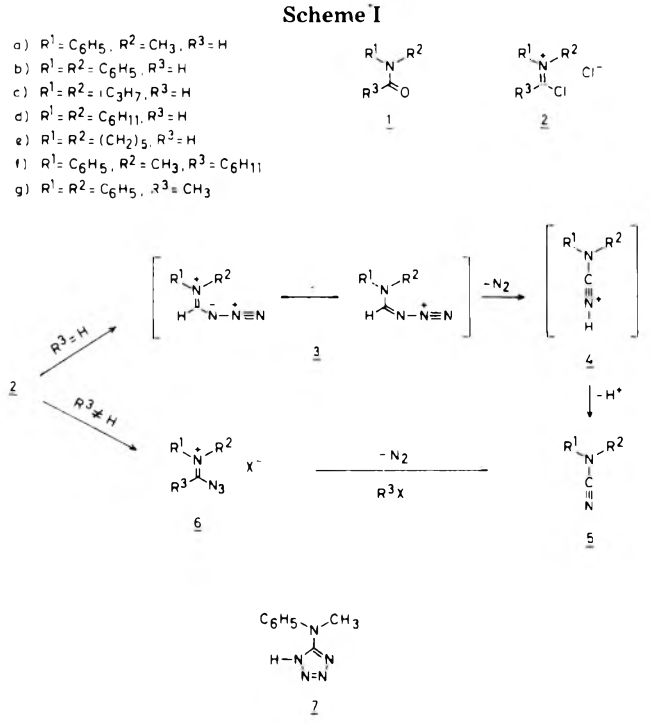
It is shown that disubstituted chloroformiminium chlorides **2** (R^3 = H) react with tetrabutylammonium azide (as well as other azide ion sources) to give the corresponding disubstituted cyanamides **5** presumably via the "Curtius like" rearrangement of an intermediate azidoformiminium salt **3**. Certain trisubstituted chloroiminium chlorides **9** undergo a related reaction with azide ion to give 1-substituted 5-disubstituted aminotetrazoles (**13**) via a trapable carbodiimidinium species **11**. Whereas the disubstituted cyanamide synthesis is a general one, the tetrazole synthesis is limited to those trisubstituted chloroiminium salts (e.g., **9**) where one of the nitrogen atom substituents and the migrating group are both aryl moieties.

The chemistry of organic molecules containing the azido moeity is rich in rearrangement reactions which stem from the propensity of these substances to lose molecular nitrogen.[2] The rearrangement of acyl azides to isocyanates (Curtius reaction[3]) and the reaction of hydrazoic acid with carbonyl compounds (Schmidt reaction[4]) are well known representatives of this general class of transpositions, while the formation of tetrazoles[5] or cyanamides[6] by the pyrolysis of geminal diazides are less frequently encountered members of this group of rearrangements. One rarely observed reaction is the rearrangement of imidoyl azides to carbodiimides.[7] This is because those reactions which are expected to yield the former substances provide tetrazoles instead. In fact, the reaction of imidoyl chlorides with azide ion constitutes one of the most general routes to 1,5-disubstituted tetrazoles and is known as the von Braun–Rudolf synthesis.[8] It occurred to us that one possible method of blocking tetrazole formation, and hence promoting rearrangement in the above instance, would be to utilize a substrate in which the nitrogen atom was disubstituted as is found in the azidoiminium salts **3, 6,** and **10,** derived from the corresponding dichlorides (Vilsmeier–Haack reagents[9]). This publication describes the results of such an investigation.

By analogy to the reactions cited above, it was expected that azidoformiminium salts **3** (Scheme I) would rearrange by the concurrent loss of molecular nitrogen and migration of hydride from carbon to nitrogen to produce, after the loss of a proton from **4,** an N,N-disubstituted cyanamide. As a first attempt to effect such a transposition, a solution of *N*-methylformanilide (**1a**) in dimethoxyethane (DME) was converted into the chloroiminium salt **2a** with oxalyl chloride, and then solid sodium azide was added below 30 °C. A vigorous reaction, accompanied by considerable gas evolution, ensued. The product mixture, the composition of which depended on the number of moles of sodium azide utilized (Table I), consisted of the starting material **1a,** *N*-methylaniline, *N*-methyl-*N*-phenylcyanamide (**5a**), and the tetrazole **7.** The cyanamide yield was maximal when 2 mol of sodium azide per mole of the iminium salt **2a** was used. Extended reaction periods or higher reaction temperatures favored the formation of the tetrazole at the expense of the cyanamide, a predictable observation in view of the known[10] genesis of tetrazoles from cyanamides and hydrazoic acid.

Scheme I

a) $R^1 = C_6H_5$, $R^2 = CH_3$, $R^3 = H$
b) $R^1 = R^2 = C_6H_5$, $R^3 = H$
c) $R^1 = R^2 = {}^iC_3H_7$, $R^3 = H$
d) $R^1 = R^2 = C_6H_{11}$, $R^3 = H$
e) $R^1 = R^2 = (CH_2)_5$, $R^3 = H$
f) $R^1 = C_6H_5$, $R^2 = CH_3$, $R^3 = C_6H_{11}$
g) $R^1 = R^2 = C_6H_5$, $R^3 = CH_3$



The above reactions were not always reproducible, presumbaly because of the meager solubility of sodium azide in DME, and consequently trimethylsilyl azide,[11] triethylammonium azide,[12] and tetrabutylammonium azide[13] were examined as more soluble azide ion sources. The cyanamide **5a** was produced in each case, but the yield thereof was the highest (Table I) and by-product formation was the lowest with tetrabutylammonium azide.[14]

The dichlorides **2b–e** were then reacted with tetrabutylammonium azide (2 mol) and the cyanamides **5b–e** were formed in every instance in preparatively useful yields (Table II). The reaction clearly is a general one.

The successful conversion of disubstituted chloroiminium chlorides into the corresponding disbustituted cyanamides was an added impetus to examine the reaction of azide ion with trisubstituted chloroiminium chlorides such as **9** (Scheme II). It was anticipated that the rearrangement of the azidoiminium salts **10** obtained thereby would generate 1-aryl-5-(*N*-alkylanilino)tetrazoles (**13**) via the highly electrophilic alkylcarbodimidinium species[15] **11.** Indeed, the reaction of tetrabutylammonium azide (2.5 equiv) with *N*-methyl-*N*-phenylchlorobenziminium chlorode (**9a**) (1 equiv), in DME solution at 50–60 °C, gave 1-phenyl-5-(*N*-methylanilino)-tetrazole (**13a**) as the principle (57%) product together with minor amounts of 1,5-diphenyltetrazole (**14a**) (8%), *N*-methylaniline (10–13%), and benzaldehyde (10–13%). The structure of **13a** was confirmed by an unambiguous synthesis from the lithium salt of *N*-methylaniline and 1-phenyl-5-chlorotetrazole. Other trisubstituted iminium salts **9b–e** were also converted into the tetrazoles **13** and **14** and other products, the relative amounts of which (Table III) depended on the nature of R^2.

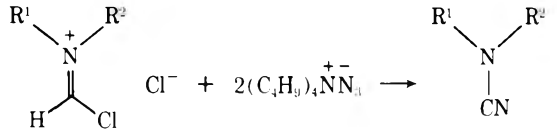
Several aspects of the data recorded in Table III are worthy

Table I. Reaction of *N*-Methyl-*N*-phenylchloroformiminium Chloride (2a) with Various Azide Ion Sources

Azide ion source	Registry no.	Moles azide per mole 2a	Products, %			
			Cyanamide 5a	Tetrazole 7	*N*-Methylaniline	*N*-Methylformanilide (1a)
NaN_3	26628-22-8	1	4	5	52	9
NaN_3		2	39	5	37	11
NaN_3		3	22	2	40	7
$(CH_3)_3SiN_3$	4648-54-8	2	27	*b*	59	*b*
$(C_2H_5)_3NHN_3$	30074-14-7	2	47	5	*b*	5
$(C_4H_9)_4NN_3$	993-22-6	2	75	*a*	9	10

[a] Not detected. [b] Not determined.

Table II. Conversion of Disubstituted Chloroiminium Chlorides into Disubstituted Cyanamides



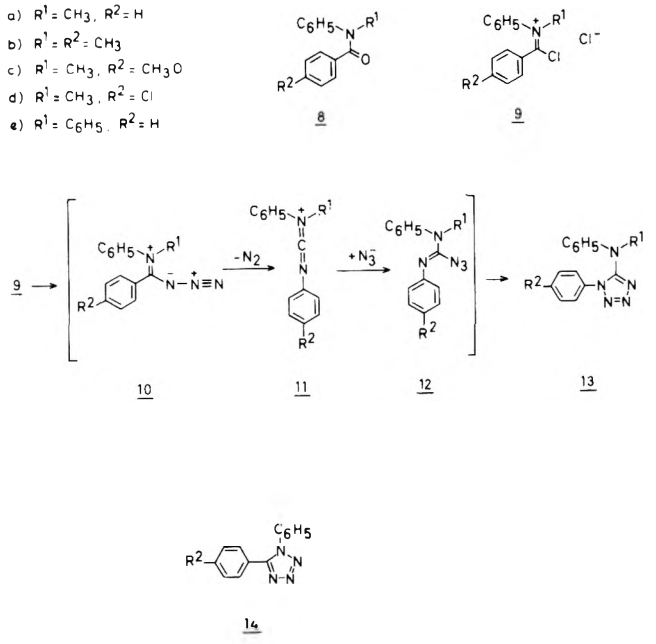
No.	R^1	R^2	Registry no.	% yield	
a	C_6H_5	CH_3	63640-93-7	75	
b	C_6H_5	C_6H_5	63640-94-8	62	
c	i-C_3H_7	i-C_3H_7	54485-04-0	45	(59)[a]
d	C_6H_{11}	C_6H_{11}	63640-95-9	44	
e		$-(CH_2)_5-$	59611-74-4	21	(41)[a]

[a] Yield by GLC.

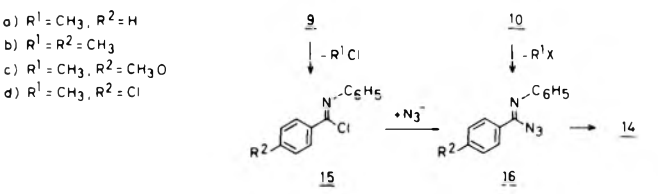
of comment. For example, what is the origin of the 1,5-diaryltetrazoles **14a–d**, *N*-methylaniline, the aromatic aldehydes, and the unsymmetrical urea **18**?

The formation of the 1,5-diphenyltetrazoles **14a–d** can be rationalized in terms of a von Braun type of degradation[16] of **9** and/or **10** (Scheme III). The intermediate imidoyl azide **16** derived directly from **10**, or indirectly via the imidoyl chloride **15**, would then cyclize to **14** in the expected[8] manner. It is probable, however, that the major portion of the 1,5-diaryltetrazole by-product was derived from **15**, which had formed prior to the addition of azide ion. This contention is based on the observation that **15a** and **15d** were formed in 80 and 85% yields (as determined by hydrolysis to the corresponding benzamides) when dimethoxyethane solutions of **9a** and **9d**

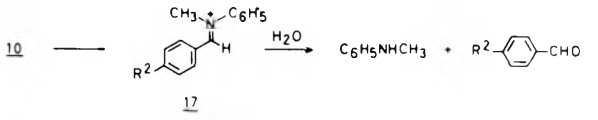
Scheme II



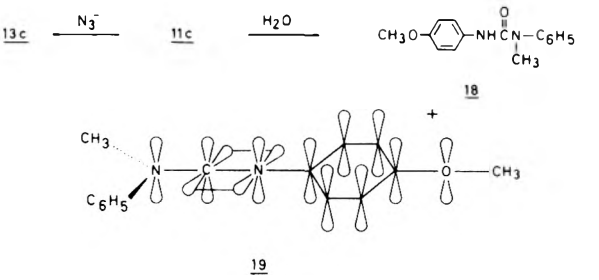
Scheme III



Scheme IV



Scheme V



were heated at reflux temperature (77 °C in Mexico City!) for 24 and 48 h. (The transformation of **8** into **9** required 4–15 h at 60 °C.) Based on the above mechanism, it is not surprising that no 1,5-diphenyltetrazole was formed in the reaction of **9e** with azide ion, since the loss of chlorobenzene from **9e** or phenyl azide from **10e** would be unlikely.

Appreciable amounts of aldehydes and *N*-methylaniline were formed in the reaction of **9a, 9b,** and **9d** with azide ion. In the case of **9a,** at least,[17] equimolar amounts of benzaldehyde and *N*-methylaniline were produced, and this was suggestive of a common intermediate for these substances. Hydrolysis of the iminium salt **17** (Scheme IV) which, in principle, could be derived by hydride transfer from the solvent to **10,** is one plausible[18] source of the above products. Reduction at the chloroiminium salt stage **9** by the solvent is ruled out, because heating **9a** and **9d** in DME gave the corresponding imidoyl chlorides **15a** and **15d** in high yield (see above), and little if any (<3%) of the expected reduction products.

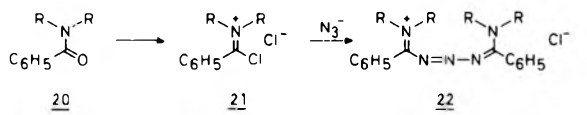
When R^2 was a methoxyl group a considerable amount (42%) of the urea **18** (Scheme V) was isolated. This substance doubtless arose by hydrolysis (during the workup of the reaction) of the carbodimidinium salt **11c**, the reaction of which with azide ion must be slow presumably because of the highly resonance stabilized nature (as shown in **19**) of this species. This latter contention was supported by the isolation of the expected tetrazole **13c** in greater yield (54%), at the expense of the urea (27%), when the reaction was extended from 2 to 24 h. Furthermore, if the reaction was conducted in the presence of excess azide ion (4 mol, see Experimental Section)

Table III. Reaction of Trisubstituted Chloroiminium Chlorides 9 with Tetrabutylammonium Azide

No.	R^1	R^2	Registry no.	Tetrazole 13	Tetrazole 14	$C_6H_5NHR^1$	p-$R^2C_6H_4CHO$	Other
a	CH_3	H	63640-97-1	57	8	10–13	10–13	
b	CH_3	CH_3	63640-98-2	30	4	Present[a]	Present	Start. mat.,[b] 21
c	CH_3	CH_3O	63640-99-3	38	Present[c]	Not det[d]	Not det.	Urea 18, 42 Start. mat., 2
d	CH_3	Cl	63641-00-9	10	28	Present	16	Start. mat., 8
e	C_6H_5	H	63641-01-0	76	0	Not det	Not det	Start. mat., 10

[a] Present by TLC, but percentage not measured. [b] Starting material, i.e., amide 8. [c] Formed in 9% yield together with 13c when 4 equiv of azide ion was used (see Experimental Section). [d] Not determined.

Scheme VI



a) R = CH_3
b) R = C_6H_5

for an extended period of time (46 h), the only products isolated were the tetrazoles **13c** (50%) and **14c** (9%).

It is significant that, of the trisubstituted azidoiminium salts **10**, the yield of rearrangement derived products was the greatest when the migrating group was 4-methoxyphenyl (i.e., **10c**). This is a forseeable result if the reactions described herein are mechanistically analogous to the Curtius, Schmidt, Beckmann, etc., rearrangements.[19]

The successful rearrangement reactions described to this point were those in which the migrating group was either hydrogen or an aryl moiety. It was of interest to determine if the reaction would also occur when the group to be transposed possessed a lesser migratory aptitude. Therefore, the chloroiminium chloride **2f**, derived from *N*-methyl-*N*-phenylcyclohexanecarboxamide, was reacted with tetrabutylammonium azide in the usual manner. A mixture of products resulted, from which *N*-methylaniline (61%) and *N*-methyl-*N*-phenylcyanamide (**5a**, 32%) were isolated. No *N*-cyclohexyl-*N*-methylanilinotetrazole was, however, present in this mixture. The iminium salt **2g**, obtained from diphenylacetamide (**1g**), reacted in an analogous fashion to give diphenylcyanamide (**5b**, 33%), but no 1-methyl-5-diphenylaminotetrazole. No cyclohexene was detectable (as 1,2-dibromocyclohexane) in the reaction of **2f** with azide ion, and therefore the formation of the cyanamides probably takes place via a fragmentation mechanism where the alkyl moiety is lost by a nucleophilic displacement reaction.

A further limitation of the above tetrazole synthesis was encountered for those substrates in which the nitrogen atom did not bear at least one aryl group. For example, the chloroiminium chlorides **21** (Scheme VI) gave orange red salts which could not be obtained analytically pure. Structure **22** has tentatively been assigned to these substances on the basis of the colored nature thereof, as well as literature precedent[20] and a less than satisfactory elemental analysis of the cyclohexyl compound **22b**.

Finally, it is worthy of note that heterocyclic quaternary azidoiminium tetrafluoroborates derived from pyridine, quinoline, isoquinoline, and benzothiazole have been reported[20,21] to be isoable, crystalline substances with thermal stabilities considerably in excess of those observed for the azidoiminium salts described herein.

Experimental Section

The melting points were determined in a Mel-Temp melting point apparatus and are not corrected. The infrared spectra were measured with a Perkin-Elmer Model 237 grating infrared spectrophotometer. The NMR spectra were obtained with a Varian T-60 spectrometer. The ultraviolet spectra were recorded on a Perkin-Elmer Model 402 ultraviolet–visible spectrophotometer. The gas–liquid partition chromatographic analyses were effected using a Hewlett-Packard Model 5750 Research chromatograph using a 6 ft × 1/8 in. SE-30 column and a flame ionization detector. The mass spectra were measured with an Atlas CH-4 spectrometer.

The reactions with the chloroiminium chlorides were carried out in anhydrous 1,2-dimethoxyethane in a nitrogen atmosphere. The apparatus used was flame dried in an atmosphere of nitrogen.

The starting amides were synthesised by known procedures, and the physical constants thereof were identical with those recorded in the literature.

The disubstituted cyanamides were prepared[22] from the appropriate secondary amine and cyanogen chloride or cyanogen bromide.

Tetrabutylammonium Azide. To a 40% tetrabutylammonium hydroxide solution (130 g, 0.2 mol) was added sodium hydroxide (4 g, 0.1 mol), sodium sulfate (28.4 g, 0.2 mol), and sufficient distilled water to give a total volume of 200 mL. A solution of sodium azide (26 g, 0.4 mol) in water (50 mL) was added, and the product was extracted with dichloromethane and worked up in the manner described by Brändström et al.[13] The solid tetrabutylammonium azide was stored in a tightly stoppered brown bottle in a desiccator containing calcium chloride. The azide is very hygroscopic and weighings were performed as rapidly as possible. The weighed samples were redried in high vacuum prior to addition to the reaction mixtures.

Preparation of the Chloroiminium Chlorides. (A) From the Tertiary Amides and Oxalyl Chloride. All of the chloroiminium chlorides except that derived from *N,N*-diphenylacetamide were prepared by the following method.

To a solution of the amide (0.11 mol) in anhydrous dimethoxyethane (10–20 mL), maintained in an atmosphere of dry nitrogen, was added (at room temperature) oxalyl chloride (1.0 mL, 0.016 mol) via a hypodermic syringe. The formation of the chloroformiminium chlorides was usually complete after 4 h at room temperature. The trialkylchloroiminium chlorides formed much more slowly, and heating at 60 °C for 4–15 h was required before consumption of the amide was complete. The progress of the reactions could be followed by the rate of gas evolution, or by TLC examination of an aliquot which had been quenched with excess *n*-butylamine. Most of the chloroiminium chlorides were only partially soluble in dimethoxyethane, and the precipitation of a white solid during the course of the reaction was another indicator of the formation of the desired salt.

(B) Preparation of the Chloroiminium Chloride 2g. The reaction of *N,N*-diphenylacetamide with oxalyl chloride in the manner described above gave a new substance which was not converted into the starting amide with water. A second equivalent of oxalyl chloride had to be added to complete the consumption of the starting material. The reaction was poured into water and extracted with dichloromethane, and the extract was dried over sodium sulfate. The extract was passed through a short column of silica gel, then removal of the solvent in vacuo left a solid, which on crystallization from hexane–dichloromethane gave a solid which decomposed with gas evolution at 113–137 °C. This substance was identified as 5-diphenylamino-2,2-dichloro-3(2*H*)-furanone on the basis of the elemental analysis, spectroscopic properties, and literature precedent:[23] IR ($CHCl_3$) 1718, 1610, 1670 cm^{-1}; NMR ($CDCl_3$) δ 4.57 (s, 1 H), 7.00–7.50 (m, 10 H); MS *m/e* (rel intensity) 323 (5), 322 (5), 321 (21), 320 (7), 319 (29), 258 (10), 256 (30), 193 (20), 164 (18), 161 (62), 159 (100), 77 (46), 46 (65).

Anal. Calcd. for $C_{16}H_{11}Cl_2NO_2$: C, 60.03; H, 3.44; Cl, 22.15; N, 4.38. Found: C, 60.18; H, 3.53; Cl, 22.05; N, 4.29.

To prepare the iminium salt **2g**, a 12.5% solution of phosgene in benzene (50 mL) was added to *N,N*-diphenylacetamide (1.16 g, 0.0055 mol), and the solution was left at room temperature for 3 days. The solvent was removed in vacuo with careful maintainance of anhydrous conditions. Anhydrous dimethoxyethane (20 mL) was added to the residue, and this solution was then reacted with tetrabutylammonium azide (see below).

Reaction of *N*-Methyl-*N*-phenylchloroformiminium Chloride 2a with Sodium Azide. To the chloroiminium chloride **2a**, prepared from 1.5 g (0.011 mol) of *N*-methylformanilide, was added finely pulverized sodium azide (1.45 g, 0.022 mol) in one portion. A vigorous gas evolution commenced in a short while, and the reaction temperature began to rise. The reaction temperature was not permitted to exceed 30 °C by occasional cooling with a water bath. After 5 h, the mixture was partitioned between water and ether, the aqueous phase was extracted with ether, and the combined extracts were washed successively with dilute hydrochloric acid, sodium bicarbonate solution, and saturated sodium chloride solution. The extract was dried over magnesium sulfate and then concentrated in vacuo. The residue was subjected to column chromatography on silica gel (30 g) using benzene and then benzene–ethyl acetate (8:1) as the eluting solvents. The cyanamide-containing fractions were evaporated to give *N*-methyl-*N*-phenylcyanamide (0.57 g, 39%, pure by TLC), which after distillation, bp 85–87 °C (0.2 mm), yielded the pure substance, mp 29–30 °C (lit.[24] 28 °C), identical with an authentic specimen.

Later chromatographic fractions afforded the starting material (0.16 g, 11%) and 5-(*N*-methylanilino)tetrazole (**7**, 0.09 g, 5%), mp 133–135 °C (lit.[10a] 139 °C).

Basification of the aqueous acidic phase described above, followed by ether extraction, gave crude (0.43 g, 37%) *N*-methylaniline.

General Procedure for the Reaction of the N,N-Disubstituted Chloroformiminium Chlorides 2 with Tetrabutylammonium Azide. To the chloroiminium chloride (0.011 mol) was added a solution of tetrabutylammonium azide (6.39 g, 0.0224 mol) in anhydrous dimethoxyethane (15 mL) in a dropwise manner, the temperature being maintained at ≤30 °C as described above. Gas evolution commenced immediately after the addition of the azide solution was started, and the precipitation of a white solid usually began shortly thereafter. This solid redissolved when the addition was completed or after warming of the mixture to 40 °C. The reactions were stirred at room temperature for 4–13 h, or in the case of **2c** and **2e**, the temperature was maintained at 40 °C for 1–2 h. The reactions were worked up as described for the sodium azide reaction, and the crude product was separated from contaminants by column chromatography on silica gel. Final purification of the cyanamide was achieved by distillation in vacuo and/or by crystallization from a suitable solvent. The cyanamides were identical with authentic specimens prepared in the manner previously referred to.

In the case of **5c** and **5e**, the reaction mixtures were subjected to quantitative analysis by GLC at 81 °C (before workup) using *N*-cyanopiperidine (**5e**) and diisopropylcyanamide (**5c**), respectively, as internal standards.

1-Phenyl-5-(*N*-methylanilino)tetrazole (13a) by the Amination of 1-Phenyl-5-chlorotetrazole. A solution of freshly distilled *N*-methylaniline (1.20 g, 0.0122 mol) in anhydrous tetrahydrofuran (25 mL), maintained in a nitrogen atmosphere, was cooled in a dry ice–acetone bath and ethereal methyllithium (6.5 mL of a 1.8 M solution) was added. The mixture was left to come to room temperature, and then solid 1-phenyl-5-chlorotetrazole (1.80 g, 0.01 mol) was added. After 2 h, ethanol (2 mL) and then water (2 mL) were added and the solution was concentrated in vacuo. The residue was partitioned between dichloromethane and water. The organic extracts were washed in turn with hydrochloric acid (3 N), water, and saturated salt solution. The extract was dried over sodium sulfate, and after removal of the solvent in vacuo the residue was crystallized from ether–hexane to give the tetrazole (1.85 g, 74%): mp 73.5–74.5 °C; UV (CH_3OH) 230, 265 nm (ε 10 000, 5010); IR (KBr) 1597, 1563 cm^{-1}; NMR ($CDCl_3$) δ 3.50 (s, 3 H), 6.57–7.00 (m, 5 H), 7.08 (s, 5 H); MS *m/e* (rel intensity) 251 (28), 223 (31), 222 (62), 118 (16), 106 (69), 105 (16), 104 (17), 91 (54), 79 (22), 78 (86), 77 (100), 65 (18), 46 (30).

Anal. Calcd. for $C_{14}H_{13}N_5$: C, 66.91; H, 5.21; N, 27.87. Found: C, 66.86; H, 5.26; N, 28.08.

Reaction of the Trisubstituted Chloroiminium Chlorides 9 with Tetrabutylammonium Azide. Formation of the Tetrazoles 13. 1-Phenyl-5-(*N*-methylanilino)tetrazole (13a). A solution of tetrabutylammonium azide (7.81 g, 0.0275 mol), in dry dimethoxyethane (20 mL), was added to a suspension of the trisubstituted chloroiminium salt **9a** (0.011 mol) in dimethoxyethane (20 mL) at 50–60 °C over a 2-min period. Vigorous gas evolution accompanied by a change in the color of the solution to dark red-orange was observed. The color faded as the reaction progressed and after 0.5 h at the above temperature the solution was poured into water. The products were extracted into ether, and the extract was washed successively with dilute hydrochloric acid, water, and saturated salt solution. The ether solution was dried over magnesium sulfate and evaporated in vacuo. Crystallization of the residue from hexane–ethyl acetate (4:1) gave the tetrazole **13a** (1.58 g, 57%), mp 74–75 °C, identical with the material prepared as described above.

The mother liquor from the above crysatllization was subjected to preparative TLC on silica gel using hexane–ethyl acetate (3:1) as the developing solvent. There was thus obtained an oil (0.12 g, 10%), identified as benzaldehyde by direct comparison of its spectral properties to those of a pure specimen, and a solid which after crystallization from methanol had mp 141–143 °C (lit.[25] 144–145 °C). This latter substance, obtained in 8% yield, was shown to be 1,5-diphenyltetrazole by direct comparison with an authentic sample.

The aqueous acidic phase from above was basified and extracted with ether. The extract was passed through a short column of silica gel to give, after evaporation of the solvent, pure *N*-methylaniline (0.15 g, 13%).

1-(4-Methylphenyl-5-(*N*-methylanilino)tetrazole (13b). The reaction of **9b** with tetrabutylammonium azide was carried out as described for **9a**, and following an identical workup there was obtained the tetrazole **13b**, mp 155–157 °C (ether–hexane), in about 30% yield: UV (CH_3OH) 233, 255 (sh) nm (ε 12 000, 6800); IR ($CHCl_3$) 1595, 1553, 1516 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (s, 3 H), 3.47 (s, 3 H), 6.58–7.13 (m, 9 H); MS *m/e* (rel intensity) 265 (27), 237 (21), 236 (34), 132 (28), 107 (38), 106 (100), 105 (61), 104 (26), 91 (25), 79 (26), 78 (23), 77 (70), 65 (17), 46 (27).

Anal. Calcd. for $C_{15}H_{15}N_5$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.85; H, 5.64; N, 26.37.

In addition, there was isolated 21% of the starting amide and 4% of 1-phenyl-5-(4-methylphenyl)tetrazole (**14b**), which had mp 131–133 °C (lit.[8] 136 °C) after crystallization from hexane–ethyl acetate.

1-(4-Methoxyphenyl)-5-(*N*-methylanilino)tetrazole (13c). The reaction with **9c** was effected in the usual way, and after workup the crude product was triturated with ether to give the tetrazole **13c** (38%) which, after crystallization from methanol, had mp 154–156 °C: UV (CH_3OH) 238, 260 (sh) nm (ε 11 500, 6890); IR ($CHCl_3$) 1595, 1555, 1515 cm^{-1}; NMR ($CDCl_3$) δ 3.47 (s, 3 H), 3.67 (s, 3 H), 6.48–7.05 (m, 9 H).

Anal. Calcd. for $C_{15}H_{15}N_5O$: C, 64.04; H, 5.37; N, 24.90. Found: C, 63.87; H, 5.38; N, 24.76.

The mother liquors from above were chromatographed on a column of silica gel (hexane–ethyl acetate). In addition to the starting material (2%), *N*-methyl-*N*-phenyl-*N'*-(4-methoxyphenyl)urea (**18**) was isolated in 42% yield. It had mp 99–100.5 °C after crystallization from water, and was identical with an authentic sample prepared from *N*-methylaniline and 4-methoxyphenyl isocyanate in hot benzene: UV (CH_3OH) 233 nm (ε 16 600); IR ($CHCl_3$) 3440, 1666, 1619, 1600, 1510 cm^{-1}; NMR ($CDCl_3$) δ 3.27 (s, 3 H), 3.67 (s, 3 H), 6.62 (d, 2 H, J = 9.2 Hz), 7.05 (d, 2 H, J = 9.2 Hz), 7.25 (m, 5 H).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.57; H, 6.51; N, 10.62.

If the reaction was allowed to proceed for 24 h, the yield of the tetrazole **13c** was 54% and that of the urea was 27%. If at the end of 22 h, 2 mol of sodium azide was added and the reaction was continued for a further 24 h (60 °C), the tetrazole **13c** (50%) and 1-phenyl-5-(4-methoxyphenyl)tetrazole (**14c**, 9%) were the only products formed. The latter compound was isolated from the mother liquors obtained from the crystallization of **13c**. After crystallization from hexane–ethyl acetate it had mp 107–109 °C (lit.[26] 110 °C).

1-(4-Chlorophenyl)-5-(*N*-methylanilino)tetrazole (13d). The product mixture, obtained in the standard manner, was separated into its components by preparative TLC on silica gel (hexane–ethyl acetate, 70:30). In this way there was isolated 4-chlorobenzaldehyde (16%), starting material (8%), 1-phenyl-5-(4-chlorophenyl)tetrazole (28%), mp 155–156 °C (lit.[27] 155.5 °C, after crystallization from methanol), and the desired tetrazole **13d** (10%). This substance had mp 165–167 °C after crystallization from methanol: UV (CH_3OH) 232, 260 (sh) nm (ε 15 900, 6220); IR ($CHCl_3$) 1603, 1592, 1554 cm^{-1}; NMR ($CDCl_3$) δ 3.50 (s, 3 H), 6.57–7.11 (m, 9 H).

Anal. Calcd. for $C_{14}H_{12}ClN_5$: C, 58.85; H, 4.23; Cl, 12.41; N, 24.51. Found: C, 58.80; H, 4.09; Cl, 12.24; N, 24.42.

1-Phenyl-5-(diphenylamino)tetrazole (13e). In addition to the starting material (10%) the only other substance formed in this reaction was the tetrazole **13e** (76%). After crystallization from ethyl acetate, it had mp 161–163 °C: UV (CH_3OH) 265 nm (ε 12 900); IR ($CHCl_3$) 1595, 1525 cm^{-1}; MS *m/e* (rel intensity) 313 (29), 285 (19),

284 (45), 169 (25), 168 (100), 167 (52), 77 (40), 46 (26).

Anal. Calcd. for $C_{19}H_{15}N_5$: C, 72.82; H, 4.83; N, 22.33. Found: C, 72.72; H, 4.87; N, 22.09.

Reaction of the Trisubstituted Chloroiminium Chloride 2f with Tetrabutylammonium Azide. The salt **2f** was prepared on a 0.022-mol scale. After the addition of the azide solution (0.055 mol) at 50–60 °C, stirring was continued at this temperature for 15 h. The solvent was distilled at atmospheric pressure, and the distillate was collected in a receiver cooled with a dry ice–acetone bath. The final pot temperature was 160 °C. The distillate was reacted with excess bromine at 0 °C, the solvent and excess bromine were removed in vacuo at room temperature (20 mm), and the residue was examined by GLC. There was no detectable 1,2-dibromocyclohexane present in this mixture.

The pot residue from above was diluted with water and extracted with dichloromethane. The extract was washed successively with dilute hydrochloric acid, sodium bicarbonate solution, and saturated salt solution. The organic phase was dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel. The cyanamide was eluted with hexane–benzene–ethyl acetate (5:4:1) and several more polar products were removed from the column with ethyl acetate. The crude *N*-methyl-*N*-phenylcyanamide (1.15 g) was distilled in vacuo as before to give a pure specimen (0.94 g, 32%) identical with the material prepared from **2a.**

Basification of the acidic fraction from above gave, after ether extraction and the usual manipulation, nearly pure *N*-methylaniline (1.43 g, 61%).

Reaction of the Chloroiminium Chloride 2g with Azide Ion. To a solution of the iminium salt **2g** (0.0055 mol), prepared from **1g** and phosgene as described above, was added a dimethoxyethane solution of tetrabutylammonium azide (0.014 mol) and the resultant was heated at reflux temperature for 18 h. The solution was poured into water and extracted with dichloromethane. The dried (sodium sulfate) extract was evaporated in vacuo, and the residue was chromatographed on a column of silica gel using hexane–benzene (4:1) as the eluting solvent. The first fractions contained diphenylamine, the cyanamide **5b** (0.350 g, 35%), identical with the material prepared from **2b,** was eluted next, and this substance was followed by the starting material (0.50 g, 43%).

Reaction of 21b with Azide Ion. Synthesis of 22b. To a suspension of the iminium salt **21b** (0.0055 M) in dimethoxyethane (10 mL) was added a dimethoxyethane solution of tetrabutylammonium azide (0.015 mol) at 50–60 °C in the usual manner. A red-orange solid precipitated immediately. This substance was collected by filtration and dried in vacuo. It could not be recrystallized, and therefore a sample was dried in vacuo for analysis. The substance thus obtained had mp 210 °C dec, gave positive Beilstein and silver nitrate tests, and decomposed, with gas evolution and the formation of *N,N*-dicyclohexylbenzamide, on treatment with aqueous ethanolic potassium hydroxide. A mass spectrum of the red salt could not be obtained: UV (CH_3OH) 382 nm (ϵ 40 800); IR ($CHCl_3$) 1560 cm^{-1}; NMR ($CDCl_3$) δ 0.83–2.17 (m, 36 H), 2.40–3.10 (m, 4 H), 3.24–3.96 (m, 4 H), 6.53–6.77 (m, 4 H), 6.87–7.33 (m, 6 H).

Anal. Calcd. for $C_{38}H_{30}ClN_5$: C, 74.05, H, 8.83; N, 11.37. Found: C, 73.00; H, 8.80; N, 11.40.

The above data are not inconsistent with structure **22b.**

Acknowledgment. We are greatful to a referree for suggesting the mechanism of formation of the urea **18** from **11c.**

Registry No.—**1a,** 93-61-8; **1b,** 607-00-1; **1c,** 3700-30-3; **1d,** 2269-63-4; **1e,** 2591-86-8; **1f,** 23824-50-2; **1g,** 519-87-9; **2f,** 63641-02-1; **2g,** 63641-03-2; **13a,** 63641-04-3; **13b,** 63641-05-4; **13c,** 63641-06-5; **13d,** 63641-07-6; **13e,** 63641-08-7; **18,** 59849-55-7; **22b,** 63641-09-8; oxalylchloride, 79-37-8; 5-diphenylamino-2,2-dichloro-3(2*H*)-furanone, 636-41-10-1; phosgene, 75-44-5; *N*-methyaniline, 100-61-8; 1-phenyl-5-chlorotetrazole, 14210-25-4.

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Reaction of Di- and Tribromotetrahydro-4*H*-pyran-4-ones with Bases

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The reaction of 3,5-dibromotetrahydro-4*H*-pyran-4-ones (**1a,b**) with morpholine in HMPA gave enamino ketones **2a,b** and **3a,b** as the major products. The reaction of 3,3,5-tribromotetrahydro-4*H*-pyran-4-ones (**5a,b**) with silver acetate in acetic acid gave a mixture of bromo α-diketones **8a,b** and their enol acetates **9a,b** exclusively. Furthermore, dehydrobromination of **8a,b** with DBU or Dabco gave corresponding 3-hydroxy-4*H*-pyran-4-ones **10a,b.** However the reaction of diethyl 3,3,5-tribromotetrahydro-4*H*-pyran-4-one-2,6-dicarboxylate (**5c**) with silver acetate in acetic acid afforded bromo α-diketones **8c,** diethyl 3-hydroxy-4*H*-pyran-4-one-2,6-dicarboxylate (**10c**), and diethyl 3,5-dibromo-4*H*-pyran-4-one-2,6-dicarboxylate (**11**).

Of the simple tetrahydro-4*H*-pyran-4-ones, only a few have received attention in the literature with respect to their oxidation product.

In this paper, we wish to report the formation of tetrahydro-4*H*-pyran-3,4-diones and their derivatives from 3,5-dibromo- or 3,3,5-tribromotetrahydro-4*H*-pyran-4-ones.

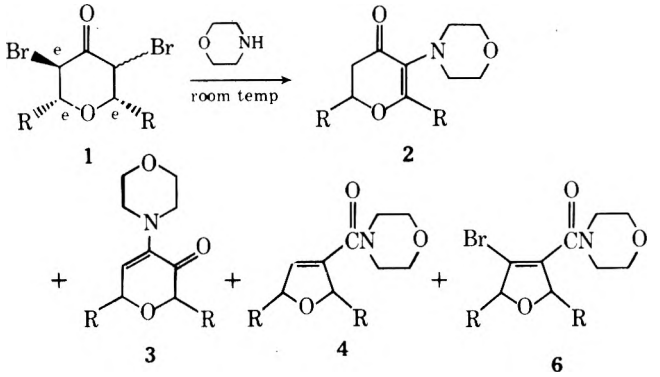
Table I. The Reaction of 1 with Morpholine in Several Solvents[a]

Dibromide	Solvent	Total yield, %[b]	Product ratio[c] 2	3	4	6
1a	HMPA	46	25	75		Tr
1b	HMPA	80	26	50	6	18
1b[d]	HMPA	80		76	6	18
1a	DMF	34	45	33	11	11
1b	DMF	72	20	20	40	20
1b[e]	DMF	55	24	24	48	4
1a	Ether	32	15	8	77	
1b	Ether	77	8	9	55	28
1b[e]	Ether	50	10	15	71	4

[a] The reaction was carried out at room temperature (15–18 °C). [b] Isolated yield. [c] The ratio was determined by GLC. [d] Large (10 equiv) excess of morpholine was used. [e] Cis isomer was used.

3,5-Dibromotetrahydro-4*H*-pyran-4-ones (**1a,b**) and 3,3,5-tribromotetrahydro-4*H*-pyran-4-ones (**5a-c**) were prepared from corresponding tetrahydro-4*H*-pyran-4-ones[1a-c] with dioxane–dibromide in ether in good yield. The reaction of *cis*-3,5-dibromotetrahydro-4*H*-pyran-4-one (**1a**) with 5 equiv of morpholine in HMPA gave 5-morpholino-2,3-dihydro-4*H*-pyran-4-one (**2a**) and 4-morpholino-3,6-dihydro-2*H*-pyran-3-one (**3a**) without any formation of Favorskii rearrangement product.

However a similar treatment of *trans*-3,5-dibromo-*cis*-2,6-dimethyltetrahydro-4*H*-pyran-4-one (**1b**) with morpholine afforded enamino ketones **2b** and **3b** as the major products together with a minor amount of 2,5-dihydro-2,5-dimethylfuran-3-carboxymorpholide (**4b**) and 4-bromo-2,5-dihydro-2,5-dimethylfuran-3-carboxymorpholide (**6b**). The

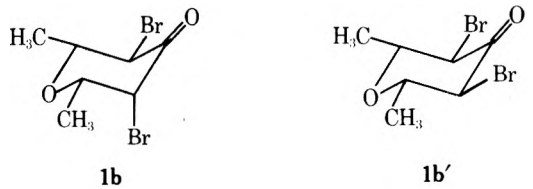


1 2 3 4 6

a, R = H
b, R = CH_3

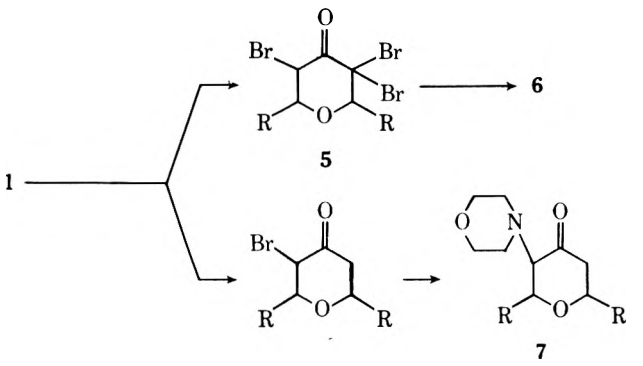
structures of these products were assigned on the basis of their IR, NMR, and mass spectra, and by elemental analysis.

The reaction of dibromide **1a,b** with morpholine in several solvents was examined and the experimental data, summarized in Table I, suggest that enamino ketones are the main products in polar aprotic solvents such as HMPA, whereas in ether, Favorskii rearrangement products predominate. Isomerization of **2** and **3** was not observed under the reaction conditions, and a large excess of morpholine increased the formation of **3** rather than that of **2**. These solvent effects are parallel to those observed in the reaction of 2,6-dibromocyclohexanone with secondary amines.[2] In the 2,6-dimethyl case, trans form **1b** was more reactive than cis form **1b**. This is due



1b **1b′**

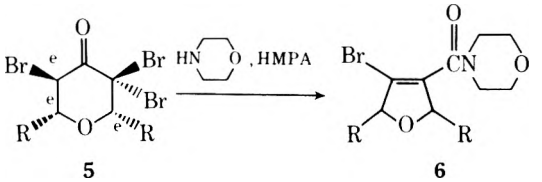
Scheme I



to the trans isomer and axial bromine undergoing a more facile back-side nucleophilic attack at C-5 by morpholine.

A possible route[3] for the formation of **6** is outlined in Scheme I. Dibromide **1** undergoes disproportionation of bromine to produce tribromide **5**, which then suffers a Favorskii rearrangement to give **6**. Although **7** has not been isolated, its presence in the reaction mixture from **1a** was suggested by GLC–mass spectroscopy.

The reaction of **5a,b** with 6 equiv of morpholine in HMPA at room temperature gave the corresponding Favorskii rearrangement products **6a,b** in quantitative yield. These results

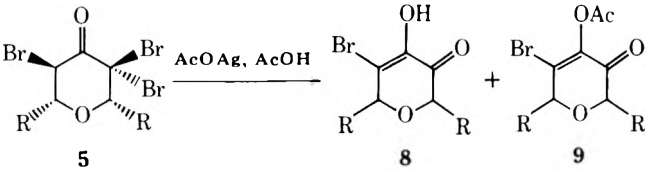


5 6

a, R = H
b, R = CH_3

suggest that the proton at C-5 was easily abstracted by morpholine, followed by ejection of the C-3 bromine atom to produce a cyclopropanone intermediate, which is then cleavaged to compound **6a,b**.

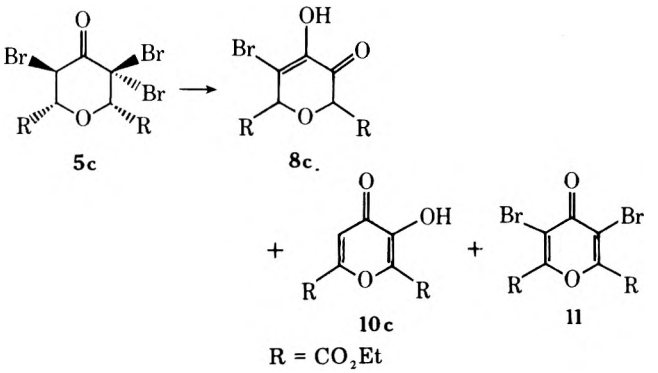
We next examined the reaction of **5a,b** with silver acetate in acetic acid, which gave hydroxypyrones **8a,b** and their enol



5 8 9

a, R = H (90%)
b, R = CH_3 (93%)

acetates **9a,b** in good yield. The proportion of these products (**8a,b**) and (**9a,b**) was determined by NMR and GLC analysis. In this case, no Favorskii rearrangement product was observed in any solvents. The reaction of **5** with silver acetate in acetonitrile afforded **9** (**a**, 90%; **b**, 88%) as a single product. Ace-



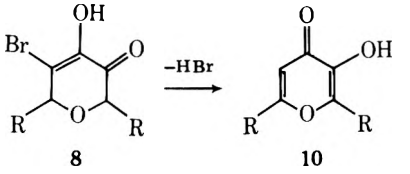
5c **8c** **10c** **11**

R = CO_2Et

tate **9** was also obtained from **8** by treatment with acetic anhydride in the presence of sodium acetate.

Similar treatment of **5c** (R = CO_2Et) with silver acetate gave hydroxypyrone **8c** (20%), diethyl meconate (**10c**, 20%), and diethyl 3,5-dibromochelidonate (**11**, 40%). It is suggested that in the case of R = CO_2Et, the proton at C-2 in the compound of **8c** initially produced is easily abstracted by weak base, permitting dehydrobromination to diethyl meconate (**10c**).

Finally, we investigated the dehydrobromination of **8a,b** with such strong bases as DBU and Dabco. The reaction of **8a** with 1,8-diazabicyclo[5.4.0]undecene (DBU) in benzene at room temperature afforded pyromeconic acid (**10a**). Similarly, 6-methyl maltol (**10b**) was obtained by the treatment of **8b**



8 **10**

a, R = H
b, R = CH_3

with diazabicyclo[2.2.2]octane (Dabco) in pyridine. The structures of 3-hydroxy-4*H*-pyran-4-ones **10a–c** were confirmed by agreement with IR, NMR, and mass spectra and mixed melting point determination with that of those authentic samples.

Experimental Section

General. All the points are uncorrected. Infrared spectra were run on a Hitachi Model 215 spectrophotometer. Proton nuclear magnetic resonance spectra were recorded on a JEOL C-60 spectrometer with tetramethylsilane as an internal reference. The mass spectra were determined on a Hitachi RMU-6E spectrometer. For column chromatography Wakogel C-200 (Wako Pure Chemical Industries) was used. *cis*-2,6-Dimethyltetrahydro-4*H*-pyran-4-one[1b] [bp 61 °C (14 mm Hg)] and *cis*-2,6-diethoxycarbonyltetrahydro-4*H*-pyran-4-one[1c] (mp 82–83 °C) were prepared by the reported method.

***cis*-3,5-Dibromotetrahydro-4*H*-pyran-4-one (1a).** Bromine (16.2 g, 0.1 mol) was added into dioxane (64 g) with stirring over a period of 30 min. Tetrahydro-4*H*-pyran-4-one[1a] (5.0 g, 0.05 mol) in 20 mL of ether was added to the mixture at 0 °C, and the mixture was then stirred for 2 h. The resulting slightly yellow tinged solution was poured into 20 mL of water. The organic layer was separated and the aqueous layer was extracted with ether. The combined ethereal solution was well washed with water and the solution was dried ($MgSO_4$). After evaporation of the ether, the residue was recrystallized from dichloromethane to give 10.5 g (82%) of **1a**: mp 156–157 °C (lit.[4] mp 156–157 °C); IR (KBr) 1745 cm^{-1}.

***trans*- and *cis*-3,5-Dibromo-*cis*-2,6-dimethyltetrahydro-4*H*-pyran-4-one (1b and 1b').** Bromination of *cis*-2,6-dimethyltetrahydro-4*H*-pyran-4-one[1b] at −15 °C by a method similar to that described for **1a** afforded only trans dibromide **1b** (87%): mp 42–43 °C; IR (KBr) 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.38 (d, 3 H, *J* = 6.0 Hz), 1.57 (d, 3 H, *J* = 6.0 Hz), 3.79 (m, 2 H, 2- and 6-axial protons), 4.33 (d, 1 H, *J* = 2.0 Hz, 3-equatorial proton), 5.02 (d, 1 H, *J* = 11 Hz, 5-axial proton).

Anal. Calcd for $C_7H_{10}Br_2O_2$: C, 29.40; H, 3.52; Br, 55.88. Found: C, 29.40; H, 3.51; Br, 55.69.

When this reaction was carried out at 0 °C, a mixture of **1b** and *cis*-dibromide **1b'** was obtained and the mixture was then chromatographed on a silica gel column using benzene–hexane (1:2) as eluent to give **1b** (66.5%) and **1b'** (13.5%): mp 149–150 °C; IR (KBr) 1745 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (d, 6 H, *J* = 6.0 Hz), 3.75 (d q, 2 H, *J* = 12 and 6.0 Hz, 2- and 6-axial protons), 4.40 (d, 2 H, *J* = 12 Hz, 3- and 5-axial protons).

Anal. Calcd for $C_7H_{10}Br_2O_2$: C, 29.40; H, 3.52; Br, 55.88. Found: C, 29.47; H, 3.60; Br, 55.88.

The Reaction of 1a with Morpholine. Morpholine (13.3 g, 0.15 mol) was added to a solution of **1a** (7.89 g, 0.03 mol) in 50 mL of HMPA with stirring at 0 °C. After the mixture was stirred for 24 h at room temperature, dry ether was added, and the precipitated morpholine hydrobromide was filtered off. Ether, excess morpholine, and HMPA were removed from the filtrate under vacuum and the residue [small amounts of **6a** and **7a** could be detected by GLC: **7a**, *m/e* 185 (M^+)] was chromatographed on a silica gel column using benzene–ethyl acetate (9:1). The earlier fraction gave 1.9 g (34.5%) of **3a** (mp 77.5–79 °C) and the latter fraction gave 0.63 g (11.5%) of **2a** (mp 83.5–85.0 °C). **2a**: IR (KBr) 1670, 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.55 (t, 2 H, *J* = 7.5 Hz), 2.85 (m, 4 H), 3.81 (m, 4 H), 4.42 (t, 2 H, *J* = 7.5 Hz), 7.13 (s, 1 H); mass (*m/e*) 183 (M^+), 98 (base).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.59; H, 7.09; N, 7.20.

3a: IR (KBr) 1675, 1615 cm^{-1}; NMR ($CDCl_3$) δ 2.93 (m, 4 H), 3.84 (m, 4 H), 4.21 (s, 2 H), 4.52 (d, 1 H, *J* = 3.0 Hz), 6.05 (t, 1 H, *J* = 3.0 Hz); mass (*m/e*) 183 (M^+), 67 (base).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.79; H, 7.17; N, 7.39.

This reaction was carried out in ether; from **1a** (7.89 g, 0.03 mole) and 13.3 g (0.15 mole) of morpholine, **2a** (0.14 g, 2.5%), **3a** (0.27 g, 5.0%), and **4a** (1.35 g, 24.5%) were obtained. **4a**: $n^{20}D$ 1.5123; IR (neat) 1650, 1613 cm^{-1}; NMR (CCl_4) δ 3.57 (s, 8 H), 4.65 (s, 4 H), 5.87 (s, 1 H); mass (*m/e*) 183 (M^+).

The Reaction of 1b with Morpholine. Similar reaction was carried out according to the procedure for **1a** described above. In place of **1a**, **1b** (8.7 g, 0.03 mole) in HMPA was used, and the resulting oil was chromatographed on a silica gel column using benzene as eluent to afford **2b** (1.26 g, 25%), **3b** (2.52 g, 40%), **4b** (0.42 g, 5.0%), and **6b** (0.87 g, 10%). **2b**: mp 85–86 °C; IR (KBr) 1690, 1615 cm^{-1}; NMR (CCl_4) δ 1.33 (d, 3 H, *J* = 6.0 Hz), 2.08 (s, 3 H), 2.28 (d, 1 H, *J* = 7.0 Hz), 2.30 (d, 1 H, *J* = 9.0 Hz), 2.90 (m, 4 H), 3.60 (m, 5 H); mass (*m/e*) 211 (M^+), 43 (base).

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 63.08; H, 8.54; N, 6.58.

3b: $n^{20}D$ 1.5068; IR (neat) 1690, 1615 cm^{-1}; NMR (CCl_4) δ 1.30 (d, 6 H, *J* = 7.0 Hz), 2.79 (m, 4 H), 3.77 (m, 5 H), 4.46 (q, 1 H, *J* = 7.0 Hz), 5.57 (d, 1 H, *J* = 2.0 Hz); mass (*m/e*) 211 (M^+), 43 (base). **4b**: $n^{20}D$ 1.5023; IR (neat) 1655, 1615 cm^{-1}; NMR (CCl_4) δ 1.24 (d, 3 H, *J* = 3.0 Hz), 1.31 (d, 3 H, *J* = 3.0 Hz), 3.55 (s, 8 H), 4.90 (br s, 2 H), 5.70 (s, 1 H); mass (*m/e*) 211 (M^+), 43 (base).

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.23; H, 8.32; N, 6.58.

6b: mp 71–73 °C; IR (KBr) 1655, 1610 cm^{-1}; NMR (CCl_4) δ 1.26 (d, 3 H, *J* = 5.0 Hz), 1.36 (d, 3 H, *J* = 5.0 Hz), 3.60 (s, 8 H), 4.55 (m, 2 H); mass (*m/e*) 276/274 ($M^+ - CH_3$), 43 (base).

Anal. Calcd for $C_{11}H_{16}BrNO_3$: C, 45.53; H, 5.56; Br, 27.54; N, 4.83. Found: C, 45.61; H, 5.52; Br, 27.79; N, 4.69.

3,3,5-Tribromotetrahydro-4*H*-pyran-4-one (5a). Tetrahydro-4*H*-pyran-4-one (3.5 g, 0.035 mol) in 20 mL of ether was added to a stirred mixture of 30 mL of dioxane and 16.8 g (0.105 mol) of bromine at room temperature. After the mixture was stirred for 6 h at 28–30 °C, the resulting reaction mixture was then poured into water. The organic layer was separated and the aqueous layer was extracted with ether. The combined ethereal solution was washed with water, dried, and evaporated under reduced pressure. Recrystallization of the residue (13.7 g) from benzene gave 10.3 g of **5a**, mp 131.5–132.5 °C, in 86.5% yield: IR (KBr) 1740 cm^{-1}; NMR ($CDCl_3$) δ 3.60 (d, 1 H, *J* = 12 Hz), 4.04 (d, 1 H, *J* = 12 Hz), 4.40 (m, 1 H), 4.53 (d, 1 H, *J* = 12 Hz), 5.63 (d d, 1 H, *J* = 7.0 and 12 Hz, 5-axial proton).

Anal. Calcd for $C_5H_5Br_3O_2$: C, 17.83; H, 1.49; Br, 71.17. Found: C, 17.83; H, 1.50; Br, 71.44.

The following compounds were also prepared from *cis*-2,6-disubstituted tetrahydro-4*H*-pyran-4-ones:[1b,c] **3,3,5-Tribromo-*cis*-2,6-dimethyl tetrahydro-4*H*-pyran-4-one (5b)**, mp 87–88 °C, in 89% yield: IR (KBr) 1745 cm^{-1}; NMR ($CDCl_3$) δ 1.54 (d, 3 H, *J* = 6.0 Hz), 1.60 (d, 3 H, *J* = 6.0 Hz), 3.65 (q, 1 H, *J* = 6.0 Hz), 3.80 (d q, 1 H, *J* = 6.0 and 11 Hz), 5.15 (d, 1 H, *J* = 11 Hz, 5-axial proton).

Anal. Calcd for $C_7H_9Br_3O_2$: C, 23.04; H, 2.49; Br, 65.70. Found: C, 23.14; H, 2.53; Br, 65.68.

Diethyl 3,3,5-tribromotetrahydro-4*H*-pyran-4-one-*cis*-2,6-dicarboxylate (5c), mp 56–58 °C, in 85% yield: IR (KBr) 1750 cm^{-1}; NMR (CCl_4) δ 1.38 (t, 6 H, *J* = 7.0 Hz), 4.35 (m, 6 H), 5.18 (d, 1 H, *J* = 11 Hz, 5-axial proton).

Anal. Calcd for $C_{11}H_{13}Br_3O_6$: C, 27.47; H, 2.73; Br, 49.84. Found: C, 27.63; H, 2.65; Br, 49.84.

The Reaction of 5a with Morpholine. Morpholine (5.2 g, 0.06 mol) was added gradually to a stirred solution of 3.37 g (0.01 mol) of **5a** in 5 mL of HMPA at 0 °C, and the mixture was then stirred for 24 h at room temperature. Dry ether was added to the reaction mixture and the precipitated morpholine hydrobromide was filtered off. Ether, morpholine, and HMPA were removed in vacuo from the filtrate and the residue was chromatographed on a silica gel column. Elution with benzene gave 2.6 g of **6a** as crystals, mp 71–73 °C, in quantitative yield:

IR (KBr) 1660 (C=O), 1620 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 3.70 (br s, 8 H), 4.77 (br s, 4 H).

Anal. Calcd for $C_9H_{12}BrNO_3$: C, 41.24; H, 5.72; Br, 30.49; N, 5.34. Found: C, 41.63; H, 4.66; Br, 30.42; N, 5.21.

Similarly, **4-bromo-2,5-dihydro-2,5-dimethylfuran-3-carboxymorpholide (6b)** was obtained as crystals, mp 71–72 °C, in quantitative yield: IR (KBr) 1655 (C=O), 1610 (C=C) cm^{-1}; NMR (CCl_4) δ 1.26 (d, 3 H, J = 5.0 Hz), 1.36 (d, 3 H, J = 5.0 Hz), 3.60 (br s, 8 H), 4.55 (m, 2 H).

Anal. Calcd for $C_{11}H_{16}BrNO_3$: C, 45.53; H, 5.56; Br, 27.54; N, 4.83. Found: C, 45.61; H, 5.52; Br, 27.79; N, 4.69.

The Reaction of 5a with Silver Acetate. A mixture of 3.79 g (11.2 mmol) of **5a** and 6.0 g (40 mmol) of silver acetate in 30 mL of acetic acid was warmed at 28–30 °C with stirring. After the mixture was stirred for 3 h, the precipitated silver bromide was filtered off, and acetic acid was removed in vacuo. The residue was chromatographed on a silica gel column using benzene as eluent to give a mixture of 2.1 g of **8a** and **9a** in 90% yield (**8a/9a** = 2:1; by GLC and NMR spectroscopic assay). **8a:** mp 77–78 °C; IR (KBr) 3350 (OH), 1675 (C=O), 1650 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 4.30 (m, 2 H), 4.57 (m, 2 H), 5.96 (br s, 1 H).

Anal. Calcd for $C_5H_5BrO_3$: C, 31.12; H, 2.61; Br, 41.40. Found: C, 31.17; H, 2.23; Br, 41.82.

9a: bp 91–93 °C (0.15 mm Hg); mp 50–51 °C; IR (KBr) 1780, 1710 (C=O), 1640 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 3 H), 4.30 (s, 2 H), 4.65 (s, 2 H); mass (*m/e*) 236/234 (M^+), 43 (base).

The Reaction of 5b with Silver Acetate. By the method similar to that described above, reaction temperature was 40–45 °C for 3 h; 7.33 g of **5b** afforded a mixture of 4.75 g of **8b** (mp 62–63 °C) and **9b** [bp 108–110 °C (0.25 mm Hg), mp 125.5–126.5 °C] in 93% yield. (**8b/9b** = 1:1). Pure **8b** and **9b** were obtained by preparative GLC (20% Silicon DC-200 column 120 °C). **8b:** IR (KBr) 3340 (OH), 1680 (C=O), 1640 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.43 (d, 3 H, J = 6.0 Hz), 1.55 (d, 3 H, J = 6.0 Hz), 4.20 (d q, 1 H, J = 2.0 and 6.0 Hz), 4.65 (d q, 1 H, J = 2.0 and 6.0 Hz), 6.33 (s, 1 H).

Anal. Calcd for $C_7H_9BrO_3$: C, 38.04; H, 4.10; Br, 36.15. Found: C, 38.10; H, 4.19; Br, 36.54.

9b: IR (KBr) 1780, 1710 (C=O), 1630 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.40 (d, 3 H, J = 6.0 Hz), 1.62 (d, 3 H, J = 6.0 Hz), 2.27 (s, 3 H), 4.25 (d q, 1 H, J = 2.0 and 6.0 Hz), 4.77 (d q, 1 H, J = 2.0 and 6.0 Hz).

Anal. Calcd for $C_9H_{11}BrO_4$: C, 41.09; H, 4.21; Br, 30.37. Found: C, 41.02; H, 4.22; Br, 30.03.

The Reaction of 5c with Silver Acetate. A mixture of 3.30 g of **5c** and 4.0 g of silver acetate in 14 mL of acetic acid was warmed at 50–55 °C for 6 h. After workup similar to that of **5a** described above, the residue was chromatographed on silica gel and eluted with benzene–isopropyl ether (4:1) to give 1.2 g of **11** and a mixture of **8c** and **10c**. The latter fraction was rechromatographed on silica gel using benzene–isopropyl ether (6:1) to afford pure 0.6 g of **8c** and 0.4 g of **10c**. **11:** mp 121–122 °C (lit.[5] mp 126 °C); IR (KBr) 1745 and 1660 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.42 (t, 6 H, J = 7.0 Hz), 4.40 (q, 4 H, J = 7.0 Hz). **8c:** mp 85–87 °C; IR (KBr) 3420 (OH), 1740, 1725, 1690 (C=O), 1645 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.30 (t, 6 H, J = 7.0 Hz), 4.27 (q, 4 H, J = 7.0 Hz), 5.27 (d, 1 H, J = 2.0 Hz), 5.43 (d, 1 H, J = 2.0 Hz), 9.57 (br s, 1 H).

Anal. Calcd for $C_{11}H_{13}BrO_7$: C, 39.19; H, 3.89; Br, 23.70. Found: C, 39.53; H, 4.13; Br, 23.21.

10c: mp 111–112 °C (lit.[6] 111.5 °C); IR (KBr) 3300 (OH), 1745, 1660 (C=O), 1610, 1595 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.36 (t, 3 H, J = 7.0 Hz), 1.40 (t, 3 H, J = 7.0 Hz), 4.43 (q, 2 H, J = 7.0 Hz), 4.50 (q, 2 H, J = 7.0 Hz), 7.20 (s, 1 H), 7.80 (br s, 1 H).

3-Hydroxy-4*H*-pyran-4-one (10a). To a mixture of 181 mg of **8a** in 3 mL of benzene was added 220 mg of 1,8-diazabicyclo[5.4.0]undecene at 0 °C. After the mixture was stirred for 48 h at 16–18 °C, 0.2 mL of concentrated hydrochloric acid was added, and the precipitated mass was filtered off and extracted with chloroform. The organic layer was washed with water and evaporated to leave an oil of 39 mg. The oil was distilled under 50 mm Hg reduced pressure and then sublimation gave 19 mg of pure **10a:** mp 115–117 °C (lit.[7] mp 117 °C). A mixed melting point determination with an authentic sample from comenic acid[7] indicated no depression.

3-Hydroxy-2,6-dimethyl-4*H*-pyran-4-one (10b). To a mixture of 2.0 g of **8b** and **9b** (**8b/9b** = 1:1) in 6 mL of pyridine was added 0.80 g of diazabicyclo[2.2.2]octane at room temperature. After the mixture was stirred for 2 h at 70–75 °C, the precipitate was filtered off and pyridine was removed under reduced pressure. The residue was then chromatographed on silica gel using benzene as eluent to give crude **10b** (0.9 g). Sublimation of the crude crystals afforded a pure sample of **10b** (0.6 g), mp 162–163 °C (lit.[8] mp 162.5 °C), in 53% yield. The infrared spectrum and the other chemical properties were identical with those of authentic sample.[9]

Registry No.—**1a,** 63641-11-2; **1b,** 63599-80-4; **1b',** 63599-81-5; **2a,** 63599-82-6; **2b,** 63599-83-7; **3a,** 63599-84-8; **3b,** 63599-85-9; **4a,** 63599-86-0; **4b,** 63599-87-1; **5a,** 63599-88-2; **5b,** 63599-89-3; **5c,** 63599-90-6; **6a,** 63599-91-7; **6b,** 63599-92-8; **8a,** 63599-93-9; **8b,** 63599-94-0; **8c,** 63599-95-1; **9a,** 63599-96-2; **9b,** 63599-97-3; **10c,** 729-63-5; **11,** 843-08-3; tetrahydro-4*H*-pyran-4-one, 29943-42-8; *cis*-2,6-dimethyltetrahydro-4*H*-pyran-4-one, 14505-80-7; morpholine, 110-91-8.

Reference and Notes

(1) (a) Terahydro-4*H*-pyran-4-one [bp 58–59 °C (15 mm Hg)] was obtained by means of ozonolysis of 4-methylenetetrahydro-4*H*-pyran in 80% yield: ref bp 59–60 °C (13 mm Hg), G. R. Owen and C. B. Reese, *J. Chem. Soc. C*, 2401 (1970). (b) C. Eskenazi, H. Sliwa, and P. Maitte, *Bull. Soc. Chim. Fr.*, 2951 (1971). (c) J. Attenburrow, *J. Chem. Soc.*, 571 (1945).
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Reaction of Thiophene-2,3-dicarbonyl Chloride with Aluminum Chloride and Benzene

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The reaction of thiophene-2,3-dicarbonyl chloride (**1**) with $AlCl_3$ and benzene has been shown to yield 4,9-dihydronaphtho[2,3-*b*]thiophene-4,9-dione (**2**), 1,1-diphenyl-1*H*-thieno[2,3-c]furan-3-one (**3**), 2,3-dibenzoylthiophene (**4**), 3-benzoylthiophene-2-carbonyl chloride (**5**), and 3-benzoylthiophene-2-carboxylic acid (**6**) depending upon the reaction conditions. Ultraviolet spectroscopy was used to analyze the neutral product mixtures composed of **2, 3,** and **4**. A discussion of possible reaction pathways in which **5** apparently leads to the remaining products is included.

The objectives of the present work were to extend the previous investigations of the thiophene series to thiophene-2,3-dicarbonyl chloride in order to determine what products are produced and to attempt to gain an understanding of the mechanism of their formation.

The reaction of benzene with phthaloyl chloride[1,2] and various furan[2-4] and pyrrole[5] derivatives has been extensively investigated. The reaction with thiophene-3,4-dicarbonyl chloride has previously been reported[6] by this laboratory. The present work reports the extension of the thiophene series to thiophene-2,3-dicarbonyl chloride (**1**). Ultimately, as many as five products were isolated and characterized. Evidence indicates that 3-benzoylthiophene-2-carbonyl chloride (**5**), the only isolated keto acid chloride, leads to all the remaining products.

Scheme I depicts the reaction sequence used for this acylation study.

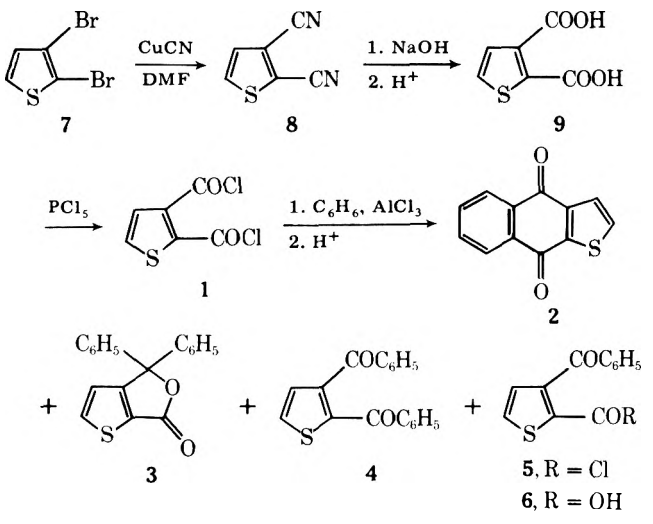
Thiophene-2,3-dicarboxylic acid (**9**) was prepared from the readily available 2,3-dibromothiophene (**7**) using a modified procedure previously used for the synthesis of thiophene-3,4-dicarboxylic acid.[7] Hydrolysis of 2,3-dicyanothiophene (**8**) using aqueous NaOH instead of the previously used ethylene glycol–KOH allowed for a more facile isolation of **9**. Substitution of phosphorus pentachloride for the previously used thionyl chloride in the synthesis of **1** eliminated the formation of thiophene-2,3-dicarboxylic acid anhydride which was shown to be present in significant amounts when thionyl chloride was used to produce **1** from **9**.

Initial investigations of product mixtures formed by the acylation of benzene with **1** readily yielded the previously described 4,9-dihydronaphtho[2,3-*b*]thiophene-4,9-dione (**2**).[7] A second neutral product, later shown to be 1,1-diphenyl-1*H*-thieno[2,3-*c*]furan-3-one (**3**), was also isolated. Residual oils of the neutral fraction indicated (TLC) a third product, later shown to be 2,3-dibenzoylthiophene (**4**). Washing the initial acylation mixtures with $NaHCO_3$ yielded a keto acid, shown to be 3-benzoylthiophene-2-carboxylic acid (**6**). Under mild reaction conditions **5** could readily be isolated as the major product.

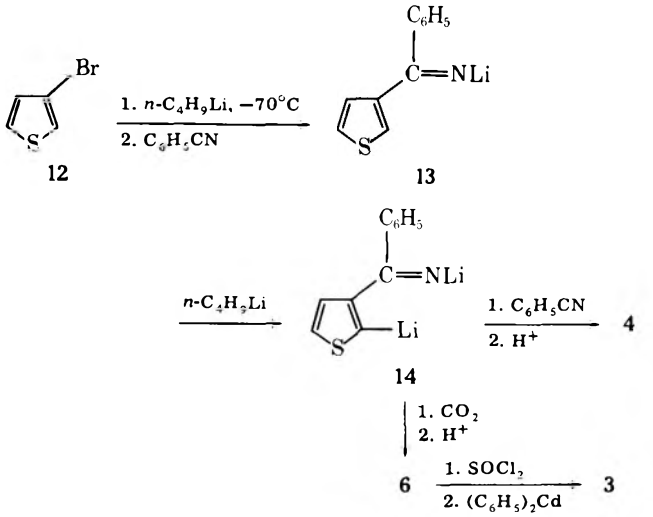
Identification of **3–6** required independent synthesis. Since **3, 5,** and **6** each have one positional isomer that theoretically could be a product, these isomers also required synthesis.

The keto acid **6**,[8] and its isomer 2-benzoylthiophene-3-carboxylic acid (**10**)[9] have been reported. The lengthy synthetic sequences described precluded their use in this work. Schemes II and III describe the routes used for the synthesis

Scheme I



Scheme II



Scheme III

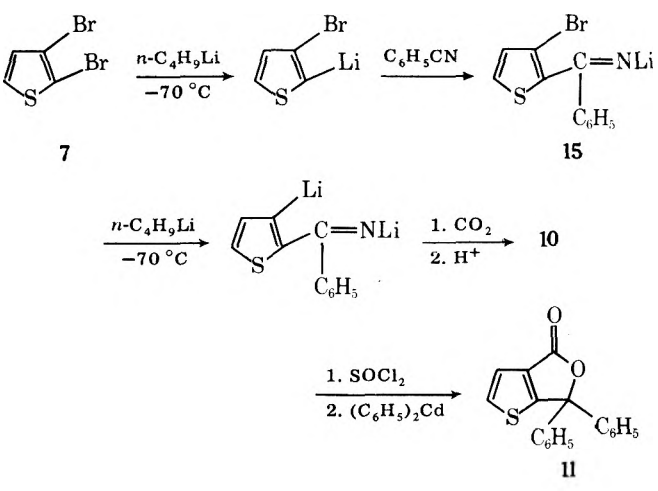


Table I. Reaction Conditions and Product Yield Data for the Acylation of Benzene with 1

Run[a,b]	Moles of C_6H_6	Solvent	Temp, °C	% yields[c] 2	3	4	5	6
1	0.5	C_6H_6	10	2.2	67	14		1.7
2	0.5	C_6H_6	25	4.0	64	13		0.97
3	0.5	C_6H_6	50	10	62	10		1.1
4	0.5	C_6H_6	80	17	50	10		1.1
5	0.02	$(CH_2Cl)_2$	0	1.5	3.4	0.9	29	9.0
6	0.02	$(CH_2Cl)_2$	25	61	7.8	2.3		
7	0.04	$(CH_2Cl)_2$	0	1.4	48	4.8	6.5	16
8	0.04	$(CH_2Cl)_2$	25	14	62	5.8		4.7

[a] 0.02 mol of diacid chloride used. [b] 0.044 mol of $AlCl_3$. [c] An average of duplicate runs.

of **3–6**, **10**, and the isomer of **3**, 3,3-diphenyl-3*H*-thieno[2,3-c]furan-1-one (**11**).

Use of 3-bromothiophene (**12**) in the one-pot reaction technique developed by Gronowitz and Michael[10] allowed for the consecutive introduction of two functional groups into the thiophene nucleus. Treatment of the intermediate **13** with a second mole of *n*-butyllithium and benzonitrile, followed by hydrolysis, gave **4** in 52% yield. Reaction of intermediate **14** with dry ice produced **6** in 70% yield. Lactone **3** was obtained in 62% yield by the reaction of the acid chloride of **6** with diphenylcadmium.[11] An attempted synthesis of **3** by means of the reaction of 3-thienyllithium with benzophenone followed by carboxylation at C-2 and lactonization of the expected hydroxy acid failed when the initial 3-thienyllithium–benzophenone adduct precipitated from the reaction mixture, thus preventing the desired hydrogen abstraction at C-2.

The success of Scheme III depends on the known[12] selective halogen–metal interchange of the 2-bromine of **7**. The 3-bromine permits carboxylation at C-3 to produce **10** without isolation of any intermediates formed from **7**.

With authentic samples of **2–6**, **10**, and **11** available, the acylation products of Scheme I were shown to be exclusively **2–6**.

In order to acquire some insight into the acylation pathway, a number of studies were carried out. A study in which the temperature and the amount of benzene were altered, resulting in product ratio changes, was first conducted. During such preliminary studies, it became apparent that an accurate method of analysis of the initial neutral acylation mixtures was needed. Isolation of each component by column chromatography was unsuccessful. Recrystallization methods, especially of the highly soluble, difficulty crystallizable **4** would result in yield data that would surely be in error. A UV method, described in the Experimental Section, readily allowed for the analysis of the initial neutral acylation mixtures containing **2–4**.

Table I lists the yields of each component formed in the acylation of benzene with **1** under various conditions. Isolated **6** from the initial $NaHCO_3$ wash is listed as a separate column. In two cases (runs 5 and 7), **5** remained in the neutral fraction after the initial $NaHCO_3$ workup and a second $NaHCO_3$ hydrolysis was used to convert the remaining **5** to **6**. The % yield of **5** was determined from **6** isolated from this second hydrolysis procedure. The remaining mixture of **2–4** was analyzed by UV.

The 1:1 ratio of **1** to benzene (runs 5 and 6) favored the formation of **2** at 25 °C (run 6). Similar results have been reported[1] for the formation of anthraquinone from phthaloyl chloride and benzene. As the temperature was decreased (run 5), the amounts of **2–4** decreased, with **5** being isolated as the major product. The formation **5** instead of its isomer reflects the tendency of **1** to form electrophilic character at the carbonyl group C-3 in its reaction with $AlCl_3$. It is interesting to note that thiophene-2,3-dicarboxylic acid anhydride was found to react with benzene and aluminum chloride in a similar manner, forming **6** exclusively.

A 1:2 ratio of **1** benzene (runs 7 and 8) indicated **3** to be the major product. These two runs are unlike results obtained with the previously reported[6] thiophene-3,4-dicarbonyl chloride which forms the corresponding quinone as the major product under these conditions. The reduction of the amounts of **5** and **6** in run 7 vs. run 8 reflects the increased probability for the reaction to go to completion.

A number of trends were noticed when benzene was used as the solvent (runs 1–4). In each case, **3** is the major product, but the amount of **3** decreases somewhat as the temperature increases, whereas the amount of **4** does not vary much. The amounts of **6** were low, indicating nearly complete reaction of **1**.

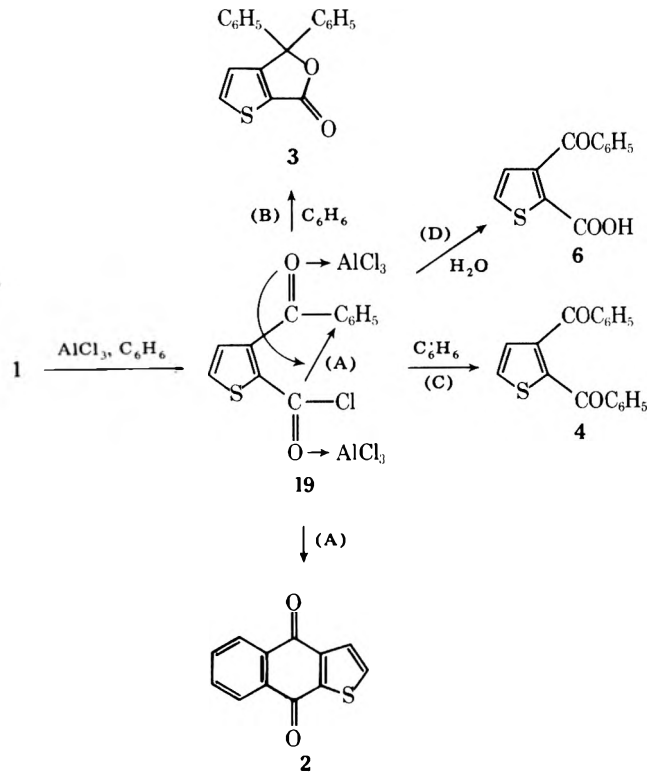
In order to acquire further mechanistic data for this reaction, experiments leading to the determination of the existence of cyclic forms of **1** were conducted. Such an intermediate could be involved in the formation of **3**, the major product in runs 1–4 and 7–8, Table I.

In the benzene series, unsymmetrical phthaloyl chloride (**16**), the pseudolactone of symmetrical phthaloyl chloride (**17**), is readily formed[13] and has been proposed[1] as the precursor to 3,3-diphenylphthalide formed in the acylation of benzene with **16**. IR analysis indicated that a carbonyl group (1790 for **17** and 1808 cm^{-1} for **16**) of any cyclic form of **1** should absorb at a higher frequency then either carbonyl of acyclic **1** (1780 and 1790 cm^{-1}). Treatment of **1** with $AlCl_3$ under conditions where **17** cyclizes to **16** resulted in recovery of acyclic **1** along with small amounts of the anhydride. Investigations of the isomeric thiophene-3,4-carbonyl chloride led to similar results. Although **3** may be formed via a low concentration of a highly reactive cyclic form of **1**, failure to isolate such species suggests its absence.

Isolation of **5** as a product in a number of acylation runs (runs 5 and 7, Table I) required investigation of its tendency to cyclize in the presence of $AlCl_3$. As in the above case of **1**, no evidence for the existence of a cyclic form of **5** could be found. Only recovery of the starting **5** contaminated with **6** was achieved. These results again contrast with the benzene series where it is known that the cyclic form of 2-benzoylbenzoyl chloride, 3-chloro-3-phenylphthalide, can be isolated and reacts with benzene in the presence of $AlCl_3$ to produce 3,3-diphenylphthalide.[14]

Although no evidence for the cyclization of **5** could be obtained, its isolation suggests its importance as an intermediate in the acylation reaction of benzene with **1**. Reaction of **5** with benzene and $AlCl_3$ at 50 °C (run 3 conditions, Table I) formed a product mixture whose composition analyzed (UV) as 2.5% **2**, 77.2% **3**, and 14.9% **4**. The acylation mixture formed with **1** at 50 °C analyzed as 8.5% **2**, 73.3% **3**, and 11.8% **4**. Since the percent composition of **2–4** usually varied by 2–3% in duplicate runs (e.g., runs 2–4, Table I) at the same conditions, the above analysis data for the acylation of benzene with **5** or **1** may be

Scheme IV



considered to be in fair agreement.

Additional evidence for the attack of the C-3 acid chloride group of **1** on benzene was achieved by the acylation of benzene with 2-benzoylthiophene-3-carbonyl chloride (**18**), the isomer of **5**. As in the reaction of **1** and **5** with benzene, **2** and **4** are produced, but also significant amounts of **11**, the isomer of **3**. Reaction of **18** at 50 °C formed a product mixture which analyzed (UV) as 28.6% **11**, 31.7% **2**, and 26.3% **4**. Since **11** was not isolated in any case when **1** was reacted with benzene, this evidence indicates the lack of importance of any intermediate formed from **1** in which the initial attack of benzene involves the C-2 acid chloride function.

In order to determine that **2**–**4** are final products in the acylation reaction and not precursors of one or both of the products, separate analytical samples of **2**–**4** were subjected to the acylation conditions at 50 °C. Each was shown to be a final product by its inertness to $AlCl_3$ in benzene.

A reaction pathway analogous to that proposed by Elderfield[15] for the acylation of benzene with phthaloyl chloride is postulated. Since no evidence could be acquired for the existence of a cyclic form of **1**, the open form is used in the proposed pathway, shown in Scheme IV. Evidence indicating that neither **2** nor **4** are formed from each other suggests a multistep pathway. Isolation of **5** and **6** as well as evidence that **2**–**4** and **6** can readily be formed from **5** suggests the common intermediate to be the $AlCl_3$–**5** complex shown as **19**. The four pathways ultimately leading to the isolated products are designated A, B, C, and D.

Intramolecular acylation, path A, is favored with a 1:1 ratio of **1** to benzene, provided the temperature is high enough (25 °C, run 6, Table I). The path of C-2 before reaction with a second molecule of benzene becomes important when a 1:2 ratio of **1** benzene is used (runs 7 and 8). This pathway also predominates in runs 1–4, in which benzene is used in large excess. Intermolecular acylation, path C, leading to **4** is not the major pathway in any of the acylation runs. This is perhaps due to steric hindrance by the C-3 benzoyl group of **19** to attack of the C-2 function on a second molecule of benzene. Hydrolysis of **19** (path D) leads to **6**.

Experimental Section

General. Melting points are uncorrected. All elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. IR spectra were recorded on a Beckman IR-8 spectrophotometer. NMR spectra were recorded on a Varian T-60 spectrometer using approximately 10% (w/v) solutions in solvents as specified using tetramethylsilane as an internal standard and the chemical shifts are expressed in δ values. The UV spectra were determined in 95% ethanol on a Jasco ORD/UV-5 spectrophotometer. UV analysis of the neutral acylation mixtures composed of **2**–**4** was facilitated, since only **2** and **4** absorbed above 290 nm. Using the molar absorbtivities of **2** and **4** at 297 and 327 nm (2660 or 11 300 and 5920 or 1800) readily allowed for the determination of the concentrations of **2** and **4**. The concentrations of **3** were determined using the molar absorbtivity of **3** at 260 nm (12 500). The mixture resulting from the acylation of benzene with **18** was performed in an analogous manner.

2,3-Dicyanothiophene (8). A stirred mixture of 2,3-dibromothiophene[16] (242 g, 1.00 mol), dry CuCN (260 g, 2.90 mol), and dry DMF (350 mL) was refluxed for 4 h. The resulting mixture was cooled to 100 °C and added to a solution of $FeCl_3 \cdot 6H_2O$ (1000 g), water (1300 mL), and 12 M HCl (250 mL). The mixture was heated at 60–65 °C for 20 min, while being flushed with N_2 to rid the system of HCN. The mixture was extracted with CH_2Cl_2 (eight 500-mL portions). The organic extract was divided into two equal parts and each was washed with 6 M HCl (two 500-mL portions), water (two 750-mL portions), and saturated $NaHCO_3$ (250 mL), and then dried ($MgSO_4$). After evaporation of the CH_2Cl_2, the resulting solid was sublimed at 90 °C (0.05 mm) to give 77.7 g (58%) of **8**: mp 115–122 °C; IR (KBr) 2207 cm^{-1}; NMR (acetone-d_6) δ 7.70 (d, $J_{4,5}$ = 5 Hz, C-4 H), 8.26 (d, C-5-H).

Anal. Calcd for $C_6H_2N_2S$: C, 53.17; H, 1.50; N, 20.89; S, 23.90. Found: C, 53.48; H, 1.44; N, 20.54; S, 23.67.

Thiophene-2,3-dicarboxylic Acid (9). A stirred, N_2-flushed solution of 2,3-dicyanothiophene (33.5 g, 0.25 mol), NaOH (40.0 g, 1.00 mol), and water (200 mL) was maintained at reflux until NH_3 evolution ceased (11 h). The reaction mixture was cooled to room temperature and extracted with ether. The aqueous mixture was added dropwise to cooled, rapidly stirred 12 M HCl (130 mL). The mixture was cooled for 12 h at 0 °C. The precipitated acid was collected and recrystallized in water (1000 mL) to give 28.7–35.9 g (67–83%) of **9**: mp 287–288 °C [lit.[17] mp 270 °C]; IR (KBr) 1710 cm^{-1}; NMR (Me_2SO) δ 7.43 (d, $J_{4,5}$ = 5 Hz, C-4 H), 7.86 (d, C-5 H), 13.60 (s, –COOH).

Thiophene-2,3-dicarbonyl Chloride (1). To thiophene-2,3-dicarboxylic acid (3.44 g, 0.02 mol) was added purified PCl_5 (8.75 g, 0.042 mol) and the mixture was heated at 125–130 °C for 12 h. The resulting mixture was cooled to 20 °C and the $POCl_3$ was removed by distillation (0.1 mm). The resulting **1** was used immediately.

Reaction of Thiophene-2,3-dicarbonyl Chloride with $AlCl_3$ and Benzene. (A) Initial Investigative Run. Dry benzene (50 mL, 0.5 mol) was added to **1** and the system was heated to 50 °C. Freshly sublimed $AlCl_3$ (5.87 g, 0.044 mol) was added in small portions. After 12 h the mixture was cooled to room temperature and poured into a mixture of ice (100 g) and 6 M HCl (100 mL). Additional benzene (300 mL) was added, the layers were separated, and the benzene extract was washed with water (two 50-mL portions) and saturated $NaHCO_3$ (100 mL), and dried ($MgSO_4$). TLC (silica gel), using benzene–hexane (1:1) as eluent, indicated three major components, having R_f values of 0.07, 0.17, and 0.22. Subsequent TLC analyses of authentic **4**, **3**, and **2** were shown to have identical R_f values, respectively.

Successive recrystallizations of the mixture readily yielded **2** and **3**, identical in all respects to authentic samples. The remaining mixture was purified of **3** by refluxing (1.75 h) the mixture in 1:1 ethanol–water (15 mL) containing 1.5 g of NaOH. The resulting mixture was extracted with benzene. The benzene layer was washed with water and dried ($MgSO_3$). Evaporation of the benzene yielded an oil, which yielded **4** when crystallized from benzene–hexane (1:1). Acidification of the initial $NaHCO_3$ wash yielded the keto acid **6**, which was identical in all respects to authentic **6** prepared by Scheme I.

(B) Benzene as Solvent (runs 1–4, Table I). After a 12-h reaction time the mixture was worked up as above to yield a neutral and an acidic residue. UV analysis of the neutral residue was used to calculate the yield data of **2**, **3**, and **4**.

(C) 1,2-Dichloroethane as Solvent (runs 5–8, Table I). Dry 1,2-dichloroethane (48.2 or 46.5 mL) was added to **1** along with the appropriate volume of dry benzene (1.8 mL, 0.02 mol or 3.5 mL, 0.04 mol). After a reaction time and workup as above, the neutral fractions of runs **6** and **8** were analyzed by UV. The initial neutral fractions of runs **5** and **7** contained substantial amounts of **5** and were rehydrol-

yzed in benzene (50 mL) and saturated $NaHCO_3$. After the mixture had been refluxed (4 h) it was cooled, the layers were separated, and the benzene layer was dried and evaporated. The resulting residue was then analyzed by UV. The yield of **6** formed by the second hydrolysis procedure is listed as percent yield of **5** in Table I.

3-Benzoylthiophene-2-carboxylic Acid (6). To a stirred solution of standardized ethereal 0.812 M *n*-butyllithium (123 mL, 0.10 mol) cooled to −70 °C was added (6 min) a solution of 3-bromothiophene[18] (16.3 g, 0.10 mol) dissolved in dry ether (50 mL). After the mixture was stirred for an additional 15 min at −70 °C, a solution of benzonitrile (10.3 g, 0.10 mol) in dry ether (50 mL) was rapidly added (1 min). After the mixture was stirred for an additional 1 h at −70 °C, the mixture was allowed to warm to room temperature over a 1-h period. The mixture was heated at reflux (10 min) and cooled to 10 °C, and a second aliquot of 0.812 M *n*-butyllithium (135 mL, 0.11 mol) was added in one portion. The mixture was heated at reflux for 2 h, cooled to −70 °C, and slowly poured under N_2 into a 1-L flask half filled with crushed dry ice. The mixture was warmed to room temperature overnight and then poured into 12 M HCl and ice. The aqueous layer was extracted with ether (two 300-mL portions). The ether extract was extracted with 1 M Na_2CO_3 (400 mL), additional water was added, and the aqueous layer was acidified with 12 M HCl (150 mL). The mixture was extracted with ether (two 250-mL portions), and the ether extract was washed with water and saturated NaCl, and dried ($MgSO_4$). Evaporation of the ether and recrystallization of the residue from benzene–benzene (2:1) afforded 16.3 g (70%) of **6**: mp 154–155 °C [lit.[8] mp 148 °C]; IR (KBr) 1675 and 1715 cm^{-1}, UV_{max} (95% C_2H_5OH) 250 nm (ϵ 16 800); NMR ($CDCl_3$) δ 7.22 (d, $J_{4,5}$ = 5 Hz, C-4 H), 7.36–7.93 (m, C-5 H and Ph), 12.58 (s, –COOH).

2,3-Dibenzoylthiophene (4). To a stirred solution of standardized ethereal 0.812 *n*-butyllithium (123 mL, 0.10 mol) cooled to −70 °C was added (8 min) a solution of 3-bromothiophene[18] (16.3 g, 0.10 mol) dissolved in dry ether (50 mL). After the mixture was stirred for an additional 15 min at −70 °C, a solution of benzonitrile (10.3 g, 0.10 mol) in dry ether (50 mL) was added (5 min). Stirring was continued for 1 h at −70 °C and the mixture was allowed to warm at room temperature over a 1-h period. The mixture was heated at reflux (15 min), cooled to 5 °C and 0.812 M *n*-butyllithium (123 mL, 0.10 mol) was rapidly added. The mixture was heated at reflux (2 h) and cooled to 7 °C, and a solution of benzonitrile (10.3 g, 0.10 mol) in ether (50 mL) was added (6 min). The mixture was allowed to warm (1 h) to room temperature and then poured into 1 M HCl (400 mL) and ice (200 g). The ether was removed by evaporation, then ethanol (100 mL) and 2 M HCl (50 mL) were added, and the mixture was heated at reflux (1 h). After evaporating most of the ethanol, the mixture was extracted with ether. The extract was washed with water, $NaHCO_3$ solution, and saturated NaCl solution, and dried ($MgSO_4$). Evaporation of the ether left an oil. After chromatography on neutral alumina (4.5 × 28 cm) with benzene and evaporation of most of the benzene with addition of hexane, the yield was 13.7 g (47%) of **4**: mp 80–81 °C; IR (KBr) 1640 and 1655 cm^{-1}; UV_{max} (95% C_2H_5OH) 260 nm (ϵ 16 900); NMR (acetone-d_6) δ 7.13–7.83 (m, C-4 H and Ph), 7.98 (d, $J_{4,5}$ = 5 Hz, C-5 H). Anal. Calcd for $C_{18}H_{12}O_2S$: C, 73.95; H, 4.14; S, 10.97. Found: C, 74.10; H, 4.20; S, 10.71.

2-Benzoylthiophene-3-carboxylic Acid (10). To a stirred solution of 0.749 M *n*-butyllithium (134 mL, 0.10 mol) cooled to −70 °C was added (5 min) a solution of 2,3-dibromothiophene[16] (24.19 g, 0.10 mol) dissolved in dry ether (50 mL). After the mixture was stirred (15 min) at −70 °C, a solution of benzonitrile (10.3 g, 0.10 mol) in ether (50 mL) was added (3 min). After stirring the mixture (15 min) at −70 °C, it was allowed to warm to room temperature (1.5 h). The mixture was then cooled to −70 °C and a second aliquot of 0.749 M *n*-butyllithium (150 mL, 0.11 mol) was added (5 min). The mixture was stirred (0.5 h) at −70 °C and then slowly poured onto crushed dry ice (500 g). The mixture was allowed to warm to 10 °C overnight and then poured into a mixture of 12 M HCl and ice. The mixture was heated at reflux (0.5 h), cooled, and then extracted with ether. The ether extract was then extracted with 1 M Na_2CO_3 (400 mL). The aqueous extract was acidified with 12 M HCl and extracted with ether (four 200-mL portions). The ether extract was washed with water and saturated NaCl solution, and then dried ($MgSO_4$). Evaporation of the ether and recrystallization of the remaining residue in 1:1 benzene–hexane (450 mL) afforded 13.36 g (58%) of **10**: mp 121–122 °C [lit.[9] mp 104 °C]; IR (KBr) 1655 cm^{-1}; UV_{max} (95% C_2H_5OH) 225 nm (ϵ 11 600), 280 (ϵ 7800); NMR ($CDCl_3$) δ 7.25–7.97 (m, C-4, C-5 H and Ph),12.74 (s, –COOH).

3-Benzoylthiophene-2-carbonyl Chloride (5). To 3-benzoylthiophene-2-carboxylic acid (4.65 g, 0.02 mol) was added purified $SOCl_2$ (20 mL). The mixture was heated at reflux (1 h), cooled to 50 °C, and most of the excess $SOCl_2$ was evaporated. The remaining **5** dried (25 °C) in vacuo (1 h): IR 1670, 1740 cm^{-1}; NMR δ 7.06 (d, $J_{4,5}$ = 5 Hz, C-4 H), 7.17–7.67 (m, Ph), 7.73 (d, C-5-H).

1,1-Diphenyl-1*H*-thieno[2,3-*c*]furan-3-one (3). To an etheral solution of diphenylcadmium[11] prepared from bromobenzene (4.379 g, 0.028 mol), magnesium (0.681 g, 0.028 mol), and $CdCl_2$ (2.786 g, 0.0152 mol) was added dry benzene (150 mL). The mixture was distilled to remove most of the ether. The mixture was cooled to 5 °C and a solution of **5** in dry benzene (50 mL) was added (7 min). The mixture was heated (2 h) at reflux, cooled to room temperature, and poured onto ice and 6 M HCl (100 mL). The mixture was warmed to 25 °C, the resulting liquid layers were separated, and the aqueous layer was extracted with benzene. The organic layers were combined, washed with water and $NaHCO_3$, and dried ($MgSO_4$). The benzene was evaporated, and the crude **3** was recrystallized from 1:2 benzene–hexane (100 mL) to yield 3.63 g (62%) of **3**: mp 144–46 °C; IR (KBr) 1755 cm^{-1}; NMR (acetone-d_6) δ 7.40 (s, Ph), 7.53 (d, $J_{5,6}$ = 5 Hz, C-5 H), 8.30 (d, C-5 H).

3,3-Diphenyl-3*H*-thieno[2,3-*c*]furan-1-one (11). A solution of diphenylcadmium prepared from magnesium (1.02 g, 0.042 mol), bromobenzene (6.60 g, 0.042 mol), and $CdCl_2$ (4.18 g, 0.0228 mol) was cooled to 5 °C and 2-benzoylthiophene-3-carbonyl chloride, prepared as **5**, was added (15 min). After a reaction time of 2.25 h, the mixture was worked up as in the preparation of **3** to yield 5.48 g (62%) of **11**: mp 118–119 °C; IR (KBr) 1755 cm^{-1}; UV_{max} (95% C_2H_5OH) 233 (ϵ 8300), 251 nm (ϵ 3800); NMR (acetone-d_6) δ 7.27 (d, $J_{5,6}$ = 5 Hz, C-6 H), 7.43 (s, Ph), 7.82 (d, C-5 H). Anal. Calcd for $C_{18}H_{12}O_2S$: C, 73.95; H, 4.14; S, 10.97. Found: C, 74.12; H, 4.33; S, 11.18.

Reaction of 2-Benzoylthiophene-3-carbonyl Chloride with $AlCl_3$ and Benzene. Reaction of 2-benzoylthiophene-3-carbonyl chloride with benzene and $AlCl_3$ at 50 °C afforded a neutral reaction fraction which UV analysis indicated had a composition of 26.3% **4**, 28.6% **11**, and 31.7% **2**.

Registry No.—**1**, 63599-98-4; **3**, 63609-69-8; **4**, 63599-99-5; **5**, 63600-00-0; **6**, 30006-03-2; **7**, 3140-93-0; **8**, 18853-42-4; **9**, 1451-95-2; **10**, 30011-75-7; **11**, 63600-01-1; **12**, 872-31-1; **18**, 63600-02-2; $AlCl_3$, 7446-70-0; benzene, 71-43-2; benzonitrile, 100-47-0; diphenylcadmium, 2674-04-6.

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Synthesis and Some Reactions of 4*H*-Pyrazole Derivatives[1]

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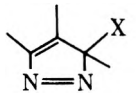
Chlorination of 1-hydroxypyrazoles and 1-hydroxypyrazole 2-oxides with *tert*-butyl hypochlorite produced 4-chloro-4*H*-pyrazole 1-oxides (**3**) and 1,2-dioxides (**4**), respectively, in good yields. Silver-assisted acetolysis and hydrolysis of **4** yielded the corresponding acetates and carbinols, but similar reactions with **3** led in acetic acid to 3-acetoxy-3*H*-pyrazole 1-oxides (**8**) and in water to decomposition of the heterocycle to acetylenes and carboxylic acids. Silver-assisted hydrolysis of a 4-chloro-4*H*-pyrazole (**15**) led to rearrangement to a 4,4-disubstituted 5-pyrazolone **16**.

Most of the reported chemistry of the nonaromatic isomers of the pyrazoles, the 3*H*- and 4*H*-pyrazoles (**1** and **2**, respectively), involves their rearrangement to the aromatic



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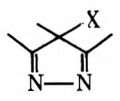

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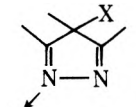
form (the van Alphen-Hüttel rearrangement[2]). We have now synthesized 4*H*-pyrazole 1-oxides and 1,2-dioxides containing functional groups which allow a study of substitution reactions in the pyrazole ring under conditions in which aromatization rearrangements are precluded.

Synthesis

Halogenation of 1-hydroxy-3,4,5-trisubstituted pyrazoles[3] and of their 2-oxides[3] produced the 4-halo derivatives corresponding to structures **3** and **4**, X = Cl (Table I). *tert*-Butyl



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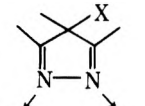

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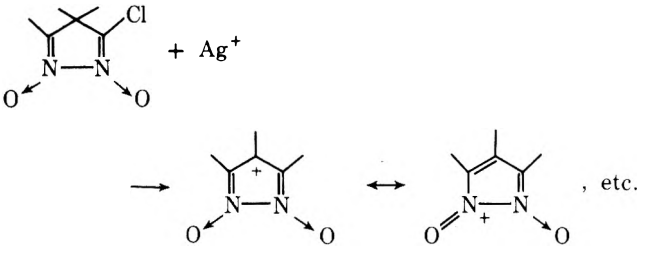
hypochlorite or gaseous chlorine worked equally well with the 1-hydroxy 2-oxides, but the 3,5-alkyl-substituted 1-hydroxypyrazoles suffered some side-chain halogenation when chlorine was used. No halogenation at any other ring position was observed. It had been reported previously that bromination of 3,4,5-trisubstituted pyrazoles gave unstable 4-bromo-4*H*-pyrazoles.[4,5] We have been able to obtain a pure crystalline 4-chloro-4*H*-pyrazole (**2**, X = Cl) but only from the 3,5-diphenyl derivatives. 3,5-Alkyl groups were chlorinated preferentially by both chlorine and *tert*-butyl hypochlorite. The *N*-oxygen substituent thus makes electrophilic substitution in the ring easier as might have been anticipated.

Lead tetraacetate oxidation of the 1-hydroxypyrazole 2-oxides yielded 4-acetoxy-4*H*-pyrazole dioxides (**4**, X = O_2CCH_3) but the yields from this reaction were uniformly low.

Some additional[6] 4-nitro-4*H*-pyrazole dioxides (**4**, X = NO_2) were prepared but they were too unstable to obtain pure samples.

Reactions

The 4-chloro-4H-pyrazole dioxides (**4**, X = Cl) reacted in a straightforward manner with both silver acetate in acetic acid and with silver nitrate in aqueous dioxane to produce the 4-acetoxy (**4**, X = CH_3CO_2) and 4-hydroxy (**4**, X = OH) derivatives. The mechanism of these reactions is not known but it is tempting to suggest that a cationic intermediate **5** is involved. Eschenmoser and co-workers[7] have shown that acyclic α-chloronitrones rapidly yield dienoid cations upon treatment with silver ion. While ion **5** might be considered



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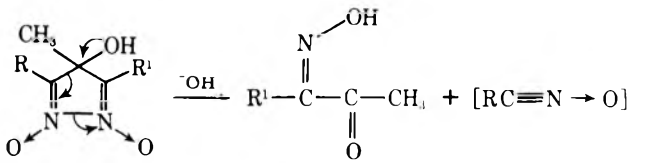
antiaromatic (4π electron monocycle), the effect of the two-electron-releasing oxygen atoms probably is dominant.

It was hoped that hydrolysis of the 4-acetoxy-4*H*-pyrazoles would provide a convenient source of the 4-carbinols, but the hydrolysis proved to be more complex than anticipated and synthetically useless. In large part the failure of this method was due to the instability of the carbinols in base. When carbinol **6a** was heated with aqueous methanolic potassium hydroxide, it was converted to 1-phenyl-1-oximinoacetone (**7a**) and diphenylfuroxan. Similarly, 2,3-butanedione monoxime (**7b**) was obtained from 4-hydroxy-3,4,5-trimethyl-4*H*-py-



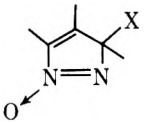
6a, R = R' = C_6H_5
b, R = R' = CH_3
c, R = CH_3, R' = C_6H_5

7a, R' = C_6H_5
b, R' = CH_3

razole 1,2-dioxide (**6b**), while the unsymmetrical carbinol **6c** gave a mixture of the two possible monoximes. The decomposition mode is pictured below; presumably the furoxan resulted from dimerization of benzonitrile oxide.

These monoximes were also obtained along with the carbinols from the acetate hydrolyses but in poor yield. The best route to the carbinols involves hydrolysis of the chlorides described above.

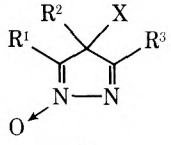
The 4-chloro-4*H*-pyrazole monoxides (**3**, X = Cl) reacted completely differently. Treatment of these compounds with silver acetate in acetic acid produced principally the 3-acetoxy-3*H*-pyrazoles (**8**, X = CH_3CO_2) accompanied in some instances by the expected derivative **3**, X = CH_3CO_2. Al-



8

though it has been determined[8] that the 3-acetates (**8**, X = CH_3CO_2) can be thermally isomerized to the 4-acetates (**3**, X = CH_3CO_2), it is likely that the 4-acetates were direct products of the substitution reaction since the temperatures employed

Table I. 4*H*-Pyrazole Derivatives



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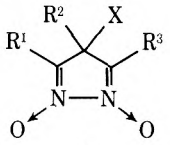


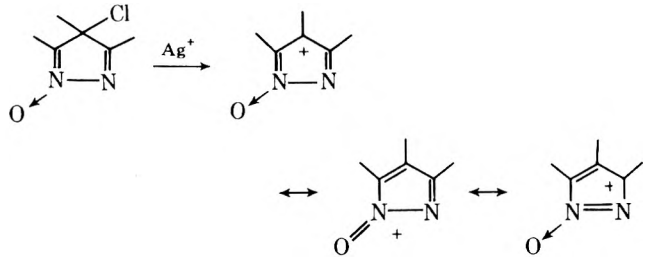
4

Compd	Registry no.	R^1	R^2	R^3	X	Yield	Mp, °C[d]	Procedure[e]	IR, cm^{-1} [a]	NMR, δ [b]
3a	61355-02-0	C_6H_5	CH_3	C_6H_5	Cl	97	113–115	A	1595, 1550	2.16 (s, CH_3)
3b	63689-82-7	CH_3	CH_3	CH_3	Cl	70	Oil[c]	A		
3c	63689-83-8	CH_3	CH_3	C_6H_5	Cl	77	62–64	A	1600, 1560	1.90 (s, $R^1 = CH_3$), 2.20 (s, $R^2 = CH_3$)
3d	63689-84-9	C_6H_5	CH_3	C_6H_5	CH_3CO_2	7	189–191	C	1755, 1610, 1565, 1540	1.93, 2.03 (s, CH_3)
3e	63689-85-0	CH_3	CH_3	C_6H_5	CH_3CO_2	4	Oil	C	1760, 1640, 1610	1.40, 2.10, 2.22 (s, CH_3)
3f	63689-86-1	C_6H_5	CH_3	C_6H_5	OH	20	243–244	Exptl section	3500, 1570	1.83 (s, CH_3), 6.90 (OH)
4a	61355-03-1	C_6H_5	CH_3	C_6H_5	Cl	86	143–145	A	1635	2.23 (s, CH_3)
4b	63689-87-2	CH_3	CH_3	CH_3	Cl	88	103–105	A	1660	1.85 (s, 4-CH_3), 2.25 (s, 3,5-CH_3)
4c	63689-88-3	CH_3	CH_3	C_6H_5	Cl	92	116–119	A	1665, 1615	2.03 (s, 4-CH_3), 2.34 (s, 3-CH_3)
4d	63689-89-4	CH_3	CH_3	$CH(CH_3)_2$	Cl	74	120–121	B	1665, 1660	1.35, 1.42, 2.97 [$CH(CH_3)_2$], 2.20 (s, 3-CH_3), 1.83 (s, 4-CH_3)
4e	61355-09-7	CH_3	C_6H_5	C_6H_5	Cl	90	127–128	B	1680, 1635	2.06 (s, CH_3)
4f	61355-07-5	CH_3	$C_6H_5CH_2$	C_6H_5	Cl	74	126–127	A	1695, 1640	2.40 (s, CH_3), 3.74 (AB quartet, CH_2)
4g	63689-90-7	Cl_3C	CH_3	Cl_3C	Cl	57	195–197	B	1500	2.25 (s, CH_3)
4h	63689-91-8	CH_3	CH_3	CH_3	CH_3CO_2	67	165–167	D	1755, 1670	1.58 (s, 4-CH_3), 2.10 (s, 3,5-CH_3, acetate CH_3)
4i	63689-92-9	CH_3	CH_3	$CH(CH_3)_2$	CH_3CO_2	70	155–156	Ref 3	1755, 1670, 1665	1.23, 1.33, 2.84 [$CH(CH_3)_2$], 1.60 (s, 4-CH_3), 2.02, 2.07 (s, 3-CH_3, acetate CH_3)
4j	63689-93-0	CH_3	CH_3	C_6H_5	CH_3CO_2	31	151–153	Ref 3	1750, 1670, 1615	1.80 (s, 4-CH_3), 2.08, 2.14 (s, 3-CH_3, acetate CH_3)
4k	63689-94-1	C_6H_5	CH_3	C_6H_5	CH_3CO_2	57	250–252	C	1750, 1635	2.03, 2.08 (s, 4-CH_3, acetate CH_3)
4l	63689-95-2	CH_3	C_6H_5	C_6H_5	CH_3CO_2	81	159–160	C	1750, 1680, 1640	1.93 (s, 3-CH_3), 2.15 (s, acetate CH_3)
4m	63689-96-3	CH_3	$C_6H_5CH_2$	C_6H_5	CH_3CO_2	76	155–156	C	1750, 1680, 1635	2.14 (s, 3-CH_3 and acetate CH_3), 3.51 (AB quartet, CH_2)
4n	63689-97-4	CH_3	CH_3	CH_3	OH	77	198–200	E	3300, 1665	1.50 (s, 4-CH_3), 2.05 (s, 3,5-CH_3), 6.10 (OH)
4o	17953-15-0	C_6H_5	CH_3	C_6H_5	OH	42	214–215	E	3300, 1625	1.78 (s, 4-CH_3), 5.28 (OH)
4p	63689-98-5	CH_3	CH_3	C_6H_5	OH	55	212–214	E	3320, 1670, 1630	1.75 (s, 4-CH_3), 2.10 (s, 3-CH_3), 7.20 (OH)
4q	63689-99-6	CH_3	CH_3	CH_3	NO_2	57	106–108	Ref 6	1680, 1560	
4r	17953-13-8	C_6H_5	CH_3	C_6H_5	NO_2	86	115	Ref 6	1640, 1545	2.35 (s, 4-CH_3)
4s	17953-14-9	CH_3	CH_3	C_6H_5	NO_2	94	107	Ref 6	1680, 1640, 1545	

[a] Measured in KBr disks. [b] Measured in $CDCl_3$ or CCl_4 at 60 mHz. [c] Used without further purification. [d] The chloro derivatives were crystallized from hexane or hexane–CH_2Cl_2. The acetates and carbinols were crystallized from methanol. [e] The procedures may be found in the Experimental Section.

(~10 °C) were much lower than those required for isomerization (100 °C).

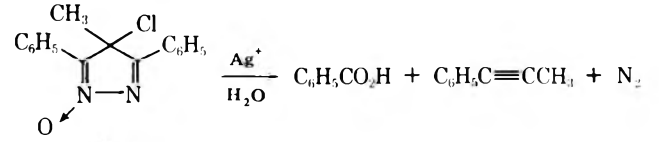
The 3-acetoxy compounds again may arise from a cation **9**, which now is unsymmetrical and in which the electrophilic character is shared by positions 3 and 4. Analogous 3-methoxy derivatives (**8**, X = OCH_3)[9] were obtained when the reactions



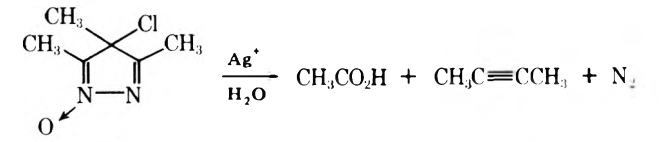
9

were carried out with silver nitrate in methanol, a result also suggestive of an ionic intermediate. However, it is also possible that the 3-derivatives are formed by an electrophilically assisted S_N2'-like reaction in which no cation is involved.

Reaction of the 4-chloro monoxides **3a** and **3b** with aqueous silver nitrate was more complex since it was accompanied by

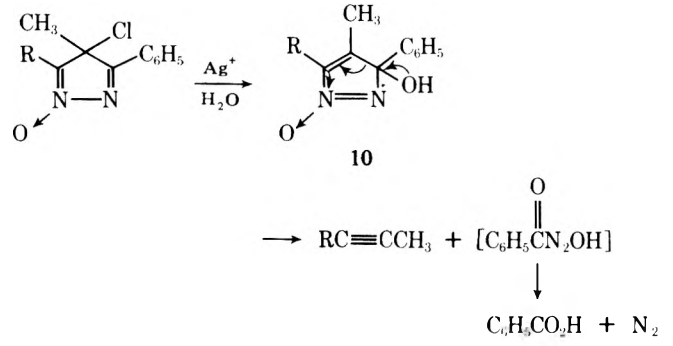


3a



3b

complete destruction of the heterocycle. The products were acetylenes, carboxylic acids, and nitrogen. If water attacks the 3 position as do methanol and acetate ion, the intermediate carbinol **10** must unravel to the products observed:



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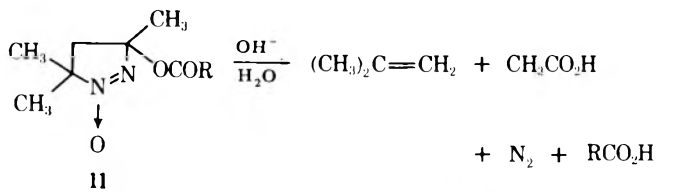
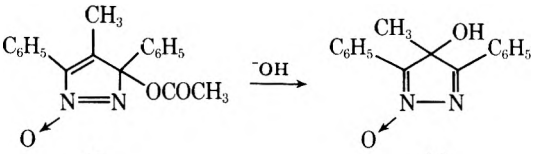
This decomposition reaction is reminiscent of that of 3-acyloxy-Δ^1-pyrazoline 1-oxides (**11**) which produced alkenes, acids, and nitrogen upon hydrolysis.[10]

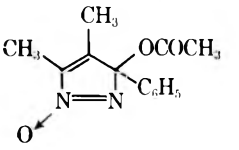


11

The hydrolysis of the 3-acetoxy-3*H*-pyrazole 1-oxides produced acetylenes and acids also. These hydrolyses were not completely straightforward, however, since some (20%) 4-hydroxy-4-methyl-3,5-diphenyl-4*H*-pyrazole 1-oxide (**3f**) was obtained from the hydrolysis of acetate **12**. Also hydrolysis of acetate **14**[3] produced 1-phenylpropyne rather than the



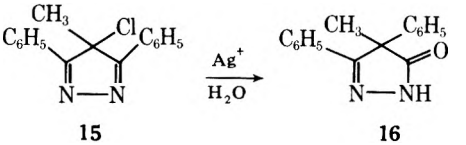
12 **3f**



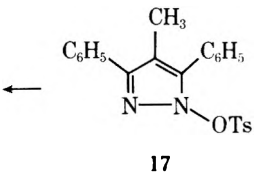
14

expected 2-butyne. It is not too surprising that nucleophilic attack occurs in the ring as well as at the acetate carbonyl group.

For comparison purposes hydrolysis of the parent 4-chloro-4*H*-pyrazoles was examined. Silver ion induced hydrolysis of the 4-chloro-4*H*-pyrazole (**15**) produced pyrazolone **16** in 78% yield. This same pyrazolone had been obtained[8] by hydrolysis of tosylate **17**. Since Closs and Heyn[4] had observed

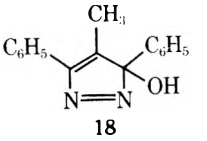


15 **16**



17

that reaction of a 4-bromo-4*H*-pyrazole with methanol yielded a 3-methoxy-3*H*-pyrazole, and in analogy to the silver ion assisted hydrolysis of the mono-*N*-oxides described above, it is reasonable to assume that carbinol **18** is an intermediate in these reactions.[11] The rearrangement of **18** to pyrazolone



18

16 is analogous to that of 4-hydroxy-4*H*-pyrazoles to 2-pyrazolin-4-ones reported[13] recently although the present one occurs at much milder temperatures.[14]

It is interesting to contrast the rearrangement of these 3-hydroxy-3*H*-pyrazoles (assumed structure) to the fragmentations observed with 3-hydroxy-1-pyrazolines which lose nitrogen when treated with either acid (with the formation of unsaturated ketones) or base (with the formation of saturated but often rearranged ketones.)[15] It is not obvious why the presence of the conjugated olefinic bond so drastically changes the chemistry of the α-hydroxy azo functionality.

Experimental Section

Preparation of 4-Chloro-3,4,5-trisubstituted 4*H*-Pyrazole 1,2-Dioxides (4) (Table I). Procedure A. *tert*-Butyl hypochlorite (10% mol excess) was added to a stirred suspension of 1–5 mmol of the 1-hydroxy-3,4,5-trisubstituted pyrazole 2-oxide[3] in 20–50 mL of CH_2Cl_2 at 0 °C. The mixture was held at 0 °C for 30 min, allowed to warm to room temperature, and evaporated to dryness under reduced pressure. The oily solid residue was dissolved in 10 mL of CH_2Cl_2 and hexane was added to turbidity. Upon cooling a solid separated. It was collected and dried in a desiccator.

Procedure B. Chlorine gas was bubbled gently through a suspension of 1–5 mmol of the 1-hydroxy-3,4,5-trisubstituted pyrazole

2-oxide[3] in 50 mL of CH_2Cl_2 at 0 °C. Dissolved gases were removed with solvent by evaporation and the residue was crystallized as in procedure A.

4-Acetoxy-3,4,5-trisubstituted Pyrazole 1,2-Dioxides (Table I). Procedure C. A solution of 1–5 mmol of the 4-chloro-4*H*-pyrazole 1,2-dioxide in 10–25 mL of glacial acetic acid was treated with an equivalent of silver acetate at 25 °C. After stirring for 30 min the mixture was filtered and diluted with 150 mL of ice water. The solid which separated was collected by filtration and recrystallized from methanol or ether.

Procedure D. An equivalent of lead tetraacetate was added to a suspension of 10 mmol of 1-hydroxy-3,4,5-trisubstituted pyrazole 2-oxide[3] in 20–40 mL of CH_2Cl_2 at 0 °C. The mixture was stirred at 0 °C for 1 h and at 25 °C for 12 h. After it was filtered, the solution was washed with 10% Na_2CO_3 and saturated NaCl and dried. The solvent was evaporated and the oily residue was induced to crystallize by stirring in cold ether.

4-Hydroxy-3,4,5-trisubstituted Pyrazole 2-Oxides (Table I). Procedure E. A solution containing 3 mmol of $AgNO_3$ in 10 mL of H_2O was added to 3 mmol of the 4-chloro-4*H*-pyrazole 1,2-dioxide in 15 mL of dioxane; the resulting mixture was stirred at 25 °C for 15 min and filtered. The filtrate was diluted with H_2O and extracted with CH_2Cl_2. The organic extracts were dried and concentrated and the residue was chromatographed on silica. The desired carbinols were eluted with ethyl acetate. The aryl-substituted pyrazole dioxides produced small amounts of 2,5-disubstituted 3,4-diazacyclopentadienone 3,4-dioxides[6] also.

Alkaline Decompositon of 3,5-Diphenyl-4-hydroxy-4-methyl-4*H*-pyrazole 1,2-Dioxide (4o) (Table I). To a solution of 0.564 g (2 mmol) of **4o** in 20 mL of CH_3OH was added 5 mL of 0.4 M KOH solution and the mixture was heated under reflux for 2 h. The cooled mixture was concentrated, extracted with ether, and worked up in the usual way. The concentrate was crystallized from CCl_4 to yield 0.25 g (75%) of 1-phenyl-1,2-propanedione 1-oxime (**7a**), mp 162–163 °C (lit.[16] mp 164–165 °C). The mother liquor from this crystallization was concentrated and chromatographed on silica. Elution with $CHCl_3$ gave 0.12 g (23%) of diphenylfuroxan, mp 113–115 °C (lit.[17] mp 114 °C).

The same procedure with carbinol **4n** produced 60% of 2,3-butanedione monoxime, mp 74–75 °C (lit.[18] mp 74.5 °C).

Chlorination of 1-Hydroxy-3,4,5-trisubstituted Pyrazoles. A slurry of the hydroxypyrazole[3] (3–10 mmol) in 50–100 mL of CH_2Cl_2 was treated with slightly less than an equivalent of *tert*-butyl hypochlorite at 0 °C. After stirring for 15 min, the mixture was concentrated and the residue was crystallized from hexane. (See Table I).

Silver-Assisted Acetolysis of 4-Chloro-4*H*-pyrazole 1-Oxides. These reactions were conducted in the same way as that described for the dioxides (procedure C) except that the mother liquor from the methanol recrystallization was concentrated and subjected to column chromatography with elution with benzene–ether mixtures.

Silver-Assisted Hydrolysis of 4-Chloro-4*H*-pyrazole 1-Oxides. Procedure E was followed except that the crude residue from the washing was chromatographed on silica. From 2.57 g of **3a** (Table I) there was obtained 0.54 g (52%) of 1-phenylpropyne by elution with hexane, bp 180–184 °C (lit.[19] bp 182–183 °C), and benzoic acid (0.72 g, 65%), eluted with ether.

A crude sample of 3,4,5-trimethyl-4-chloro-4*H*-pyrazole 1-oxide, prepared by procedure A, in 20 mL of dioxane was treated at −15 °C with aqueous $AgNO_3$. The reaction flask was connected to a trap held at −78 °C and the mixture was stirred for 2 h at room temperature. The contents of the cold trap were analyzed by infrared and NMR spectroscopy and identified as 2-butyne.

Alkaline Hydrolysis of 3,5-Diphenyl-4-methyl-3-acetoxy-3*H*-pyrazole 1-Oxide (12). A mixture of 0.62 g (2 mmol) of **12**[3] in 25 mL of dioxane and 0.3 g of KOH in 10 mL of water was heated under reflux for an hour, cooled, neutralized, and extracted with ether. The organic residue was chromatographed on silica and eluted with chloroform. There was obtained 47.2 mg (25%) of 1-phenylpropyne, 0.1 g (19%) of **3f** (Table I), and 35 mg (27%) of benzoic acid.

3,5-Diphenyl-4-chloro-4-methyl-4*H*-pyrazole (15). A solution of 2.44 g (0.01 mol) of 3,5-diphenyl-4-methylpyrazole[20] in 50 mL of CH_2Cl_2 was treated with 1.2 g (0.011 mol) of *tert*-butyl hypochlorite at 5 °C. After a few minutes the mixture turned bright yellow. After 15 min the mixture was concentrated to ~20 mL, diluted with 40 mL of hexane, and chilled. The bright yellow solid was collected and dried: mp 112–114 °C dec; IR (KBr) 1515 cm^{-1}; NMR (CCl_4) δ 1.99 (s, CH_3).

Anal. Calcd for $C_{16}H_{13}ClN_2$: C, 71.51; H, 4.88; Cl, 13.19; N, 10.42. Found: C, 71.38; H, 4.91; Cl, 13.11; N, 10.60.

Hydrolysis of 3,5-Diphenyl-4-chloro-4-methyl-4*H*-pyrazole. A solution of 0.1 g (0.4 mmol) of **15** in 20 mL of dioxane was treated at room temperature with an equivalent of $AgNO_3$ in 7 mL of H_2O. After stirring for 15 min, the mixture was filtered, diluted with water, and extracted with CH_2Cl_2. The dried extracts were concentrated and chromatographed on silica gel. Elution with benzene yielded 72 mg of 3,4-diphenyl-4-methyl-5-pyrazolone (**16**), mp 183–184 °C, identical in all respects with authentic material.[8]

Registry No.—**12,** 17953-47-8; **15,** 61355-01-9; 1-hydxoxy-3,5-diphenyl-4-methylpyrazole 2-oxide, 17953-33-2; 1-hydroxy-3,4,5-trimethylpyrazole 2-oxide, 17953-31-0; 1-hydroxy-4,5-dimethyl-3-phenylpyrazole 2-oxide, 15674-34-7; 1-hydroxy-4,5-dimethyl-5-isopropylpyrazol 2-oxide, 63690-00-6; 1-hydroxy-3,4-diphenyl-5-methylpyrazole 2-oxide, 63690-01-7; 1-hydroxy-5-methyl-4-benzyl-3-phenylpyrazole 2-oxide, 63690-02-8; 1-hydroxy-3,5-trichloromethyl-4-methylpyrazole 2-oxide, 63690-03-9; 3,5-diphenyl-4 methylpyrazole, 17953-46-7.

References and Notes

(1) This research was supported in part by a grant from the National Cancer Institute, National Institutes of Health, CA 10742.
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(14) It is possible that the present rearrangement is of the 1,2-semipinacolic or semibenzilic acid type rather than a thermal 1,5-sigmatropic rearrangement, but no experiments to distinguish these possibilities have been carried out.
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Carbon-13 Nuclear Magnetic Resonance Studies of Heterocycles Bearing Carbon–Sulfur and Carbon–Selenium Bonds: 1,3,4-Thiadiazole, 1,3,4-Selenadiazole, and Tetrazole Derivatives[1]

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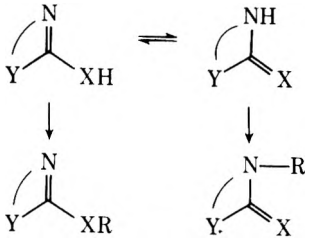
A number of 1,3,4-thiadiazole and selenadiazole thiols and selenols (**2, 3, 5, 6, 7,** and **9**) have been synthesized. ^{13}C NMR is shown to offer a reliable method for distinguishing thiones and selones from the corresponding thiol and selenol derivatives. All the thiols and selenols studied are shown to exist as their thione and selone tautomers, respectively. Substitution of selenium for exocyclic sulfur (at C-2) leads to a shielding effect at the carbon of attachment and (for selones) a deshielding effect at C-5 (see Table I), suggestive of transmission of inductive effects across the ring chalcogen. Substitution of selenium for ring sulfur results in deshielding at both C-2 and C-5; comparison with models shows this effect to be essentially independent of the number of ring nitrogens. The possible origin of this deshielding effect is discussed. These correlations have been extended to the tetrazole series, where they have been used to establish the structure of the tetrazolium salt (**27**) (obtained by alkylation of **24a**) and its mesoionic solvolysis products (**28** and **29**). Some ^{13}C–^{77}Se coupling data are presented.

^{13}C NMR is a powerful tool for structure determination in organic chemistry. Among other advantages, it makes possible the direct observation of functional groups such as carbonyl and thiocarbonyl. ^{13}C chemical shifts have been determined for a number of thiocarbonyl functions,[2] and a quantitative relationship between thiocarbonyl and carbonyl chemical shifts has been put forward.[2b] Our interest has lain in the application of ^{13}C NMR to functional groups containing carbon–selenium bonds, and their comparison with the corresponding carbon–sulfur functions. A further objective of our work has been to establish methods of distinguishing between substitution on nitrogen and on sulfur or selenium in derivatives of heterocyclic thiols and selenols (see eq 1). Since



(1)

X, Y = S, Se

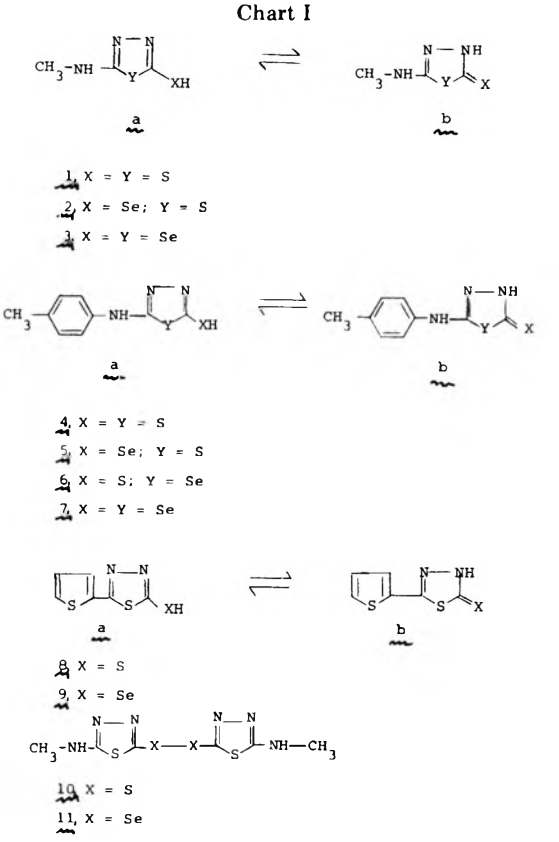
structural assignments for such materials are often difficult using existing methods, the development of ^{13}C NMR correlations in this field has considerable value.

Results and Discussion

1,3,4-Thiadiazole and 1,3,4-Selenadiazole Derivatives. The compounds examined in this phase of our study are shown in Chart I. Literature methods were used for the preparation of **1**[3] and **4**,[4] while **8** was obtained by treatment of potassium 3-(2-thenoyl)dithiocarbazate[5] with concentrated sulfuric acid at 10 °C. Treatment of 4-(*p*-tolyl)-3-selenosemicarbazide[6] with thiophosgene afforded **6.** Heterocyclic selenols **2, 3, 5, 7,** and **9** were prepared by the action of carbon diselenide[7] on the corresponding thio or seleno hydrazides. Oxidation of **1** with hydrogen peroxide gave the disulfide **10;** the corresponding diselenide **11** was obtained by air oxidation of a methanolic solution of **2.**

^{13}C NMR data for some 1,3,4-thiadiazole derivatives are presented in Table I. Substitution of selenium for sulfur leads, in general, to a decrease in line intensity for the carbon of attachment.[8] The data for **1** and **2** show that these materials exist predominantly as the thione and selone tautomers (b) (Chart I), respectively. This is shown by using disulfide **10** and

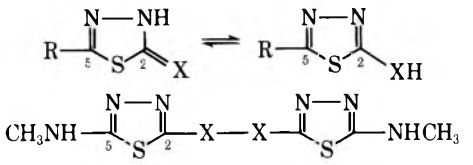
Chart I



diselenide **11** as model compounds; their ^{13}C NMR spectra should approximate those of the thiol (**1a**) and selenol (**2a**) tautomers. However, conversion of **1** into **10,** and of **2** into **11,** results in large changes in chemical shift, upfield for C-2 and downfield for C-5, such that the positions of the C-2 and C-5 resonances are reversed. This is consistent only with the conversion of the thione (**1b**) and selone (**2b**) tautomers into **10** and **11,** respectively. The assignments of the C-2 and C-5 signals are confirmed by the undecoupled spectra, in which the C-5 carbons appear as multiplets owing to long-range coupling with the methyl and NH protons, while the C-2 carbons still give rise to singlets.

The C-2 line shows a marked upfield shift on going from sulfur to selenium, both for the change thione → selone (**1, 2;** $\Delta\delta_{Se-S} = -12.1$ ppm) and for disulfide → diselenide (**10, 11;** $\Delta\delta_{Se-S} = -8.6$ ppm). The C-5 line shows a corresponding downfield shift on going from thione to selone ($\Delta\delta_{Se-S} = 3.6$

Table I. ^{13}C NMR Chemical Shifts of 1,3,4-Thiadiazole Derivatives[a]



Compd	δ[b] C-2	δ[b] C-5	δ[b] Other	Δδ Se−S[c] C-2	Δδ Se−S[c] C-5
1	180.6	161.6	CH_3: 29.9		
10	148.6	173.0	CH_3: 31.2	(−32.0)	(11.4)
2[d]	168.5	165.2	CH_3: 30.35	−12.1	3.6
11	140.0	173.1	CH_3: 31.2	−8.6	0.1
4	181.1	156.6	C-1′: 137.4 C-2′: 117.6 C-3′: 129.4 C-4′: 131.2 CH_3: 20.3	(−28.5)	(7.9)
5	170.5	160.2	C-1′: 137.2 C-2′: 117.6 C-3′: 129.4 C-4′: 131.4 CH_3: 20.3	−10.6	3.6
8	187.2	154.2			
9	177.8	158.2		−9.4	4.0

[a] In Me_2SO-d_6. [b] Parts per million downfield from internal tetramethylsilane. [c] Δδ values for the changes thione → disulfide and selone → diselenide are shown in parentheses. [d] Spectrum run at 18 °C.

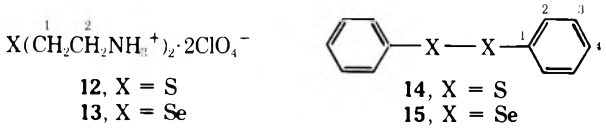
Table II. ^{13}C NMR Chemical Shifts for Simple Chalcogenides

Compd	C-1	C-2	C-3	C-4
12[a]	28.9	39.6		
13[a]	20.5	40.7		
$\Delta\delta_{Se-S}$ ($\delta_{13} - \delta_{12}$)	−8.4	+1.1		
14[b]	136.0	127.2	129.3	127.4
15[b]	130.1	130.8	129.3	127.7
$\Delta\delta_{Se-S}$ ($\delta_{15} - \delta_{14}$)	−5.9	+3.6	0	+0.3

[a] Solvent: D_2O (Me_4Si external reference). [b] Solvent: Me_2SO-d_6 (Me_4Si internal reference).

ppm), but in the disulfide–diselenide pair this line remains essentially unchanged. Other thione–selone pairs (**4**, **5** and **8**, **9**) show similar trends.

Comparison with some simple chalcogenides (**12**, **13**, **14**, and **15**; see Table II) suggests that these shifts are due mainly to



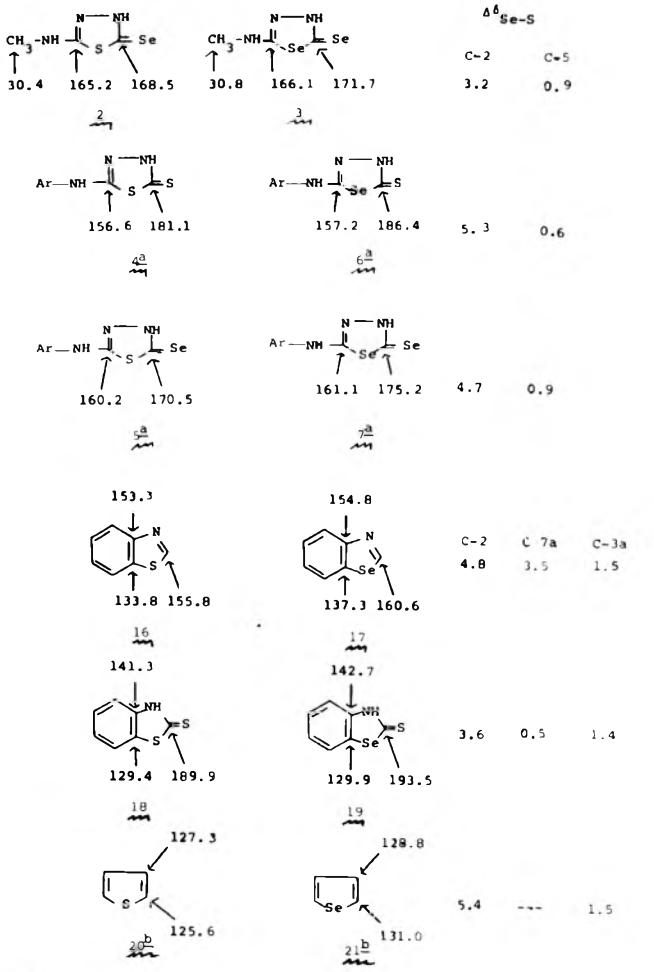
12, X = S
13, X = Se

14, X = S
15, X = Se

inductive effects, resulting primarily from the lower electronegativity of selenium as compared to sulfur. What is remarkable, however, is the strong deshielding effect of selenium on C-5 in the thiadiazole-2-selones. It is of the same order as the deshielding of the ortho carbon in phenyl diselenide, and implies transmission of a strong inductive effect via the ring sulfur. Similar effects have been observed in comparative studies of ^{13}C NMR spectra of 2-substituted furans, thiophenes, selenophenes, and tellurophenes.[9]

In contrast, substitution of ring sulfur by selenium results in a marked deshielding effect (3–5 ppm) at C-2 and a much smaller deshielding effect at C-5. Similar effects are observed (see Scheme I) when one compares benzoselenazoles and selenophene with the sulfur analogues. The data on thiophene

Scheme I



[a] Ar = *p*-tolyl. [b] Values taken from ref 9.

and selenophene are taken from the work of Gronowitz and his co-workers;[9] their findings are consistent with earlier studies.[10,11] Introduction of a thione function at C-2 of benzoselenazole decreases the deshielding effect of selenium at C-7a, in conformity with the trends already noted for 1,3,4-selenadiazoles. This deshielding effect may be accounted for by a decrease in total charge density on the α carbons, resulting from a greater tendency for the d orbitals of the heteroatom to accept electrons from the ring for selenium than for sulfur. The latter effect apparently outweighs the opposite trend anticipated on the basis of differences in electronegativity between the two heteroatoms. Recent correlations of the ^{13}C NMR shifts of thiophene and selenophene with CNDO/2 calculations of total charge densities are consistent with this view.[9] The smaller deshielding effect observed for C-3a in the benzazole pairs **16** and **17**, and **18** and **19**, is insensitive to substitution at C-2 and is similar to that observed[9] for C-3 in thiophene (**20**) and selenophene (**21**).

The effect of selenium on the ^{13}C chemical shifts of azoles may thus be summarized as follows. Substitution of exocyclic sulfur by selenium results in an upfield shift at the carbon of attachment, whereas substitution of ring sulfur by selenium results in a downfield shift at the adjacent carbon, and these effects are essentially independent of the number of ring nitrogens.

Tetrazole Derivatives. Table III shows the ^{13}C chemical shifts of some tetrazole derivatives. 1-Phenyl-1,2,3,4-tetrazole-5-thiol (**22**) exists predominantly as the thione tautomer (**22b**), in agreement with the findings of Lieber et al.[12] The chemical shift of the tetrazole carbon (C-5; see Chart II) comes close to those observed for 1-phenyl-4-(1′-piperidinometh-

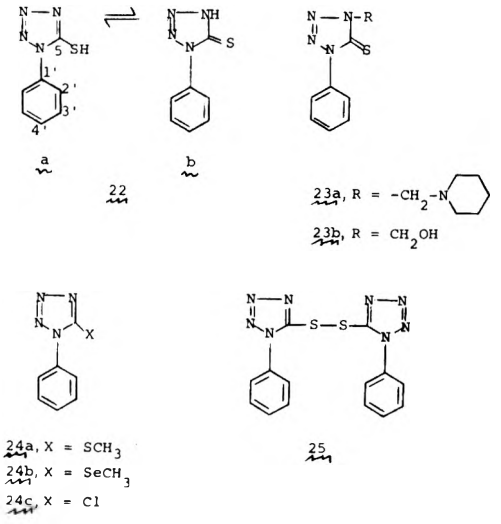
Table III. ^{13}C NMR Chemical Shifts of Tetrazole Derivatives[a]

Structure	δ, ppm C-5	C-1′	C-2′	C-3′	C-4′	Other
22	163.8	134.0	124.3	129.2	129.5	
	165.0	135.4	124.1	129.6	129.6[b]	
23a	164.7	135.0	123.8	129.1	129.4	NCH_2N: 70.4; C-2″: 51.6; C-3″: 25.9; C-4″: 23.6[c]
	165.4	136.0	124.3	129.5	129.6	NCH_2N: 70.6; C-2″: 52.0; C-3″: 26.4; C-4″: 24.2[b]
23b	163.2	134.2	124.3	129.5	129.7	CH_2: 70.4
24a	155.1	133.1	124.3	130.0	130.5	CH_3: 15.2
24b	148.0	133.7	124.4	130.0	130.6	CH_3: 8.6
25	152.3	132.8	124.9	129.7	130.8	
24c	146.1	132.3	125.3	129.9	131.1	

[a] In Me_2SO-d_6. [b] In dioxane-d_8. [c] In chloroform-d.

yl)-Δ^2-1,2,3,4-tetrazoline-5-thione (**23a**) and the 4-(hydroxymethyl) analogue **23b**, the structures of which have been established by the work of Postovskii and Nirenburg.[13] The

Chart II



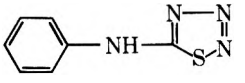
thio ether **24a**, prepared by methylation of **22** with methyl iodide,[14] shows a signal at 155.1 ppm for C-5. The corresponding seleno ether **24b**, obtained somewhat surprisingly by the action of methanolic bis(methoxymagnesium) diselenide[15] on 5-chloro-1-phenyl-1,2,3,4-tetrazole (**24c**), shows its C-5 resonance at 148.0 ppm, giving $\Delta\delta_{Se-S} = -7.1$ ppm, similar to the value ($\Delta\delta_{Se-S} = -8.7$ ppm) observed for the 1,3,4-thiadiazole disulfide/diselenide pair (**10, 11**) considered earlier. The methyl resonances show an upfield shift of the same order ($\Delta\delta_{Se-S} = -6.6$ ppm). The tetrazolyl disulfide **25**, as expected, behaves like the thio ether **24a**, while the chlorotetrazole **24c** shows aromatic ^{13}C shifts like those of **24b**. The tetrazole series thus shows trends similar to those observed for the 1,3,4-thiadiazole and 1,3,4-selenadiazole series. Furthermore, recent work by L'abbé and his co-workers[16] includes ^{13}C NMR spectral data for 1-benzyl- and 1-phenyl-Δ^2-1,2,3,4-tetrazoline-5-thione and their N- and S-substituted derivatives, and their values for C-5 chemical shifts are very similar to ours.

The following example illustrates the diagnostic value of the ^{13}C chemical shift correlations just described. Alkylation of **24a** with triethyloxonium fluoroborate gives a stable, crystalline tetrazolium salt, which on treatment with sodium hydrogen sulfide yields a yellowish white solid A, $C_9H_{10}N_4S$, presumably formed by nucleophilic attack by SH^- with loss of methanethiolate anion. Treatment with sodium hydrogen selenide gives the yellow selenium analogue B, $C_9H_{10}N_4Se$. The C-5 chemical shifts of these materials are 173.5 and 165.8 ppm, respectively. These values are inconsistent with a 1,4-disubstituted thione (selone) structure, for which our correlations would predict C-5 chemical shifts in the vicinity of 164 (thione) and 155 (selone) ppm. UV spectral data (Table IV) support this conclusion, as well as indicating that these compounds are structural analogues, differing only in the chalcogen. The UV spectrum of 5-anilino-1,2,3,4-thiatriazole (**26**)

Table IV. UV Spectral Data[a]

Compd	λ_{max}, nm	ε
A. $C_9H_{10}N_4S$	228	12 400
	255	9 600
	340	2 600
B. $C_9H_{10}N_4Se$	234	11 600
	270	7 800
	362	1 840
23a	285	4 800
26	240	8 600
	284	8 400
	302	11 400

[a] Solvent, 95% ethanol; concn, 5×10^{-5} M.

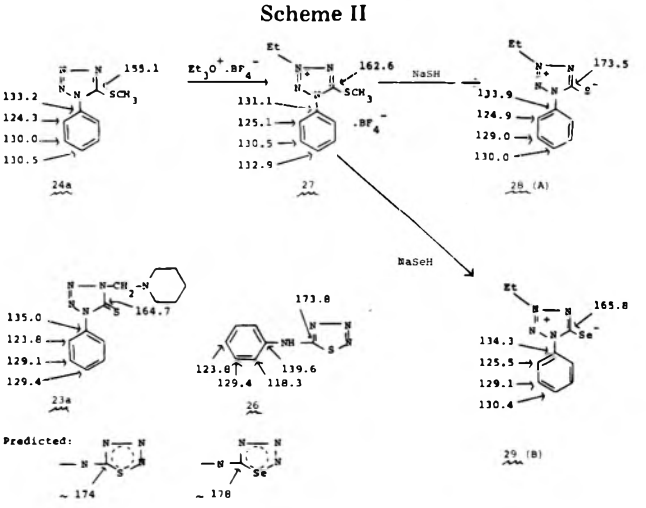


26

is quite different, suggesting that we are not dealing with a 1,2,3,4-selenatriazole/thiatriazole pair either.

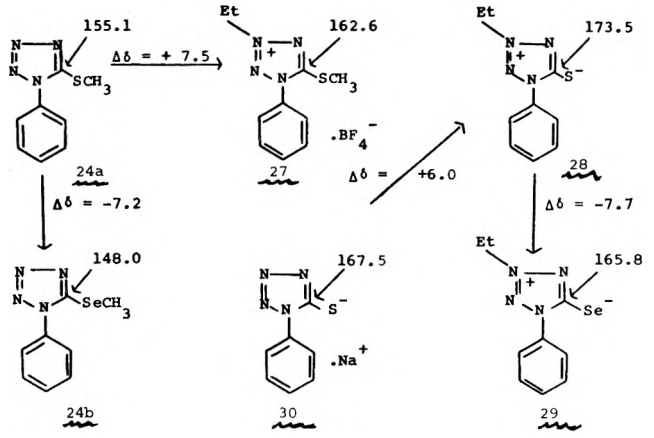
We propose structure **27** for the tetrazolium salt and structures **28** and **29** for compounds A and B, respectively (Scheme II), on the basis of the ^{13}C NMR and UV evidence. First, the ^{13}C benzenoid shifts in these materials are similar to those of other 1-phenyltetrazoles, but very different from those of 5-anilino-1,2,3,4-thiatriazole (**26**), despite the close-

Scheme II



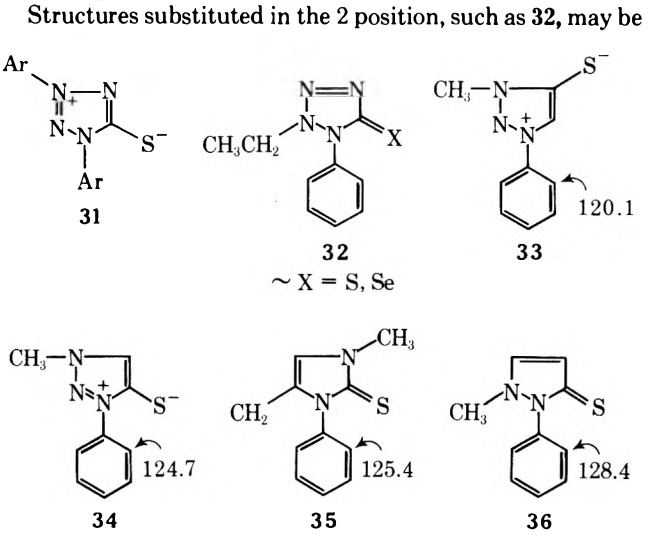
ness of the thiatriazole C-5 signal (173.8 ppm) to the observed shift (173.5 ppm) in A. Second, if the latter were a thiatriazole derivative, one would expect the selenium analogue B to show the deshielding effect of ring selenium. The C-5 signal should appear around 178 ppm. Instead, changing from sulfur to selenium gives rise to a strong shielding effect. Third, this shielding effect is almost exactly what one would expect for *exocyclic* selenium in the tetrazole series (Scheme III). In

Scheme III



addition, comparison with the 1-phenyltetrazole-5-thiolate anion (**30**) shows that the C-5 (tetrazole) resonance is shifted downfield on going from the latter to the mesoionic *N*-ethyl derivative **28** by an amount comparable with the deshielding effect observed on going from 5-methylthio-1-phenyl-1,2,3,4-tetrazole (**24a**) to the 3-ethyl-5-methylthio-1-phenyl-1,2,3,4-tetrazolium cation (**27**). This effect must be due largely to lowering of the electron density of the tetrazole ring. The mesoionic structures **28** and **29** are thus aryl–alkyl analogues of the known 1,3-diaryl-1,2,3,4-tetrazolium 5-thiolates **31**,[17] whose structures have recently been confirmed by x-ray crystallographic studies.[18]

Structures substituted in the 2 position, such as **32**, may be



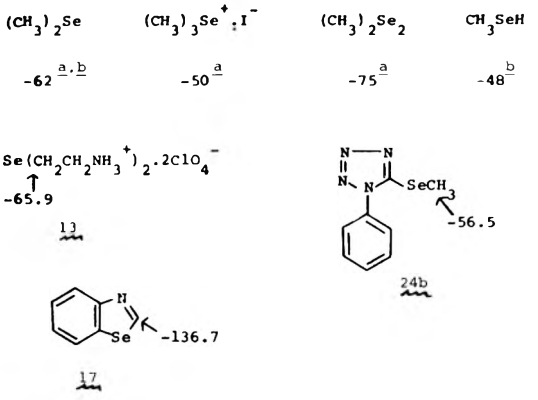
31 **32** **33**

34 **35** **36**

excluded on the basis of the ^{13}C chemical shift of the ortho benzenoid carbons in **27**, **28**, and **29**. Begtrup's studies[19] on phenyl-substituted azoles show wide variations in the chemical shifts of the ortho benzenoid carbon, which are ascribed to the effect of steric hindrance on the extent of interannular conjugation, the direction of shift being downfield with increasing steric hindrance. Pertinent examples from Begtrup's work[19] are **33**, **34**, **35**, and **36**. **27**, **28**, and **29** show signals for the ortho benzenoid carbon near 125 ppm, like the model compounds **34** and **35**, and so must have only one substituent adjacent to the phenyl group, whereas **32** should show an ortho carbon signal near 128 ppm, as does **36**. Further support for this conclusion comes from recent work[20] by Lippmann and his co-workers on the acylation of tetrazole-5-thiols, which suggests that the 1-phenyl group exerts a considerable steric effect at the 2 position. This effect may be expected to operate in the alkylation of 5-methylthio-1-phenyltetrazole, since quaternization reactions are frequently sensitive to steric factors. It is possible, too, that alkylation at the 3 position is facilitated by electron release from the 1-nitrogen. Finally, the mass spectra of **28** and **29** both show a prominent peak at *m/e* 105, consistent with the ion $C_6H_5N{\equiv}N^+$. The latter would be an expected fragmentation product of **28** and **29**, but not of **32**.

^{13}C–^{77}Se Coupling. ^{13}C–^{77}Se coupling data reported in the literature[21,22] encouraged us to look for such coupling in the present work. The natural abundance (7.58%) of ^{77}Se permits observation of ^{77}Se satellites in ^{13}C NMR spectra, provided the primary is sufficiently intense. Our results, together with representative literature data, are summarized in Scheme IV.

Scheme IV. ^{13}C–^{77}Se Coupling Constants for C–Se Bonds, Hz



[a] Values taken from ref 21. [b] Values taken from ref 22.

The signs of the coupling constants are assumed to be negative, in consonance with the earlier findings.[21,22] Bis(2-aminoethyl) selenide perchlorate (**13**) and the tetrazole derivative **24b** both give values for sp^3-hybridized carbons similar to those reported[21,22] in the literature, whereas a value of −136.7 Hz is observed for C-2 of benzoselenazole (**17**; sp^2), suggesting that direct ^{13}C–^{77}Se coupling constants for sp^2 carbons should be roughly twice as large as those for sp^3 carbons. We had hoped to investigate the question of whether ^{13}C–^{77}Se coupling might be sensitive to the state of hybridization of selenium as well as of carbon, but the low intensity of signals due to nonprotonated carbons attached to selenium[8] have so far prevented us from doing so.

Experimental Section

^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer at ambient temperature and for 0.25–1.0 M solutions in Me_2SO-d_6 containing tetramethylsilane as internal reference, unless otherwise stated. For decoupled spectra flip angles were normally 18–27°, and sensitivity enhancement and apodization parameters were −0.4 and 0.187, respectively. Coupled spectra were observed by the gated decoupling technique, using a 2-s pulse delay. Spectra of organoselenium compounds were run in the dark. IR spectra were determined on Perkin-Elmer 421 or 621 spectrophotometers, and UV spectra on a Cary 14 spectrophotometer. ^1H NMR spectra were recorded on a Varian T-60 spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Carbon diselenide was obtained from Strem Chemicals, Inc., Danvers, Mass., and used as received; all experiments with this reagent were performed in a good hood and in subdued light, with exclusion of oxygen and moisture. Residues were destroyed using ethanolic potassium hydroxide or ethanol–piperidine mixtures. Benzene was dried over Linde Molecular Sieve, pore size 4 Å.

Reactions with Carbon Diselenide: 1,3,4-3*H*-Thiadiazoline-2-selone (2). A solution of 4-methyl-3-thiosemicarbazide (1.05 g, 10.0 mmol) in refluxing benzene (250 mL) was dried azeotropically (Dean–Stark trap), after which the trap was replaced by an Allihn condenser connected to an absorption trap containing ethanolic potassium hydroxide. The apparatus was then purged with dry nitrogen, after which carbon diselenide (0.80 mL, 2.14 g, 12.6 mmol) in dry benzene (50 mL) was added dropwise to the stirred, refluxing mixture during 0.5 h. Stirring and reflux were continued for a further 2 h, by which time evolution of hydrogen selenide had virtually ceased. The mixture, still under nitrogen, was allowed to cool, and the precipitated product collected, washed with benzene, and immediately dried in vacuo over phosphoric oxide, potassium hydroxide, and paraffin wax shavings. The selone (2) (1.80 g; 93%) was a fluffy pink solid: mp 123.5–124 °C dec; UV λ_{max} (95% ethanol) 338 nm (ϵ 12 800); ^{1}H NMR δ_{Me_4Si} (Me_2SO-d_6) 2.86 (d, J = 5 Hz, 3), 7.69 (q, J = 5 Hz, 1), 13.99 (br s, 1).

Anal. Calcd for $C_3H_5N_3SSe$: C, 18.56; H, 2.60; N, 21.65; S, 16.52; Se, 40.68. Found: C, 18.45; H, 2.50; N, 21.69; S, 16.74; Se, 40.54.

The following compounds were prepared similarly.

5-Methylamino-1,3,4-3*H*-selenadiazoline-2-selone (3) (93% from 4-methyl-3-selenosemicarbazide[23]): pale orange solid; mp 143–144 °C dec; UV λ_{max} (95% ethanol) 267 (ϵ 2400), 343 nm (13 600); ^{1}H NMR δ_{Me_4Si} (Me_2SO-d_6) 2.81 (d, J = 4 Hz, 3), 7.57 (br q, 1), 13.75 (br s, 1).

Anal. Calcd for $C_3H_5N_3Se_2$: C, 14.95; H, 2.09; N, 17.43; Se, 65.52. Found: C, 14.67; H, 2.30; N, 16.88; Se, 66.15.

5-(*p*-Toluidino)-1,3,4-3*H*-thiadiazoline-2-selone (5) [95% from 4-(*p*-tolyl)-3-thiosemicarbazide[4]]: pale pink felted needles; mp 156–157 °C dec; UV λ_{max} (95% ethanol) 239 (ϵ 13 600), 296 (5500), 343 nm (16 800); ^{1}H NMR δ_{Me_4Si} (Me_2SO-d_6) 2.28 (s, 3), 7.17 (m, 2), 7.32 (m, 2), 10.18 (s, 1), 14.25 (br s, 1).

Anal. Calcd for $C_9H_9N_3SSe$: C, 40.01; H, 3.36; N, 15.55; S, 11.86; Se, 29.22. Found: C, 40.08; H, 3.34; N, 15.65; S, 11.79; Se, 29.05.

5-(*p*-Toluidino)-1,3,4-3*H*-selenadiazoline-2-selone (7) [95% from 4-(*p*-tolyl)-3-selenosemicarbazide[6]]: pale yellowish fluffy needles; mp 168.5–170 °C dec; UV λ_{max} (95% ethanol) 236 (ϵ 16 400), 286 (sh) (6600), 354 nm (19 200); ^{1}H NMR δ_{Me_4Si} (Me_2SO-d_6) 2.25 (s, 3), 7.19 (m, 2), 7.33 (m, 2), 10.10 (br s, 1), 13.67 (br s, 1).

Anal. Calcd for $C_9H_9N_3Se_2$: C, 34.09; H, 2.86; N, 13.25; Se, 49.80. Found: C, 34.19; H, 2.93; N, 13.12; Se, 49.98.

5-(2-Thienyl)-1,3,4-3*H*-thiadiazoline-2-selone (9) (72% from thiophene-2-thiocarbohydrazide[24]): greenish-yellow plates; mp 137–139 °C dec; UV λ_{max} (95% ethanol) 240 (ϵ 7000), 287 (7500), 372 nm (14 000); ^{1}H NMR δ_{Me_4Si} (Me_2SO-d_6) 7.25 (d × d, J = 3.6, 5.0 Hz, 1), 7.71 (d × d, J = 3.6, 1.2 Hz, 1), 7.91 (d × d, J = 5.0, 1.2 Hz, 1).

Anal. Calcd for $C_6H_4N_2S_2Se$: C, 29.15; H, 1.63; N, 11.33; S, 25.94; Se, 31.94. Found: C, 28.92; H, 1.59; N, 11.30; S, 25.75; Se, 31.76.

5-(*p*-Toluidino)-1,3,4-3*H*-selenadiazoline-2-thione (6). 4-(*p*-Tolyl)-3-selenosemicarbazide[6] (0.9 g, 3.9 mmol) was dissolved in dimethylformamide (25 mL) by warming on the steam bath. The solution was cooled to 25 °C and a solution of thiophosgene (0.3 mL, 4.6 mmol) in ether (25 mL) added dropwise with stirring. The resulting mixture was stirred for a further 2.5 h at room temperature and then poured into water (200 mL). The oil which appeared solidified slowly on standing. The crude product was stirred with 1 N hydrochloric acid for 15 min, then collected and digested with 1 N sodium hydroxide. Reacidification of the alkaline digest with concentrated hydrochloric acid furnished the thione as a pale yellow flocculent solid, mp 199–201 °C dec (0.5 g, 47%). Recrystallization from ethanol gave yellow-brown prisms: mp 198–200 °C dec; IR ν_{max} 3110, 2900 (NH), 1600, 1560, 810 cm^{-1}; ^{1}H NMR δ_{Me_4Si} (Me_2SO-d_6) 2.25 (s, 3), 7.13 (m, 2), 7.28 (m, 2), 9.88 (s, 1), 13.30 (br s, 1).

Anal. Calcd for $C_9H_9N_3SSe$: C, 40.01; H, 3.36; N, 15.55; S, 11.86; Se, 29.22. Found: C, 40.16; H, 3.40; N, 15.54; S, 11.71; Se, 29.16.

5-(2-Thienyl)-1,3,4-3*H*-thiadiazoline-2-thione (8). Thiophene-2-carboxylic acid hydrazide (25 g, 0.18 mol) was added to a solution of potassium hydroxide (11.8 g, 0.18 mol) in anhydrous ethanol (200 mL). To the resulting yellow solution was added carbon disulfide (25 mL, 0.42 mol) and the mixture was stirred at room temperature. After 5 min, a thick yellow precipitate formed. The mixture was stirred for a further 10 min, after which the product was collected, washed with ethanol and then with ether, and dried in vacuo, giving potassium 3-(2-thenoyl)dithiocarbazate, mp 273–276 °C dec (42 g, 93%) (lit.[5] mp 284–285 °C). Without further purification, the foregoing dithiocarbazate salt (41.5 g, 0.16 mol) was added slowly, with stirring, to concentrated sulfuric acid (200 mL), the temperature being maintained at 10–15 °C. After addition was complete, the mixture was stirred for a further 1 h, during which time the temperature was allowed to rise to 25 °C. The resulting slightly turbid solution was poured into ice–water (1500 mL) and the yellow precipitate that formed was collected, washed with water, and dissolved in 1% aqueous potassium hydroxide (1500 mL). After filtration to remove traces of insoluble material, the yellow solution was reacidified with concentrated hydrochloric acid, and the resulting yellow precipitate was collected and washed with water. The product was partially dried and then recrystallized from an ethanol–water mixture (260 mL, 2:1). The thione was obtained as pale yellow needles: mp 199–200 °C (10.1 g, 32%; lit.[5] mp 193–194 °C); IR ν_{max} 3067, 2860 (NH), 1550, 1500, 1416, 1288, 736, 729 cm^{-1}; UV λ_{max} (95% ethanol) 232 (ϵ 6700), 265 (8100), 350 nm (ϵ 16 600); ^{1}H NMR δ_{Me_4Si} (Me_2SO-d_6) 7.31 (d × d, J = 4, 5 Hz, 1), 7.51 (d × d, J = 4, 1.5 Hz, 1), 7.80 (d × d, J = 5, 1.5 Hz, 1), 14.51 (br s, 1).

Anal. Calcd for $C_6H_4N_2S_3$: C, 35.98; H, 2.01; N, 13.99; S, 48.02. Found: C, 35.80; H, 1.92; N, 13.83; S, 47.82.

Bis(5-methylamino-1,3,4-thiadiazol-2-yl) Disulfide (10). Aqueous hydrogen peroxide (30%; 1.7 mL, 15 mmol) was added dropwise to a solution of 5-methylamino-1,3,4-thiadiazole-2-thiol (1.47 g, 10 mmol) in methanol (50 mL) during 5 min. The resulting bright yellow solution was stirred until precipitation of the product was complete (2 h). Collection furnished the disulfide as a yellow solid, mp 205–206 °C dec (1.35 g, 92%); IR ν_{max} (KBr) 3320 (sh), 3220 (NH); UV λ_{max} (2-methoxyethanol) 282 (sh) (ϵ 8200), 324 nm (10 300); ^{1}H NMR δ_{Me_4Si} (Me_2SO-d_6) 2.96 (d, J = 5 Hz, 3), 8.19 (br q, J = 5 Hz, 1).

Anal. Calcd for $C_6H_8N_6S_4$: C, 24.65; H, 2.76; N, 28.74; S, 43.86. Found: C, 24.66; H, 2.76; N, 28.88; S, 43.96.

Bis(5-methylamino-1,3,4-thiadiazol-2-yl) Diselenide (11). A solution of the selone (2; 100.4 mg) in methanol (5 mL) was freed from traces of elemental selenium (Celite), and the clear filtrate was stored in an open vessel in the dark. After 3 days the product was collected, washed with methanol, benzene (to remove any colloidal selenium), and finally again with methanol, and air dried. The diselenide formed orange needles or prisms: mp 200–202 °C dec (78.5 mg, 79%); IR ν_{max} 3400 (sh), 3200 (NH); UV ν_{max} (2-methoxyethanol) 264 (ϵ 9300), 280 (9600), 325 nm (7600); ^{1}H NMR δ_{Me_4Si} (Me_2SO-d_6) 2.93 (d, J = 4.5 Hz, 3), 7.99 (br q, J = 4.5 Hz, 1).

Anal. Calcd for $C_6H_8N_6S_2Se_2$: C, 18.66; H, 2.09; N, 21.76; S, 16.60; Se, 40.89. Found: C, 18.72; H, 2.09; N, 21.73; S, 16.70; Se, 40.61.

Bis(2-aminoethyl) Sulfide Perchlorate (12). Perchloric acid (70%; 2.87 g, 0.02 mol) was added dropwise to a stirred solution of bis(2-aminoethyl) sulfide (1.20 g, 0.01 mol) in anhydrous ethanol (25 mL), which was maintained at 0 °C. The mixture was stirred for a further 15 min after addition was complete, and the solid was then collected and washed sparingly with anhydrous ethanol, followed by ether. The product (2.74 g) had mp 187.5–188.5 °C. Recrystallization by dissolution in methanol, followed by gradual addition of absolute ethanol to the boiling solution until all the methanol had been displaced, gave the pure perchlorate salt as cream-colored needles, mp 189.5–190.5 °C (2.45 g).

Anal. Calcd for $C_4H_{14}Cl_2N_2O_8S$: C, 14.96; H, 4.39; Cl, 22.08; N, 8.72; O, 39.86; S, 9.98. Found: C, 15.07; H, 4.39; Cl, 21.86; N, 8.72; O, 39.98; S, 10.05.

Bis(2-aminoethyl) Selenide Perchlorate (13). 2,2′-Bis(2-aminoethyl) selenide was prepared from aziridine and hydrogen selenide by the method of Kroll and Bolton.[25] A solution of the diamine (26.35 g) in absolute ethanol (400 mL) was saturated with hydrogen chloride and the crystalline precipitate (31.17 g; mp 147–148.5 °C) was recrystallized twice by dissolution in methanol, followed by addition of ethanol to the boiling solution until all methanol had been displaced, giving needles, mp 149.5–150 °C (21.75 g). A further recrystallization gave an analytical sample of the hydrochloride: mp 150–151 °C; ^{1}H NMR δ_{Me_4Si} (Me_2SO-d_6) 2.94, 3.04 (aa′ bb′ multiplet, 8), 8.40 (br s, 6).

Anal. Calcd for $C_4H_{14}Cl_2N_2Se$: C, 20.02; H, 5.88; Cl, 29.54; N, 11.67; Se, 32.90. Found: C, 20.09; H, 5.83; Cl, 29.74; N, 11.69; Se, 32.87.

A solution of the foregoing hydrochloride (2.4 g) in water (5 mL) was treated with aqueous sodium hydroxide (4 mL; 50%) at 0 °C and the liberated diamine was isolated by extraction of the mixture with ether, followed by evaporation of the dried ethereal extracts. The oil so obtained was taken up in absolute ethanol and treated with perchloric acid (2.87 g; 70%) at 0 °C, and the resulting precipitate was collected and recrystallized from methanol–ethanol by the method described above. The perchlorate formed needles, mp 162–163 °C (2.32 g).

Anal. Calcd for $C_4H_{14}Cl_2N_2O_8Se$: C, 13.05; H, 3.83; Cl, 19.27; N, 7.61; Se, 21.45. Found: C, 13.28; H, 4.06; Cl, 18.81; N, 7.65; Se, 21.70.

5-Methylthio-1-phenyl-1,2,3,4-tetrazole (24a). 1-Phenyl-1,2,3,4-tetrazole-5-thiol (35.6 g, 0.20 mol) was added to a solution of potassium hydroxide (14.02 g, 0.25 mol) in methanol (178 mL), and

the resulting solution was stirred while methyl iodide (126.5 g, 0.89 mol) was added dropwise. The mixture was stirred under reflux for 4.5 h, then cooled and poured into water (300 mL). Extraction of the mixture with ether (2 × 300 mL), followed by evaporation of the dried (sodium sulfate) ether phase, gave a residue which was recrystallized (Norit) from ethanol. The methylthio derivative was obtained as plates: mp 78.5–80 °C (27.0 g; 70%; lit.[14] mp 84 °C); UV λ_{max} (95% ethanol) 228 (ε 7700), 242 (sh) nm (7000); ^{1}H NMR δ_{Me_4Si} (Me_2SO-d_6) 2.84 (s, 3), 7.80 (s, 5).

Anal. Calcd for $C_8H_8N_4S$: C, 49.98; H, 4.19; N, 29.14; S, 16.68. Found: C, 49.96; H, 4.26; N, 29.20; S, 16.73.

5-Methylseleno-1-phenyl-1,2,3,4-tetrazole (24b). This preparation was carried out in subdued light under an atmosphere of nitrogen. A methanolic solution of bis(methoxymagnesium) diselenide was prepared, according to the procedure of Günther,[15] from magnesium (0.75 g, 31 mg-atom), red selenium (1.97 g, 25 mg-atom), and methanol (40 mL), in the presence of a trace of iodine. The reagent was allowed to cool somewhat and a warm solution of 5-chloro-1-phenyl-1,2,3,4-tetrazole (4.52 g, 25 mmol) in methanol (100 mL) was added dropwise with stirring during 15 min. Stirring was continued for 1 h at room temperature (color change from red-brown to gray) and then for 2 h under reflux. The mixture was then filtered (Celite), and the filtrate was evaporated under reduced pressure (bath temperature <40 °C). The semisolid residue (8.23 g) was triturated with ether and the insoluble material removed. Evaporation of the ether filtrate under reduced pressure and trituration of the residue with hexane gave a grayish solid, mp 60–70 °C (2.22 g), which on dissolution in ethyl acetate, followed by gradual addition of hexane to the cloud point, gave 5-methylseleno-1-phenyl-1,2,3,4-tetrazole as pale orange masses: mp 88–89 °C (0.82 g, 14%); IR ν_{max} (CsI) 1596, 1571, 1499, 1410, 1371, 1269, 1231, 1012, 768, 692, 540, 398 cm^{-1}; UV λ_{max} (95% ethanol) 230 nm (ε 6800); ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 2.77 (s, 3), 7.58 (s, 5).

Anal. Calcd for $C_8H_8N_4Se$: C, 40.20; H, 3.37; N, 23.42; Se, 33.01. Found: C, 40.31; H, 3.33; N, 23.57; Se, 32.79.

3-Ethyl-5-methylthio-1-phenyl-1,2,3,4-tetrazolium Fluoroborate (27). A solution of triethyloxonium fluoroborate (14.2 g, 75 mmol) in dry dichloromethane (100 mL) was added dropwise to a stirred solution of 5-methylthio-1-phenyl-1,2,3,4-tetrazole (14.4 g, 75 mmol) in dichloromethane (100 mL), and stirring was continued for 8 days. The solid which had separated was collected, dissolved in dichloromethane, and reprecipitated with ether. The pure tetrazolium salt had: mp 156.5–157.5 °C (9.9 g); IR ν_{max} 1598, 1500, 1450, 1424, 1055 (vs, BF_4^-), 776, 695 cm^{-1}; UV λ_{max} (CH_2Cl_2) 271 (sh) nm (ε 4000); ^{1}H NMR δ_{Me_4Si} (Me_2SO-d_6) 1.69 (t, J = 7.5 Hz, 3), 2.88 (s, 3), 5.05 (q, J = 7.5 Hz, 2), 6.80 (s, 5).

Anal. Calcd for $C_{10}H_{13}BF_4N_4S$: C, 38.98; H, 4.25; B, 3.51; F, 24.65; N, 18.18; S, 10.41. Found: C, 39.05; H, 4.28; B, 3.52; F, 24.37; N, 18.36; S, 10.33.

Evaporation of the remaining dichloromethane filtrate gave further product, which, after dissolution in dichloromethane and reprecipitation with ether, gave material with mp 145–149 °C (14.4 g). Despite the lower melting point, this fraction was identical (^{1}H NMR) with the analytical sample. Prolonged drying in vacuo reduced the total weight of product from 24.3 to 23.1 g (100%).

3-Ethyl-1-phenyl-1,2,3,4-tetrazolium 5-thiolate (28). Sodium (313.6 mg, 13.64 mmol) was dissolved in methanol, and the resulting solution was cooled to 5 °C and saturated (stirring) with hydrogen sulfide during 2.5 h. A slurry of 3-ethyl-5-methylthio-1-phenyl-1,2,3,4-tetrazolium fluoroborate (1.85 g, 6.00 mmol) in methanol (75 mL) was then added slowly during 0.5 h, with continued passage of hydrogen sulfide. After all the tetrazolium salt had been added, passage of gas and stirring were continued for a further 0.5 h, during which time the mixture was allowed to reach room temperature. The hydrogen sulfide supply was then disconnected and the mixture stirred gently in a closed system overnight. The resulting yellow solution was freed from hydrogen sulfide by passage of a stream of nitrogen for 2.5 h, after which the mixture was taken to dryness under reduced pressure. Addition of water to the residue removed most of the color, leaving a crystalline product which was collected, mp 104–109 °C (1.13 g). Recrystallization from an ethyl acetate–hexane mixture (2:1 v/v) gave 3-ethyl-1-phenyl-1,2,3,4-tetrazolium 5-thiolate as faintly yellowish-white prisms: mp 114.5–115 °C (0.90 g, 73%); IR ν_{max} 1594, 1589, 1496, 1359, 1178, 774, 769, 733, 693, 689 cm^{-1}; ^{1}H NMR δ_{Me_4Si} (Me_2SO-d_6) 1.60 (t, J = 7 Hz, 3), 4.70 (q, J = 7 Hz, 2), 7.4–8.1 (m, 5).

Anal. Calcd for $C_9H_{10}N_4S$: C, 52.41; H, 4.89; N, 27.16; S, 15.54. Found: C, 52.35; H, 4.93; N, 27.20; S, 15.37.

3-Ethyl-1-phenyl-1,2,3,4-tetrazolium 5-Selenolate (29). This reaction was carried out in subdued light under an atmosphere of nitrogen. A deaerated mixture of sodium hydrogen carbonate (0.84 g, 10 mmol), water (67 mL), and ethanol (22 mL) was stirred at 0 °C while hydrogen selenide [generated by addition of 1.5 N sulfuric acid (13.2 mL, 20 mequiv) to aluminum selenide (0.97 g, 3.3 mmol)] was introduced. To the resulting solution of sodium hydrogen selenide was quickly added a solution of 3-ethyl-5-methylthio-1-phenyl-1,2,3,4-tetrazolium fluoroborate (1.54 g, 5 mmol) and sodium hydrogen carbonate (0.42 g, 5 mmol) in water (77 mL) and ethanol (35 mL). The resulting amber solution was allowed to reach room temperature during 2 h, after which stirring was continued for a further 22 h. The mixture was then freed from hydrogen selenide in a stream of nitrogen. All effluent gases were passed through sodium hydroxide and lead acetate traps. The reddish-tan solid which had separated was collected, washed with water, dried, and recrystallized from an ethyl acetate–hexane mixture to give 3-ethyl-1-phenyl-1,2,3,4-tetrazolium 5-selenolate as yellow needles: mp 128.5–129 °C (0.90 g, 71%); IR ν_{max} 1600, 1501, 1345, 1335, 1170, 780, 724, 700 cm^{-1}; ^{1}H NMR δ_{Me_4Si} (Me_2SO-d_6) 1.58 (t, J = 7.5 Hz, 3), 4.72 (q, J = 7.5 Hz, 2), 7.4–8.0 (m, 5).

Anal. Calcd for $C_9H_{10}N_4Se$: C, 42.70; H, 3.98; N, 22.13; Se, 31.19. Found: C, 42.91; H, 3.89; N, 22.24; Se, 30.94.

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Registry No.—**1b,** 27386-01-2; **2b,** 63528-58-5; **3b,** 63528-59-6; **4b,** 14731-25-0; **5b,** 63528-60-9; **6b,** 63528-61-0; **7b,** 63528-62-1; **8b,** 41526-33-4; **9b,** 63528-63-2; **10,** 32873-72-6; **11,** 63528-64-3; **12,** 63528-65-4; **13,** 63528-66-5; **13** HCl analogue, 63528-67-6; **14,** 882-33-7; **15,** 1666-13-3; **16,** 95-16-9; **17,** 273-91-6; **18,** 149-30-4; **19,** 10486-58-5; **22b,** 86-93-1; **23a,** 16618-41-0; **23b,** 32550-63-3; **24a,** 1455-92-1; **24b,** 62638-96-4; **24c,** 14210-25-4; **25,** 5117-07-7; **26,** 13078-30-3; **27,** 62638-94-2; **28,** 62681-14-5; **29,** 62638-95-3; carbon diselenide, 506-80-9; 4-methyl-3-thiosemicarbazide, 6610-29-3; 4-methyl-3-selenosemicarbazide, 5943-43-1; 4-(*p*-tolyl)-3-thiosemicarbazide, 13278-67-6; 4-(*p*-tolyl)-3-selenosemicarbazide, 14223-52-0; thiophene-2-thiocarbohydrazide, 63528-68-7; thiophene-2-carboxylic acid hydrazide, 2361-27-5; 3-(2-thenoyl)dithiocarbazate, 63528-69-8; bis(2-aminoethyl) sulfide, 871-76-1; bis(2-aminoethyl) selenide, 27974-50-1; bis(methoxymagnesium) diselenide, 14310-09-9; triethyloxonium fluoroborate, 368-39-8.

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Mode of Attack by Crude Papain on Racemic Z-Dipeptides That Contain a β-Alanine Residue during Anilide and Phenylhydrazide Syntheses

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A crude extract of papain exclusively attacked the carbonyl of an α-amino acid residue of Z-β-Ala-DL-Ala and Z-DL-Ala-β-Ala during catalyzed reactions with aniline or phenylhydrazine as the nucleophiles. The optical purities of the resultant, insoluble products, Z-β-Ala-L-Ala-NHPh, Z-β-Ala-L-Ala-NHNHPh, Z-L-Ala-NHPh, and Z-L-Ala-NHNHPh, were all substantially above 90%.

In papain-catalyzed reactions with nucleophiles, attack on a reactive Z dipeptide[1] can occur either at the carboxyl terminal[2] or at the carbonyl group[2,3] of the amide structure that joins the two amino acid residues. It was the purpose of the current study to examine the reactions of aniline and phenylhydrazine with the two racemic Z dipeptides that combine β-alanine with DL-alanine, when a crude papain extract was used as the catalyst. Although β-alanine is a well-known residue of the natural dipeptides, carnosine or anserine, it is not a component residue of proteins. Crude papain[4] contains a mixture of sulfhydryl proteases,[5,6] Enz-SH. It has frequently been utilized as a chiral, catalytic agent for resolutions of N-blocked DL-amino acids,[7,8] using a variety of nucleophiles.[8-11]

The reaction of Z-β-Ala-DL-Ala with RNH_2 in the presence of papain gave the Z-β-Ala-L-Ala-NHR derivatives with the peptide bond intact. Optical purities of the resultant anilide or phenylhydrazide were both approximately 99%.

Z-β-Ala-CO-NH-DL-Ala-COOH

$$\xrightarrow[\text{papain}]{RNH_2} \text{Z-β-Ala-CO-NH-L-Ala-CO-NHR (insoluble)} + \text{Z-β-Ala-CO-NH-D-Ala-COOH (soluble)}$$

On the other hand, with the β-Ala residue as the carboxyl terminal residue, the attack occurred at the peptide structure to give Z-L-Ala-NHR plus β-Ala. Respective optical purities of the anilide and phenylhydrazide were about 94 and 99%.

Z-DL-Ala-CO-NH-β-Ala-COOH

$$\xrightarrow[\text{papain}]{RNH_2} \text{Z-D-Ala-CO-NH-β-Ala-COOH (soluble)} + \text{Z-L-Ala-CO-NHR (insoluble)} + \text{NH}_2\text{-β-Ala-COOH (soluble)}$$

Similar reactions were encountered when the L enantiomers, Z-β-Ala-L-Ala and Z-L-Ala-β-Ala, replaced the corresponding racemic modifications. Important details are summarized in Tables I and II. As might have been anticipated, on the basis of the absence of a β-Ala residue in proteins, crude papain did not catalyze such reactions with Z-β-Ala or Z-β-Ala-β-Ala. Furthermore, Z-β-Ala-D-Ala and Z-D-Ala-β-Ala were equally unproductive when appropriately tested.

An investigation of the pH dependence of yield was made for reactions of Z-β-Ala-Gly and Z-Gly-β-Ala with NH_2Ph and NH_2NHPh. Again, the nucleophilic attack was made exclusively on the carbonyl of the α-amino acid residue. pH optima are shown for the sole, insoluble products: Z-β-Ala-Gly-NHPh (pH 4.75); Z-β-Ala-Gly-NHNHPh (pH 4.25); Z-Gly-NHPh (pH 4.50); Z-Gly-NHNHPh (pH 4.25).

Thin-layer chromatography[2] on plastic plates coated with silica gel established that each successful catalysis yielded an insoluble product with a single structure. R_f values of reference compounds are recorded in Table III.

Experimental Section

Preparation of Active Crude Papain. The crude, active papain necessary for these experiments was prepared by a slight modification of the procedure outlined by Bennett and Niemann.[4]

Reactions of Z-β-Ala-L-Ala and Z-β-Ala-DL-Ala with Aniline and Phenylhydrazine. A mixture of 0.5000 g of Z-β-Ala-L-Ala, 0.26 mL of aniline or phenylhydrazine, 0.1000 g of papain, 0.1000 g of L-cysteine·HCl·H_2O, 25 mL of 0.50 buffer at pH 4.5, and 2 mL of hexamethylphosphoramide was filtered and then incubated at 40 °C. At appropriate time intervals, the solid reaction product was removed by suction filtration, washed with distilled water, dried in the incubator for several days, and weighed. When necessary, the solid was treated with carbon in methanol and filtered four times by suction filtration, with the terminal filtration through a fritted glass funnel. Sufficient methanol was used each time to remove all product from the funnel. Purified product was isolated either by rotary evaporation under reduced pressure or else evaporation in a Petri dish under the hood: % N Calcd for Z-β-Ala-Ala-NHPh 11.38, found 11.10; % N Calcd for Z-β-Ala-L-Ala-NHNHPh 14.68, found 14.32. Reactions of Z-β-Ala-DL-Ala were done on four times the scale of Z-β-Ala-L-Ala. Mixture melting points with corresponding products from Z-β-Ala-L-Ala showed no change.

The Behavior of Z-L-Ala-β-Ala and Z-DL-Ala-β-Ala toward Analine and Phenylhydrazine. For Z-L-Ala-β-Ala the solution contained 0.5000 g of Z-L-Ala-β-Ala, 0.52 mL of aniline or phenylhydrazine, 0.1000 g of papain, 0.1000 g of L-cysteine·HCl·H_2O, 25 mL of 0.50 M buffer at pH 4.5, and 2.0 mL of hexamethylphosphoramide. Following filtration, the solution was incubated at 40 °C. After appropriate time intervals, insoluble product was removed by suction filtration, dried for several days in the incubator, and then weighed. A mixture melting point for the anilide product with known Z-L-Ala-NHPh[2,7] exhibited no change. Similarly, the Z-L-Ala-NHNHPh from this study when mixed with known compound[12] showed no change in melting point. After purification: % N Calcd for Z-L-Ala-NHPh 9.39, found 9.62; % N Calcd for Z-L-Ala-NHNHPh 13.41, found 13.52. Reactions of Z-DL-Ala-β-Ala were performed in exactly twice the quantities used for Z-Ala-β-Ala. After purification: % N Calcd

Table I. Insoluble Products from Z-β-Ala-L-Ala and Z-β-Ala-DL-Ala

Product (mp, °C)	Incubation period, h	Wt, g	$[\alpha]^{25°C}_D$ in pyridine	% L enantiomer
Z-β-Ala-L-Ala-NHPh (187–188)	0–48	0.215	−48.0°	100
	48–168	0.382		
Z-β-Ala-Ala-NHPh[a] (187–188)	0–48	0.321	−47.1°	99
	48–168	0.448		
Z-β-Ala-L-Ala-NHNHPh (181–182)	0–48	0.375	−46.6°	100
	48–168	0.357		
Z-β-Ala-Ala-NHNHPh[a] (181–182)	0–48	0.447	−45.2°	99
	48–168	0.617		

[a] The product from Z-β-Ala-DL-Ala may contain some D enantiomer. Hence, Ala is used rather than L-Ala in designating the compound.

Table II. Insoluble Products from Z-L-Ala-β-Ala and Z-DL-Ala-β-Ala

Product (mp, °C)	Incubation period, h	Wt, g	$[\alpha]^{25°C}_D$ in pyridine	% L enantiomer
Z-L-Ala-NHPh (160–161)	0–24	0.2305	−36.3°	100
	24–48	0.0754		
	48–72	0.0118		
Z-Ala-NHh[a] (161–162)	0–24	0.2811	−31.7°	94
	24–48	0.0688		
Z-L-Ala-NHNHPh (153–155)	0–24	0.1373	−31.8°	100
	24–48	0.0506		
Z-Ala-NHNHPh[a] (153–155)	0–24	0.0979	−31.1°	99
	24–48	0.1033		
	48–168	0.1188		

[a] The reactant was Z-DL-Ala-β-Ala. Therefore, Ala, rather than L-Ala, is used to designate the product.

Table III. R_f Values of Standard Reference Compounds for Solvent Systems[a] of Methanol–Chloroform–Hexane

Compound	R_f value at 25 °C
Z-Gly-NHPh	0.28
Z-L-Ala-NHPh	0.36
Z-β-Ala-Gly-NHPh	0.04
Z-β-Ala-L-Ala-NHPh	0.16
Z-Gly-NHNHPh	0.17
Z-L-Ala-NHNHPh	0.28
Z-β-Ala-Gly-NHNHPh	0.06
Z-β-Ala-L-Ala-NHNHPh	0.10

[a] Volume proportions: for all anilides, 3:19:19; for all phenylhydrazides, 2.5:20:15.

for Z-Ala-NHPh 9.39, found 9.51; % N Calcd for Z-Ala-NHNHPh 13.41, found 13.37. Mixture melting points with known Z-L-Ala-NHPh[2,7] or Z-L-Ala-NHNHPh[12] displayed no change.

The Failure of Z-β-Ala, Z-β-Ala-β-Ala, Z-β-Ala-D-Ala, and Z-D-Ala-β-Ala as Suitable Substrates. Similar experiments were devised for attempted catalysis of reactions of these four potential substrates with aniline and phenylhydrazine as those used for the successful reactions. Reaction products were not obtained.

The pH Dependence of Yield for Reactions of Z-β-Ala-Gly or Z-Gly-β-Ala with Aniline and Phenylhydrazine. The general procedures have been outlined previously for similar experiments for other substrate combinations.[9-12] Hexamethylphosphoramide was added as a solubilizing agent for these Z-dipeptides. After incubation at 40 °C, single, insoluble reaction products were formed in each case. For each product, the pH optimum is given first, followed by the pH range that permitted at least one-half of the maximum yield to be obtained, then the incubation period, and finally the nitrogen analysis for new compounds. Z-β-Ala-Gly-NHPh: pH optimum 4.75; pH range 3.6–5.5; 6 days; % N Calcd 11.83, found 11.62. Z-β-Ala-Gly-NHNHPh: pH optimum 4.25; pH range 3.6–5.9; 6 days; % N Calcd 15.13, found 15.07. Z-Gly-NHPh: pH optimum 4.50; pH range 4.0–4.8; 4 days; mixture melting point with known Z-Gly-NHPh[9] no change. Z-Gly-NHNHPh: pH optimum 4.25; pH range 3.4–4.8; 4 days; mixture melting point with known Z-Gly-NHNHPh[7,12] no change. The melting points for Z-β-Ala-Gly-NHPh 182–183 °C; for Z-β-Ala-Gly-NHNHPh 164–165 °C.

Thin-Layer Chromatography of Solid Reaction Products Formed as a Result of Papain Catalysis. In order to confirm that each product obtained as an insoluble solid was solely the result of maintenance of the peptide structure or singularly the result of its cleavage, thin-layer chromatography was employed in a manner similar to procedures recently described.[2] The thin-layer plates plastic coated with silica gel were Baker-flex, silica gel IB2. A short wavelength UV light source was used to locate positions of migrated spots.

Determination of Optical Rotations of Optically Active Products from Reactions Catalyzed by Crude Papain. All optical rotations were determined by means of a Rudolph Model 80 high-precision polarimeter. Water-jacketed tubes were used, either 1 or 2 dm in length, depending on the substance being studied. The temperature was controlled at 25 °C by means of a constant-temperature bath. The concentration was about 1 g per 100 mL of solution. Eastman Spectrograde pyridine was used as the solvent.

Source of Potential Substrates. Z-β-Alanine and Z-β-alanyl-β-alanine were purchased from Sigma Chemical Co., St. Louis, Mo. All other Z dipeptides were made available through Dr. P. Grogg of Biosynthetika, Liestal, Switzerland.

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Registry No.—Papain, 9001-09-6; Z-β-Ala-L-Ala, 56120-15-1; Z-β-Ala-DL-Ala, 63250-94-2; aniline, 62-53-3; phenylhydrazine, 100-63-0; Z-β-Ala-L-Ala-NHPh, 63250-95-3; Z-β-Ala-L-Ala-NHNHPh, 63250-96-4; Z-L-Ala-β-Ala, 41273-31-8; Z-DL-Ala-β-Ala, 63250-97-5; Z-L-Ala-NHPh, 42166-73-4; Z-L-Ala-NHNHPh, 28861-55-4; Z-β-Ala-Gly, 58171-88-3; Z-Gly-β-Ala, 13029-38-4; Z-β-Ala-Gly-NHPh, 63250-98-6; Z-β-Ala-Gly-NHNHPh, 63250-99-7; Z-Gly-NHPh, 6833-09-6; Z-Gly-NHNHPh, 21855-71-0.

References and Notes

(1) Z is the accepted abbreviation for *N*-benzyloxycarbonyl.
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Ring-Closure Reactions. 10.[1] A Kinetic Study for the Formation of Macrocyclic Aromatic Ethers. Lack of the Rigid Group Effect on Large-Ring Formation[2]

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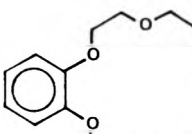
As a quantitative approach to the evaluation of the rigid group effect on large ring formation, the kinetics of the base-induced cyclization of a series of substrates $HOZO(CH_2)_{12}Br$, in which Z denotes varying phenylene and naphthylene moieties, have been studied. When allowance is made for the slightly different nucleophilicity of the anionic end in the various bifunctional compounds, the ease of ring closure turns out to be practically unaffected by the very different geometry and size of the rigid moieties. This remarkable result, which is at variance with widely accepted ideas, is discussed and compared with our previous findings in the field of many-membered ring formation.

In 1951 Baker et al.[3] suggested that the ease of ring closure of a long-chain bifunctional compound should be greatly enhanced by the presence of a number of atoms composing the chain itself held in the form of a rigid group suitable for ring closure. The *o*-phenylene unit was considered as a clean-cut example of a structural moiety fitting these requirements, since in ortho-disubstituted benzene derivatives at least four carbon atoms lie in the same plane with angles of approximately 120°.[3] Following Baker's arguments, Ziegler[4] explicitly referred to the "rigid group principle" as a general rule for many-membered ring formation.

While there is no doubt that such an effect can operate in the medium-ring region,[5,6] as to the large rings experimental evidence so far available is either scanty or even questionable. For example, the fact that compound **1** has been synthesized in far higher yield than compound **2** (80 and 1.8%, respectively)[7] was taken[8] as a clean-cut example of the rigid group effect. Such an interpretation is not very safe because the reaction conditions (base–solvent systems) as adopted for the preparation of the two compounds were not comparable with each other. Furthermore, the formation of macrocyclic monomeric (**3**) and dimeric (**4**) *o*-phthalate esters has been



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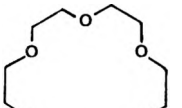

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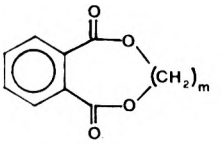

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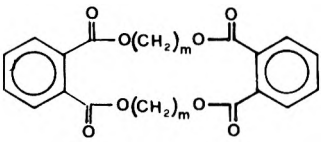

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claimed to be facile because of the presence of the rigid group(s) OOCC=COO,[8] but the evidence for such an ease is by no means convincing.

It has been suggested[4] that the rigid group should act by restriction of the rotational freedom in the open-chained precursor and, possibly, by reduction of the strain energy due to nonbonded interactions in the ring-shaped transition states.

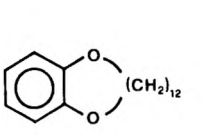
In recent studies[1,9] we have reported that both entropies and ethalpies of activation are only slightly dependent of chain length when large rings are formed, the latter being very close to the values of the strainless intermolecular counterparts. Hence, in the large-ring region little or no gain in the entropy term is expected upon reduction of the number of rotors by one unit nor any significant decrease of the strain energy upon introduction of a rigid group in an already strainless (or nearly so) transition state. In accordance with the above observations, evidence has been presented[1] that in the large-ring region ease of ring closure, as quantitatively expressed by the effective molarity, EM, is fairly insensitive to structural effects. EM values relative to five different reaction series lie well within a factor of 10, in spite of the fact that in two out of the five series a rigid group, viz., an *o*-phenylene unit, is present. It appears from these findings that the rigid group effect has a limited scope and should be either small or negligible for large rings.

A systematic investigation aimed at the elucidation of this problem calls for a kinetic study of the cyclization reactions of several α,ω-bifunctional compounds in which rigid groups of varying geometry and size have been incorporated. Reaction 1, in which Z denotes phenylene and naphthylene moieties, appeared to be suitable to the end under several respects. It had been extensively studied by Ziegler and Lüttringhaus[10] from the preparative point of view. Furthermore, macrocyclic aromatic ether formation via intramolecular Williamson synthesis is suitable for accurate kinetic work, as was shown by us in a series of recent papers.[1,6,11]

$$Br(CH_2)_mOZO^- \xrightarrow{k_{intra}} \overline{(CH_2)_mOZO} + Br^- \qquad (1)$$

$$MeOZO^- + BuBr \xrightarrow{k_{inter}} MeOZOBu + Br^- \qquad (2)$$

In this work we wish to report on the kinetics of the base-induced formation of macrocyclic diethers **5**–**9** from the



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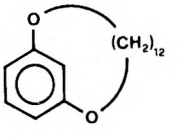

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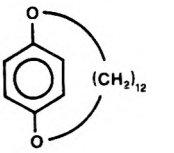

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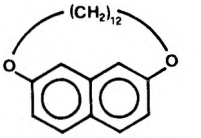

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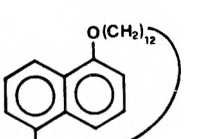

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Table I. Yields, Physical Constants, and Analytical Data for the Preparation of Mono-12-bromododecyl Ethers 11a–14a

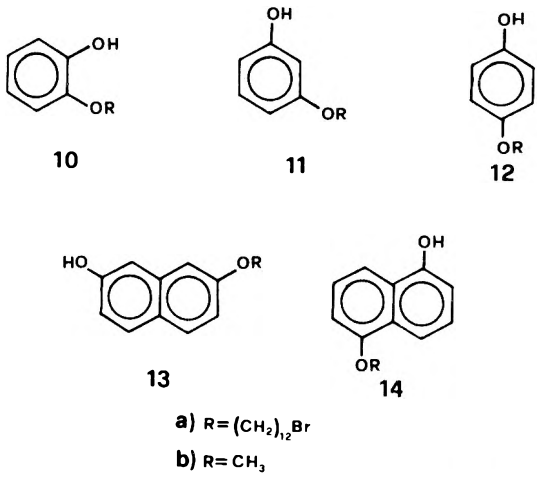
Compd	Registry no.	Yield, %	Mp, °C	Anal. Calcd, % C	H	Br	Found, % C	H	Br
11a	63163-44-0	33	55–57	60.50	8.18	22.36	60.36	8.22	22.20
12a	63163-45-1	35	80–82	60.50	8.18	22.36	60.63	8.20	22.34
13a	63163-46-2	37	93.5–95	64.86	7.67	19.61	65.01	7.64	19.72
14a	63163-47-3	26	76–77			19.61			19.24

Table II. Yields and Physical Constants of Monomethyl Ethers 10b–14b

Compd	Registry no.	Yield,%	Mp, °C, or $n^{20}D$	Lit. mp, °C, or $n^{20}D$	λ_{max}[a]	$10^{-3}\epsilon_{max}$[a]
10b	90-05-1	*b*	1.5434	1.5429[c]	280 (314)	3.0 (5.3)
11b	150-19-6	47	1.5506	1.5520[c]	278 (309)	2.3 (4.1)
12b	150-76-5	*b*	54.5–56.0	57.0[c]	297 (337)	3.3 (3.9)
13b	5060-82-2	41	113–115	117[d]	330 (374)	3.3 (5.2)
14b	3588-80-5	33	132–133 dec	140[e]	332 (364)	7.6 (12.9)

[a] UV data in Me_2SO solution. Values in parentheses refer to the corresponding anions obtained in the presence of excess KOH. [b] Commercial product. [c] "Handbook of Chemistry and Physics", Chemical Rubber Publishing Co., 50th ed, Cleveland, Ohio, 1969–1970. [d] O. Fischer and F. Hammerschmidt, *J. Prakt. Chem.*, [2] **94**, 24 (1916). [e] O. Fischer and C. Bauer, *J. Prakt. Chem.*, [2] **94**, 13 (1916).

mono-12-bromododecyl ethers of catechol, resorcinol, hydroquinone, and 2,7- and 1,5-dihydroxynaphthalene (compounds **10a–14a**, respectively). The dodecamethylene bridge



spanning the arylenedioxy groupings is a common structural unit, which ensures the above macrocycles to be essentially strainless, i.e., large rings, as shown by inspection of space-filling molecular models. In order to account for any possible difference in the nucleophilicity of the various oxide ions, the strictly analogous intermolecular reactions (eq 2) were also considered, namely the alkylation reactions with butyl bromide of the anions derived from the monomethyl ethers **10b–14b**.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer 257 spectrophotometer, from 2% solutions in CCl_4. Proton magnetic resonance spectra were recorded on a Jeol JNM-C60HL spectrometer, using Me_4Si as the internal reference. Ultraviolet spectra were recorded on a Beckman DB-GT instrument, fitted with a Kontron W+W 1100 recorder. Mass spectra were obtained on a AEI MS12 spectrometer. All melting and boiling points are uncorrected.

1,12-Dibromododecane (Fluka), resorcinol (Erba RP), hydroquinone (Erba RP), 2,7-dihydroxynaphthalene (Aldrich), and 1,5-dihydroxynaphthalene (Aldrich) were all reagent-grade commercial samples and used without further purification. Tetramethylammonium hydroxide (10% aqueous solution) was from Merck.

Mono-12-bromododecyl Ethers (10a–14a). o-Hydroxyphenyl 12-bromododecyl ether (**10a**) was available from a previous investigation.[12] All the other compounds were prepared according to the following general procedure. To a boiling solution of 1,12-dibromododecane (0.03 mol) and the appropriate dihydroxy compound (0.15 mol) in ethanol (70 mL) a solution of KOH (0.03 mol) in a small amount of ethanol was added in ca. 1 h. The reaction was carried out in a nitrogen atmosphere in order to prevent the oxidation of the aromatic compound in the alkaline reaction medium. The solution was refluxed until neutral (3–5 h), then most of the solvent was distilled off. Benzene was added to the residue and the last traces of solvent were removed by azeotropic distillation. The dry, solid residue obtained was finely ground in a mortar and extracted for several hours in a Soxhlet apparatus. Pentane was used as the extracting solvent in the case of compounds **11a** and **12a**, and hexane for compounds **13a** and **14a**. The desired products were obtained in a practically pure form by simply cooling the paraffinic extracts. For kinetic and analytical purposes, the compounds were further purified by elution with benzene on silica gel. Structure assignments were based on spectral data and elemental analyses. All the compounds showed strong hydroxyl absorption in the IR spectra at 3580–3600 cm^{-1}. The ^1H NMR spectra (in CCl_4 at 55 °C for **12a** and CD_3COCD_3 for **11a**, **13a**, and **14a**) were consistent with the expected structures and no extra peak was present. For all compounds common signals are present, namely those due to the $O(CH_2)_{12}Br$ grouping: δ 4.0 (br t, OCH_2), 3.5 (br t, CH_2Br), 1.3–2.0 (br m, with a prominent peak standing at δ 1.4, "central" methylene protons). The signal due to the OH group was in all cases detected as a sharp singlet, extremely variable in position. Complex multiplets were present in the aromatic proton region of the spectra of **11a**, **13a**, and **14a**, while **12a** exhibited a singlet at δ 6.7. Yields, physical constants, and analytical data of the synthesized compounds are listed in Table I.

Monomethyl Ethers (10b–14b). Guayacol (**10b**) (Merck) was purified by distillation. Hydroquinone monomethyl ether (**12b**) (Fluka) was crystallized twice from benzene. The other compounds were prepared as follows. To a stirred mixture of the appropriate dihydroxy compound (0.121 mol) and CH_3I (0.056 mol) in Me_2SO (140 mL) kept under CO_2-free nitrogen was added KOH (0.056 mol) dissolved in a small amount of EtOH. The mixture was then left at room temperature under nitrogen until neutral (2–4 h). Compound **11b** was isolated by fractional distillation of the residue obtained after aqueous workup and ether extraction. In the two other cases, isolation of the pure products was carried out as indicated above for the mono-12-bromododecyl ethers. All the compounds were further purified by elution with benzene on silica gel. IR and ^1H NMR spectra were consistent with the expected structure. Yield and physical constants are reported in Table II.

Hydroquinone Dodecamethylene Ether (7) and 2,7-Dihydroxynaphthalene Dodecamethylene Ether (8). The present cyclization procedure is an improvement over that previously described,[12,13] in which a suspension of excess NaOH was employed. The experimental conditions were changed by the device of adding the base, Me_4NOH, in a 1:1 mole ratio with respect to the mono-12-bro-

mododecyl ethers of hydroquinone and 2,7-dihydroxynaphthalene, **12a** and **13a**, respectively. In the general procedure, the reaction was carried out in a 250-mL, three-neck flask equipped with a magnetic stirrer. The central neck was fitted with a gas inlet and outlet and the two side necks were capped with silicon rubber. The flask was charged with Me_2SO (100 mL), thoroughly fluxed with pure nitrogen, and immersed in an oil bath heated at 80 °C. A nitrogen overpressure was kept throughout. The reagents were added to the well-stirred solvent by means of two glass hypodermic syringes whose needles were inserted through the septum-capped side necks. One syringe contained 10 mL of a 0.20 M solution of Me_4NOH in 80% Me_2SO and the other 2 mmol of the bifunctional compound dissolved in the minimum amount of Me_2SO. The addition was prolonged for ca. 2 h, care being taken to add the two reagents at the same rate. To this end a trace of fluorene as a visual indicator in the reaction medium was of a great aid, since the intense red color due to the anionic form appears in the presence of a slight excess of base. After the addition was over the mixture was cooled and worked up with a standard procedure. The pure ring compounds were obtained by column chromatography on silica gel with benzene as eluent. Compound **7**, 82% yield, mp 46–47 °C, M^+ 276.

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.46; H, 10.29.

Compound **8**, 95% yield, mp 111.5–113 °C, M^+ 326.

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 81.55; H, 9.38.

The ^1H NMR spectra were found to be in accordance with the expected structures. Apart from the ethereal methylene protons, which appeared as a partially resolved triplet centered at δ 4.1, the other methylenes of **7** are shown (in CCl_4) as a broad multiplet at δ 0.8–1.9, with a prominent peak at δ 0.9. Clearly the paracyclophane structure of **7** is responsible for the significant upfield shift due to transannular interaction of the central protons of the dodecamethylene bridge with the π-electron cloud of the aromatic nucleus.[14] In compound **8**, which has a (2,7)naphthalenophane structure, the bridge lies apart from the aromatic nucleus. In the ^1H NMR spectrum (in $CDCl_3$) of this compound the central methylene protons are shown at a "normal" position, namely, as a multiplet at δ 1.3–2.2, with a prominent peak at δ 1.45.

Kinetic Measurements. The mixed solvent (99% aqueous Me_2SO, v/v) and the KOH stock solution (1.61×10^{-2} N in 93% Me_2SO) were prepared and handled as previously reported.[9] Purification of Me_2SO according to the method of Bordwell et al.[15] did not lower any further the concentration of the acidic impurities (see general part). The kinetics were followed spectrophotometrically at wavelenghts corresponding to the absorption maxima of the conjugate bases of the substrates, and the optical density of the solutions was monitored for several half-lives. The concentration of the aromatic hydroxy compounds was in the range 1.5 to 2.5×10^{-4} M in both cyclization and intermolecular reactions, the latter being run in the presence of excess butyl bromide, viz., 5×10^{-3} to 3×10^{-2} M. The experimental data were treated according to the method of Guggenheim,[16] with Δ values not less than 2 or 3 half-lives. First-order plots were linear up to 80–85% reaction for both cyclizations and intermolecular alkylations.

Results and Discussion

We have recently reported[12,13] that use of the NaOH–Me_2SO system in macrocyclic ether formation via intramolecular Williamson synthesis is very convenient as compared to the classical Ziegler and Lüttringhaus' conditions,[10] namely, K_2CO_3 in AmOH under high dilution. Our cyclization procedure, which afforded fair to good yields of cyclic products without excessively high dilution, was further improved in the present work (see Experimental Section) when applied to the cyclization of compounds **12a** and **13a**. The ring compounds **7** and **8** were obtained in very good yields, namely, 82 and 95%, respectively, which can be compared with a 79% yield previously reported[12] for the formation of **5** from **10a**. These results indicate that in Me_2SO solution these cyclization reactions are virtually free from side reactions. Therefore, the kinetics were carried out under conditions close to those of the preparative runs, namely, in 99% aqueous Me_2SO at 25 °C. The anions derived from compounds **10–14** were generated in situ by the addition of a calculated amount of a KOH stock solution, as previously reported in our kinetic work on the lactonization of ω-bromoalkanoic acids.[9] Because the phenolic

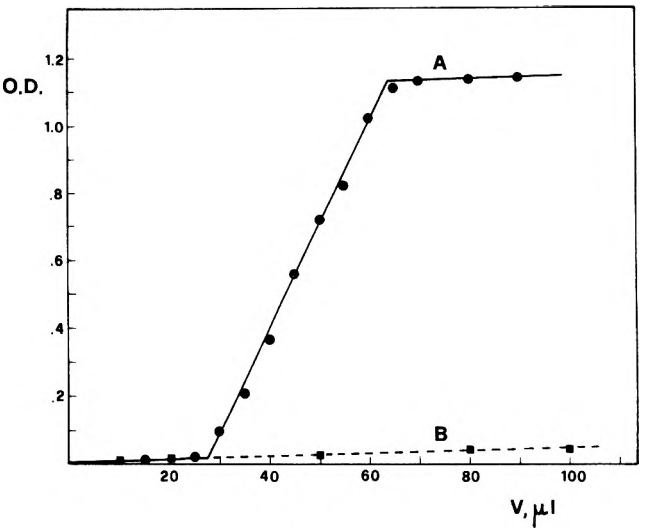


Figure 1. (A) Spectrophotometric titration at 374 nm of **13b** (2.51 mL, 2.09×10^{-4} M) in 99% Me_2SO with KOH 1.61×10^{-2} M in 93% Me_2SO. (B) Blank titration.

hydroxyl is significantly less acidic than carboxyl, the effectiveness of the KOH–99% Me_2SO system in promoting complete dissociation of the former was checked by spectrophotometric titration in some cases. A typical titration curve is reported in Figure 1. The consumption of base before the appearance of any absorption due to the anionic form of the substrate was attributed to the presence of acidic impurities in the solvent. The amount of base used up was found to be reproducible, and to correspond to an acidity of 1.80×10^{-4} N. As reported in the Experimental Section, it was not possible to reduce it any further by additional purifications of the solvent. The linearity of the titration curve indicates that in each point up to the equivalence point the amount of anionic form produced equals the total amount of added base, less that required by the blank titre. This means that the equilibrium

$$ROZOH + OH^- \rightleftharpoons ROZO^- + H_2O \qquad (3)$$

is quantitatively shifted to the right even at the low concentrations (ca. 2×10^{-4} M) used in the spectrophotometric titrations, which were similar to those in the kinetic runs. The kinetic runs were started by the fast addition of a very small volume (ca. 50–60 μL) of the KOH stock solution to a solution (2.5 mL) of the hydroxy compound. Since accuracy was poor in this operation, and any excess of base was undesirable, the latter was added in defect. Judging from the absorption of the solutions immediately after the addition of base, 50–90% of the starting hydroxy compound was neutralized. Under the given conditions, clean first-order behavior was obtained for the cyclization reactions with no effect of higher order contributions due to the polymerization reaction.[17]

The kinetic results are collected in Table III for both intra- and intermolecular reactions. The k_{intra} values span a factor of <6, indicating that the ease of ring closure is only slightly affected by the marked changes in geometry of the bifunctional substrates. In fact, most of the observed rate differences may be explained in terms of the varying nucleophilicity of the anionic end of the bifunctional substrate, as shown by the fact that k_{inter} values turn out to be sensitive to structural effects in much the same way as k_{intra} values. Thus, the differences in k_{intra} values largely disappear in the corresponding EM values, which are found to lie within a factor of 2. These results clearly indicate that the ease of ring closure to the examined large-ring diethers, as quantitatively expressed by the related EM values, is largely independent of the geometry and

Table III. Kinetic Data for the Cyclization Reaction (1) and for the Corresponding Intermolecular Model Reaction (2) in 99% Aqueous Me_2SO at 25.0 ± 0.2 °C

Compd	10^3k_{intra}, s^{-1} [a]	$10k_{inter}$, $M^{-1}s^{-1}$ [b]	10^2EM, M [c]	Log EM
10	9.04 ± 0.11	2.95 ± 0.03	3.06	−1.51
11	3.56 ± 0.04	1.53 ± 0.04	2.33	−1.63
12	7.22 ± 0.13	4.68 ± 0.20	1.54	−1.81
13	1.59 ± 0.04	1.07 ± 0.06	1.49	−1.83
14	1.59 ± 0.01	0.84 ± 0.01	1.90	−1.72

[a] Average from three independent runs. [b] Average from four to six independent runs. [c] Calculated as k_{intra}/k_{inter}.

size of the rigid moiety of the reacting molecule. Furthermore, they provide additional, independent evidence on the insensitiveness to structural effects of the ease of large-ring formation in general. We have shown[1] that available EM values related to the formation of rings with more than 12 members and belonging to five different reaction series exhibit remarkable insensitiveness to structural effects. Log EM data cluster around an average value of −1.54, with a standard deviation 0.23. Table III now shows that the present values fit well into the same picture. Inclusion of these data into the existing set provides a new average value of −1.57 ± 0.22.

In conclusion, on the basis of the experimental evidence collected in this and in previous work, we believe that the operation of the rigid group effect on large-ring formation can be definitely ruled out, and that, in particular, no "magic" properties must be attributed to the *o*-phenylene unit.

Acknowledgment. Professor Illuminati's helpful suggestions are greatly acknowledged.

Registry No.—7, 7125-23-7; 8, 63163-48-4; 1,12-dibromododecane, 3344-70-5; 1,3-benzenediol, 108-46-3; 1,4-benzenediol, 123-31-9; 2,7-naphthalenediol, 582-17-2; 1,5-naphthalenediol, 83-56-7.

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Structural Elucidation with Nuclear Magnetic Resonance Spectroscopy. Diels–Alder Adducts of 1-Aminoanthracene and Maleic Anhydride: Restricted Rotation about the Aryl C(1)–N Bond and Intrinsic Asymmetry about the Imide (N_{sp^2}–C_{sp^3}) System

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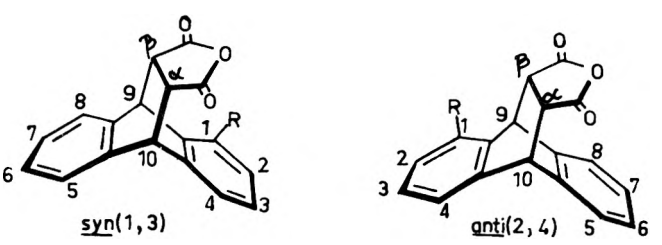
Diels–Alder reaction of 1-acetamidoanthracene and maleic anhydride yields a mixture of two isomeric adducts: syn (~35%) and anti (~65%). The configurations of both the adducts have been assigned with the help of NMR spectra of their imide derivatives. Restricted rotation and nonplanar conformation about the aryl C(1)–N bond have been demonstrated in the C(1)–N$(COCH_3)_2$ derivatives of the isomeric adducts. The steric effect of the C(1) substituent on the intrinsic asymmetry of the imide (N_{sp^2}–C_{sp^3}) system has been observed.

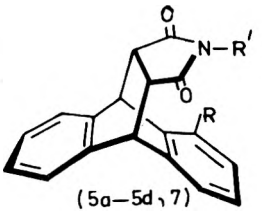
The characteristic feature of anthracene behaving as a diene and its ability to undergo Diels–Alder reaction with various dienophiles is a well-documented phenomenon. The Diels–Alder reaction, where there is possibility of the formation of more than one product, has been extensively investigated. The formation of two isomeric adducts syn[1a] and anti[1a] and their dependence on the nature of the 2 substituent in the Diels–Alder reaction of C(2) substituted anthracene and maleic anhydride have been demonstrated.[1b] Isolation of the two corresponding isomeric adducts in the case of C(2)-substituted anthracene and maleic anhydride and their characterization with the help of spectroscopic methods have been reported.[2] Substitution of anthracene in the 1 position, rather than the 2 position, may have a larger steric effect on the reacting centers, and the present investigations have been un-



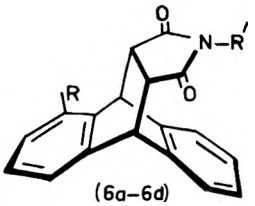
1, 2, R = $NHCOCH_3$
3, 4, R = $N(COCH_3)_2$

dertaken to probe the nature of the Diels–Alder reaction of 1-aminoanthracene and maleic anhydride

In this paper, we report the isolation of two isomeric adducts, *syn*-**1** and *anti*-**2**, from the Diels–Alder reaction of 1-acetamidoanthracene and maleic anhydride. The proposed structures of the two isomeric adducts have been demonstrated by converting them into their diacetyl derivatives **3** and **4** and into the imide derivatives **5a–d** and **6a–d**. Conversion to imides increases the solubility in $CDCl_3$ in which the NMR spectra were recorded. The mutual magnetic interaction of R and R′ has been carefully taken into account for the configurational assignment. As expected, no remarkable interaction of R and R′ has been observed in the spectra of the anti adduct, while the syn adduct exhibits a significant interaction between them. Further spectral studies of these compounds have revealed a phenomenon of restricted rotation about the aryl C(1)–$N(COCH_3)_2$ bond and the steric effect of the C(1) substituent (R) on the conformation of the imide group (R′).



(5a–5d, 7)



(6a–6d)

5a, 6a, R′ = $N(COCH_3)_2$; R = $N(COCH_3)_2$
5b, 6b, R′ = $CH_2C_6H_5$; R = $N(COCH_3)_2$
5c, 6c, R′ = $CH(CH_3)_2$; R = $N(COCH_3)_2$
5d, 6d, R′ = CH_2CH_3; R = $N(COCH_3)_2$
7, R′ = $CH(CH_3)_2$; R = $NHCOCH_3$

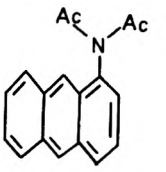
Experimental Section

All the melting points (°C) are uncorrected. NMR spectra were recorded in $CDCl_3$ with Me_4Si as an internal reference on a Varian A-60D spectrometer at 45 °C. δ (ppm) values were recorded from Me_4Si in the NMR data (s, singlet; br s, broad singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet). IR spectra were recorded using Nujol mull techniques on a Perkin-Elmer 257 spectrophotometer, and the characteristic absorptions ν_{max} (cm^{-1}) were noted: m, medium; s, strong; w, weak. The elemental analyses (C and H) of the compounds (**1–4, 5a–d, 6a–d,** and **7–9**) were within acceptable experimental limits and were submitted for review.

Preparation of Compounds. 1-Aminoanthracene was prepared by the reduction of 1-aminoanthraquinone by zinc dust and alkali as in the case of 2-aminoanthracene from 2-aminoanthraquinone.[1b] 1-Aminoanthraquinone (10 g) was stirred with 10% sodium hydroxide (100 mL) and zinc dust (8 g) at room temperature for about 30 min. It was slowly heated and the temperature of the reaction mixture was maintained at 85–90 °C. Zinc dust (10 g) was then introduced into the reaction mixture in two equal instalments at an interval of 30 min each, and heating was continued with constant stirring for 24 h at 90 °C.[2b] The solid material from the reaction mixture was collected and washed several times with water. Soxhelet extraction with acetone and then recrystallization from ethanol gave 1-aminoanthracene (6 g, 70%) as greenish-yellow plates, mp 126–127 °C (lit.[3] mp 127 °C).

1-Acetamidoanthracene. 1-Aminoanthracene (3 g) was stirred with an excess of acetic anhydride (20 mL) at room temperature for 3 h. A solid material appeared and was collected, washed with water, and recrystallized from ethanol. 1-Acetamidoanthracene appeared as greenish-yellow needles (3.2 g, 91%), mp 210 °C (lit.[3] mp 212 °C).

Reaction of 1-Acetamidoanthracene and Maleic Anhydride. A mixture of 1-acetamidoanthracene (2 g) and maleic anhydride (2 g) was heated under reflux in dry benzene (15 mL) for 8 h, with constant stirring. The adduct appeared as a white insoluble substance in benzene, while the excess maleic anhydride went into solution. The solid material was collected (~2.5 g) and traces of maleic anhydride were removed by sublimation at 110 °C. When subjected to fractional crystallization from acetone (25 mL), the first product *syn*-**1** appeared almost completely in about 24 h. The second product *anti*-**2** was recovered from the filtrate by evaporation and recrystallized from a benzene–petroleum ether mixture. From isolation and spectral analysis, the mixture was found to comprise about 35% of the syn adduct and ~65% of the anti adduct (total yield ~90%).



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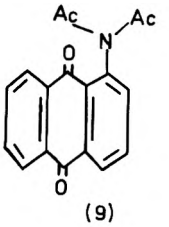

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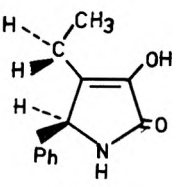

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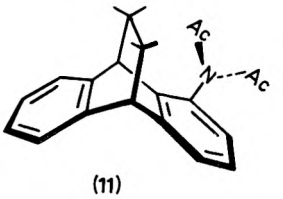

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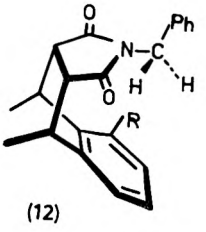

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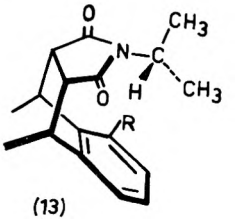

(13)

***syn*-1-Acetamido-9,10-dihydroanthracene-9,10-*endo*-α,β-succinic Anhydride** (**1**): mp 282–284 °C; IR 3250 (m, NH), 1865 (m), 1780 (s), 1665 (m), 1600 (w), 1540 (w).

***anti*-1-Acetamido-9,10-dihydroanthracene-9,10-*endo*-α,β-succinic Anhydride** (**2**): mp 268–270 °C; IR 3380 (m, NH), 1865 (m), 1780 (s), 1685 (m), 1600 (w), 1540 (w).

***syn*-1-Diacetamido-9,10-dihydroanthracene-9,10-*endo*-α,β-succinic anhydride** (**3**) was obtained by heating under reflux 450 mg of the adduct **1** with an excess of acetic anhydride (15 mL) for 3 h, and was recrystallized from a benzene–*n*-hexane mixture. The *anti*-1-diacetamido adduct **4** was also obtained similarly.

Compound 3: mp 215–217 °C; IR 1860 (w), 1840 (w), 1780 (s), 1720 (s), 1700 (m), 1615 (w), 1590 (w); NMR 2.20 (s, 3 H), 2.40 (s, 3 H), 3.40 (t, 2 H), 4.92 (m, 2 H), 6.90–7.40 (m, 7 H).

Compound 4: mp 242–243 °C; IR 1860 (w), 1830 (w), 1770 (s), 1700 (s), 1580 (w); NMR 1.78 (s, 3 H), 2.78 (s, 3 H), 3.56 (t, 2 H), 4.71 (m, 1 H), 4.96 (m, 1 H), 6.95–7.60 (m, 7 H).

Preparation of 5a and 6a. The isomeric adducts **1** and **2** were treated with hydrazine hydrate (equimolar) in ethanol with constant stirring at room temperature, and the respective *N*-aminoimides obtained were acetylated with acetic anhydride in the presence of a few drops of pyridine to give **5a** and **6a**. Both the compounds were recrystallized from ethanol.

5a: mp 260–262 °C; IR 1780 (w), 1700 (s), 1590 (w), 1500 (w); NMR 1.33 (s, 3 H) 1.63 (s, 3 H), 2.50 (s, 3 H), 2.70 (s, 3 H), 3.43 (t, 2 H), 4.95 (m, 2 H), 6.95–7.51 (m, 7 H).

6a: mp 220–221 °C; IR 1770 (w), 1690 (s), 1600 (w), 1510 (w); NMR 0.95 (s, 3 H), 1.81 (s, 3 H), 2.50 (s, 3 H), 2.71 (s, 3 H), 3.48 (t, 2 H), 4.75 (m, 1 H), 5.10 (m, 1 H), 7.00–7.60 (m, 7 H).

Preparation of 5b–d, 6b–d, and 7. The compounds **5b–d** and **6b–d** were obtained by condensing the anhydride adducts **1** and **2** with the corresponding primary amines, at 110–120 °C for 2 h. The adduct (500 mg) was mixed thoroughly with its equivalent of the primary amine and heated at 120 °C for 2 h. The product obtained was cooled, washed with water, and recrystallized from benzene. At first, 1-acetamido-9,10-dihydroanthracene-9,10-*endo*-α,β-succinimide of the corresponding adduct was obtained, which on acetylation gave the 1-diacetamido derivatives in quantitative (70–80%) yields. Compound **7** was obtained by condensing the adduct **1** with isopropylamine and recrystallized from a benzene–petroleum ether mixture. The 1-diacetamidoimides **5a–d** and **6a–d** were recrystallized from ethanol.

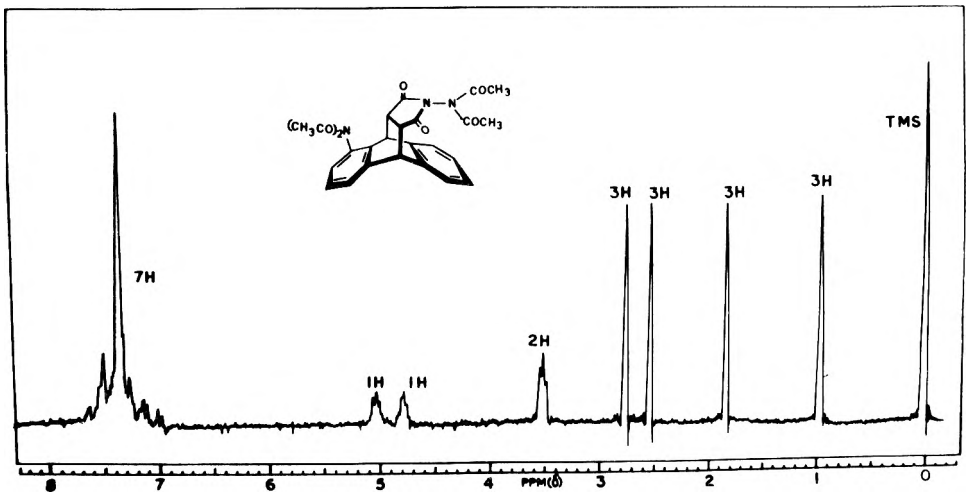

Figure 1. 60-MHz NMR spectrum of **6a** in $CDCl_3$ at 45 °C.

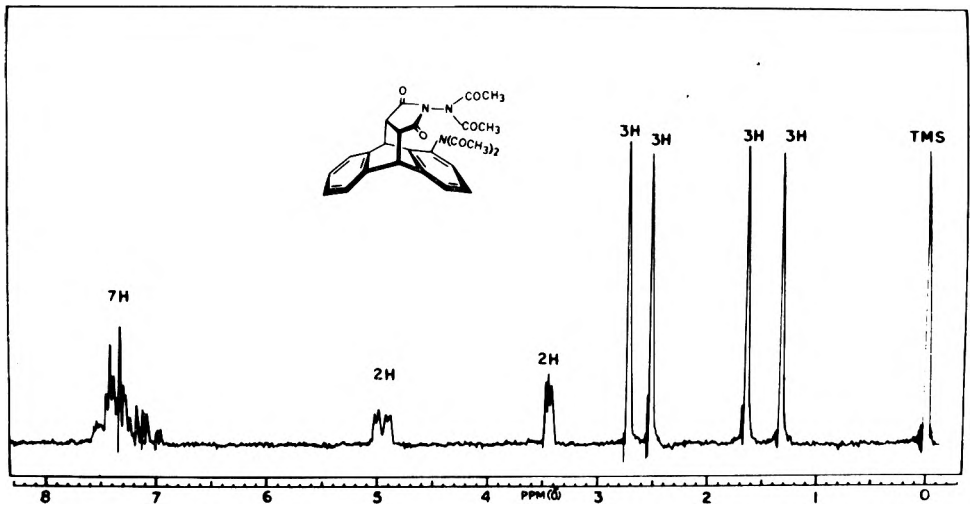

Figure 2. 60-MHz NMR spectrum of **5a** in $CDCl_3$ at 45 °C.

5b: mp 256–258 °C; IR 1780 (w), 1710 (s), 1610 (w), 1590 (w); NMR 1.97 (s, 3 H), 2.15 (s, 3 H), 3.16 (t, 2 H), 4.30 (m, 2 H), 4.66 (m, 1 H), 4.83 (m, 1 H), 6.70–7.40 (m, 12 H).

6b: mp 213–214 °C; IR 1780 (w), 1720 (s), 1660 (m), 1610 (w), 1600 (w); NMR 1.70 (s, 3 H), 2.66 (s, 3 H), 3.18 (t, 2 H), 4.23 (s, 2 H), 4.63 (m, 1 H), 4.80 (m, 1 H), 6.60–7.45 (m, 12 H).

5c: mp 222–223 °C; IR 1770 (w), 1710 (s), 1690 (s), 1600 (w), 1460 (s); NMR 0.83 (d, 3 H, J = 7 Hz), 1.10 (d, 3 H, J = 7 Hz), 1.91 (s, 3 H), 2.55 (s, 3 H), 3.09 (m, 2 H), 3.70–4.40 (m, 1 H), 4.80 (m, 2 H), 7.00–7.46 (m, 7 H).

6c: mp 219–220 °C; IR 1780 (w), 1700 (s), 1680 (s), 1620 (w), 1590 (w); NMR 0.84 (d, 6 H, J = 7 Hz), 1.76 (s, 3 H), 2.70 (s, 3 H), 3.13 (m, 2 H), 3.60–4.30 (m, 1 H), 4.63 (m, 1 H), 4.86 (m, 1 H), 6.90–7.55 (m, 7 H).

5d: mp 216–218 °C; IR 1780 (w), 1710 (s), 1620 (w), 1590 (w); NMR 0.71 (t, 3 H, J = 7 Hz), 1.93 (s, 3 H), 2.58 (s, 3 H), 3.20 (m, 4 H), 4.86 (m, 2 H), 7.00–7.60 (m, 7 H).

6d: mp 230–231 °C; IR 1770 (w), 1700 (s), 1680 (s), 1590 (w); NMR 0.40 (t, 3 H, J = 7 Hz), 1.78 (s, 3 H), 2.73 (s, 3 H), 2.95–3.33 (m, 4 H), 4.70 (m, 1 H), 4.90 (m, 1 H), 6.90–7.10 (m, 7 H).

7: mp 243–244 °C; IR 3250 (m, NH), 1780 (w), 1720 (s), 1680 (s), 1620 (w), 1600 (w), 1540 (m); NMR 0.87 (dd, 6 H, J = 7 Hz, $\Delta\nu$ = 2 Hz), 2.25 (brs, 3 H), 3.15 (t, 2 H), 3.70–4.30 (m, 1 H), 4.80 (m, 1 H), 5.10 (m, 1 H), 7.10–7.60 (m, 8 H).

Preparation of 8 and 9. 1-Diacetamidoanthracene (8) and 1-diacetamidoanthraquinone (9) were obtained by refluxing 1-acetamidoanthracene and 1-aminoanthraquinone, respectively, with acetic anhydride. The compound 8 was recrystallized from ethanol and **9** from a ethanol–acetone mixture.

8: mp 164 °C; IR 1710 (s), 1685 (s), 1620 (w), 1460 (m); NMR 2.33 (s, 6 H), 7.25–8.43 (m, 9 H).

9: mp 216–217 °C; IR 1710 (s), 1670 (m), 1590 (m), 1465 (m); NMR 2.32 (s, 6 H), 7.50–8.51 (m, 7 H).

Results and Discussion

The two isomeric Diels–Alder adducts have different (N–H) stretching vibrations in their IR spectra: one of the adducts shows an absorption at 3380 (cm^{-1}) characteristic of normal secondary amide vibrations and the other has a characteristic (N–H) absorption at 3250 (cm^{-1}). The absorption at 3250 (cm^{-1}) could result from the possible hydrogen bonding between the (N–H) and the anhydride ring. Since an intramolecular hydrogen bonding between the (N–H) and the anhydride ring is possible in the syn adduct, the absorption at the lower frequency (3250 cm^{-1}) can be attributed to the syn adduct **1** and that at the higher frequency (3380 cm^{-1}) to the anti adduct **2.**

Restricted rotation about the N–N bond in tetraacylhydrazine systems has been successfully exploited in assigning the configuration of various Diels–Alder adducts,[2-4] and when applied to the present adducts this system also discloses considerable information. In the NMR spectrum (Figure 1) of **6a,** each of the diacetyls has a pair of singlets, one at δ 0.96 (3 H) and 2.50 (3 H) for the N'-diacetyls ($\Delta\nu$ = 92.4 Hz) and another at δ 1.81 (3 H) and 2.71 (3 H) for the C(1)-N-diacetyls ($\Delta\nu$ = 54 Hz). The chemical shifts of the N'-diacetyls are almost exactly the same as were observed in the case of the unsubstituted anthracene adduct.[5] The magnetic environ-

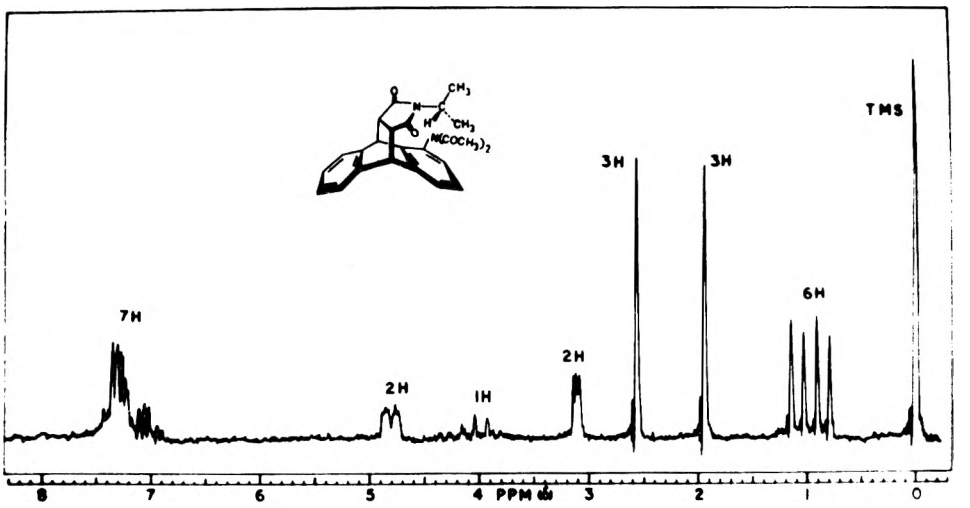

Figure 3. 60-MHz NMR spectrum of **5c** in $CDCl_3$ at 45 °C.

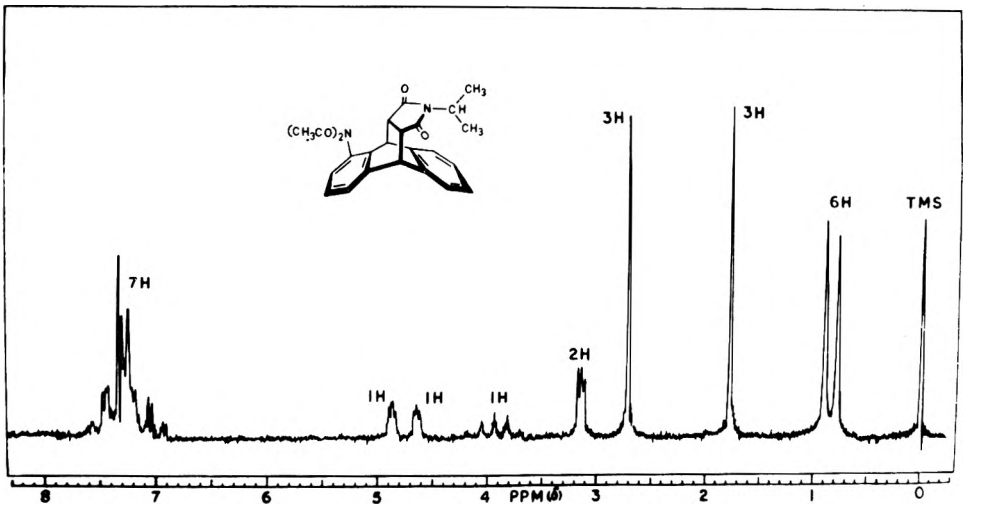

Figure 4. 60-MHz NMR spectrum of **6c** in $CDCl_3$ at 45 °C.

ments of the N′ substituents are more or less the same in the anti adduct and unsubstituted anthracene adduct. The C(1) substituent, being far away, fails to interact with the N′ substituent. In the case of **5a**, the NMR spectrum (Figure 2) exhibits a similar pattern, showing two resonance signals at δ 1.33 (s, 3 H) and 2.50 (s, 3 H) for the *N*′-diacetyls and a pair of singlets at δ 1.63 (3 H) and 2.70 (3H) for the C(1)-*N*-diacetyls. One of the *N*′-diacetyls that is syn to the cage moiety in the nonplanar conformation in **5a** has been deshielded by the C(1) substituent and appears at δ 1.33 instead of appearing at the usual position at δ 0.96. Such a deshielding effect on the *N*′-diacetyls was also observed in the case of the syn (cis) adduct of 2-diacetamidoanthracene.[2] While the C(1)-*N*-diacetyl resonances remain almost the same in the spectra of **4** and **6a**, a large difference in the resonances of the C(1)-*N*-diacetyl in **3** and **5a** indicates the possible influence of the imide group on the C(1) substituent. From the spectra of **5a** and **6a** a possible configurational assignment can be made. The two adducts **1** and **2** are virtually similar except for the orientation of the C(1) substituent with respect to the anhydride ring, and one could expect different substituent effects in the derivatives of the two isomers. The isomer **5a**, where the N′ substituent has been influenced by the C(1) substituent, can be assigned the syn configuration, while the other, where the C(1) substituent has little effect on the N′ substituent, the anti configuration. To substantiate this argument further, we have introduced a few centers at the imide plane (**5b–d, 6b–d**) that could be influenced by the C(1) substituent. The C(1)-*N*-diacetyl has caused a large dissymmetry about the imide plane in the syn adduct and its effects are readily observed in the spectra of **5b–d.**

In the spectrum of **5b**, the methylene protons of the benzyl group resonate as a multiplet at δ 4.30 (approximately an overlapping AB quartet) and the C(1)-*N*-diacetyl signals are separated by 10 Hz ($\Delta\nu$). In the case of **6b** the benzyl methylene protons appear as a singlet at δ 4.23 (2 H) and the two C(1)-*N*-diacetyl signals are separated by 58 Hz ($\Delta\nu$). The appearance of a multiplet for the methylene group could be due to the nonequivalence of the hydrogens arising out of the influence of the C(1) substituent which helps in developing a prochiral center[6] at the methylene carbon. Such chemical-shift nonequivalence of the methylene group is comparable to that observed in the case of **10**,[6,7] *dl*-2,2′-bis(acetoxymethyl)diphenyl,[8] and in 9-benzyltriptycenes,[9] where the diastereotopicity of the methylene protons has been explained on steric grounds. For the same reason, the isopropylmethyl groups in **5c** are diastereotopic and appear as a pair of doublets (Figure 3) at δ 0.83 (3 H) and 1.10 (3 H) (J = 7 Hz, $\Delta\nu$ = 16 Hz). In the case of **6c**, there is only a doublet (Figure 4) for the isopropylmethyls at δ 0.84 (6 H, J = 7 Hz). The C(1)-*N*-diacetyls appear as two singlets at δ 1.91 and 2.55 ($\Delta\nu$ = 38.4 Hz) in the case of **5c**, while they appear at δ 1.76 and 2.70 ($\Delta\nu$ =

56.4 Hz) in the case of **6c**. In the case of **5d** and **6d**, each of the diacetyls appears as a pair of singlets with an internal chemical shift ($\Delta\nu$) of 39 and 57 Hz, respectively. The methyl group of ethylimide has been appreciably deshielded (δ 0.71) by the C(1) substituent in the syn adduct **5d** as compared to that in the anti adduct **6d** (δ 0.40).

We have observed the effect of the C(1) substituent R on the resonance of the imide substituent R′ in **5a–d**. Another interesting feature observed in all these derivatives is the effect of R′ on R. In all four derivatives **6a–d** the C(1)–*N*-diacetyl resonances R remain almost unaffected with different substituents R′ in the anhydride ring, whereas in the case of the syn adduct **5a–d** a continuous change in the resonance of the C(1) substituent is observed, indicating the possible influence of R′ on R. These observations demonstrate further the *syn*-**1** and *anti*-**2** configurations of the two isomeric adducts.

In the case of the Diels–Alder reaction of 2-acetamidoanthracene and maleic anhydride, a 52:48 ratio of the isomeric adducts syn/anti was reported.[1] Though the electronic factors contributed by the acetamido group at the C(1) and C(2) positions of anthracene toward reacting centers appear to be almost the same, in the present case the anti isomer has been found to be the major product (65%). Sterically, the acetamido group at the C(1) position will have a larger effect on the reacting center as compared to that at the C(2) position of anthracene and, possibly, steric factors might have caused such a variation in the isomer ratio (35:65) of the syn/anti.

Restricted Rotation about the Aryl C(1)–N Bond. The appearance of two singlets for the C(1)–*N*-diacetyls in the NMR spectra of both the configurational isomers could possibly be due to the restricted rotation about the aryl C(1)–N bond, comparable to that observed in the case of ortho substituted arylimides.[10] High-energy barriers[10,11] ($\Delta G^{\ddagger}$ = 17–24 kcal/mol) to rotation about the aryl C–N bond in various ortho-substituted arylimides have been attributed to the steric interaction between the ortho substituent and the carbonyl groups in the planar transition state. Steric hindrance about the C(1)–N bond in *N*-benzenesulfonyl-8-nitro-1-naphthylglycine enabled Mills and Elliot[12] to resolve it. Such steric interactions between the C(1)–*N*-diacetyls and the C(9) substituent are expected in the present adducts and in compounds **8** and **9**. Molecular models further support that even the C(9)–H will hinder the rotation of the acyl system about the C(1)–N bond. However, the C(1)–*N*-diacetyls appear as a sharp singlet in the spectra of both **8** (δ 2.33, 6 H) and **9** (δ 2.32, 6 H), indicating the magnetic equivalence of the acetyl groups in both cases. The introduction of the C(9)–C(10) bridge in the anthracene nucleus (as in the present adducts) could be responsible for the nonequivalence of the C(1)–*N*-diacetyls.

From the spectral patterns observed for the derivatives of both isomers and for **8** and **9**, a nonplanar conformation **11** about the C(1)–N bond, where the acyl system lies in a plane perpendicular to the plane of the cage benzo ring, could be proposed. In such a nonplanar conformation, the C(9)–C(10) bridge would provide different magnetic environments for the two acetyl groups, while the latter would assume a symmetrical pattern in the case of **8** and **9**. The acetyl group oriented syn to the bridge appears upfield and the other anti to the bridge resonates at a lower field. The possibility of a partial double-bond formation about the C(1)–N bond, that may also account for the restricted rotation, is very unlikely, not only because the N atom is attached to two carbonyl groups, but any planar arrangement about the C(1)–N bond will suffer from a severe steric crowding. Free rotation about the C–N bond, and, hence, a singlet for the diacetyls, was observed in the corresponding syn and anti adducts with the diacetamido substituent at the C(2) position,[2] demonstrating further that it is the C(9) substituent (or C(9) hydrogen) and not the ortho hydrogens that influence the rotation of the C(1)–N bond in the present case.

Intrinsic Asymmetry of the Imide (N_{sp^2}–C_{sp^3}) Group. The spectral pattern shows that the methylene protons in **5b** and the isopropyl methyl groups in **5c** are diastereotopic. Accordingly, similar behavior of these groups is expected in the derivatives of the anti adducts **6b** and **6c**, but the benzylic methylene protons in **6b** appear as a singlet and the isopropyl methyl groups in **6c** as a normal doublet (Figure 4). The observed multiplicity in the resonance signals of these protons, only in the case of the syn isomer, can be explained on the basis of the chirality[9] of these compounds where the methylene protons in **5b** and the isopropyl methyl groups in **5c** are magnetically nonequivalent. In the case of the anti isomer, since the site of chirality [the C(1) substituent] lies away from the diastereotopic groups, the degree of nonequivalence diminishes and, hence, no signal multiplicity of the diastereotopic groups has been observed. The C(1) substituent R exerts a strong steric influence to induce intrinsic asymmetry[6,13] on these imide groups R′ and this is vividly seen on a comparative examination of the spectral patterns of the derivatives of the two isomeric adducts. With the monoacetyl substituent at the C(1) position, the isopropyl methyl groups in **7** resonate as an interlacing double doublet at δ 0.87 (6 H, J = 7 Hz, $\Delta\nu$ = 2 Hz), indicating thereby a small interaction with the C(1) substituent, while the two isopropyl methyl groups in **5c** resonate at δ 0.83 and 1.10 (Figure 3) with an internal chemical shift of 16 Hz. On steric considerations, preferred conformations of the type **12** and **13** could be proposed for **5b** and **5c**, where the steric interactions between the C(1) substituent R and the imide substituent R′ would be reduced to a minimum.

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Registry No.—**1**, 63512-03-8; **2**, 63568-21-8; **3**, 63512-04-9; **4**, 63568-22-9; **5a**, 63512-05-0; **5b**, 63512-06-1; **5c**, 63512-07-2; **5d**, 63512-08-3; **6a**, 63568-23-0; **6b**, 63568-24-1; **6c**, 63568-25-2; **6d**, 63597-42-2; **7**, 63512-09-4; **8**, 63512-10-7; **9**, 63512-11-8; 1-aminoanthracene, 610-49-1; 1-aminoanthraquinone, 82-45-1; 1-acetamidoanthracene, 63512-12-9; maleic anhydride, 108-31-6; hydrazine hydrate, 7803-57-8; benzylamine, 100-46-9; ethylamine, 75-04-7; isopropylamine, 75-31-0.

References and Notes

(1) (a) The prefixes syn and anti were used in the sense that the adduct with the anhydride ring toward the substituent is syn and that with the anhydride ring away from the substituent is anti.[1b] These terms are retained in the present text. Cis and trans[2] terms for such isomeric adducts have also been used. (b) F. Kaplan and H. Conroy, *J. Org. Chem.*, **28**, 1593 (1963).
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Synthesis of Adamantane Derivatives. 37.[1] A Convenient and Efficient Synthesis of 1-Azidoadamantane and Related Bridgehead Azides, and Some of Their Reactions

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Several bridgehead azides such as 1-adamantyl (**2**), 3,5-dimethyl-1-adamantyl (**5**), 3,5,7-trimethyl-1-adamantyl (**10**), 1-bicyclo[3.3.1]nonyl (**14**), and 3-homoadamantyl azide (**18**) were prepared in high yields from the corresponding bridgehead alcohols on treatment with sodium azide in 57% H_2SO_4–$CHCl_3$. Azides **2**, **5**, and **10** were decomposed in 95% H_2SO_4 to afford the rearranged products, 4-azahomoadamantan-3-ol derivatives **3**, **7**, **8**, and **12**, which were also obtained from the corresponding bridgehead alcohols on treatment with sodium azide in 95% H_2SO_4. Azides **5**, **10**, **14**, and **18** were converted to the corresponding bridgehead amines **6**, **11**, **15**, and **19**.

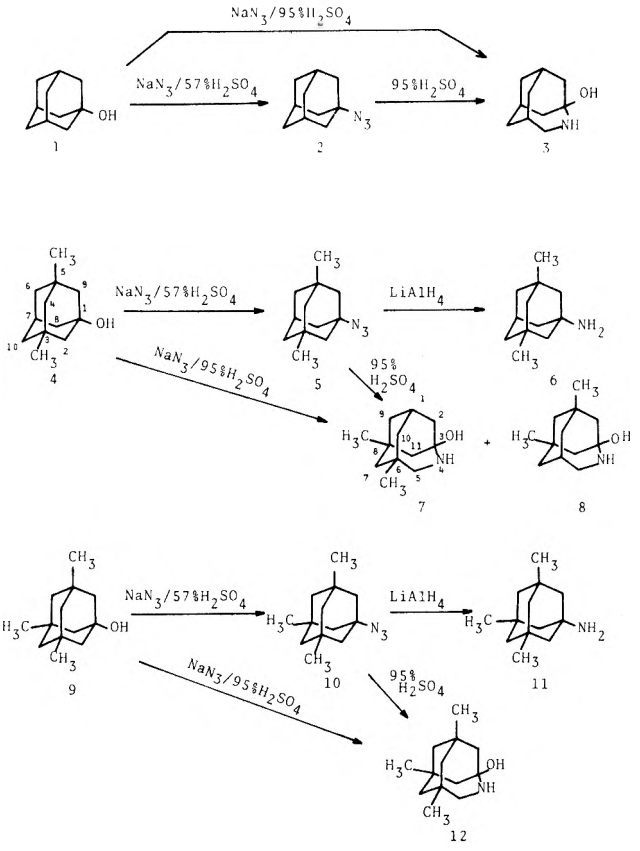
Organic azides are well known as an excellent synthetic starting material, however, synthetic studies by using bridgehead azides seem to be quite limited:[2] this might be due to the lack of a facile and efficient method for introduction of the azide group at bridgehead positions. For example, 1-azidoadamantane (**2**) has been prepared previously via a direct substitution method of 1-bromoadamantane with sodium azide in dimethyl sulfoxide by us[3] or via a diazo-transfer method to 1-aminoadamantane by Quast and Eckert,[4] but the former method gives only a moderate yield of **2** and the latter method requires vigorous anhydrous conditions and longer reaction times. The direct substitution method was considerably improved recently by Miller[5] by using zinc chloride as the catalyst, but the reaction is quite slow. This paper deals with a convenient and efficient synthesis of **2** and related bridgehead azides as well as some of their reactions.

Results and Discussion

In view of the fact that secondary and tertiary aryl carbinols can be converted to the corresponding azides with hydrazoic acid in trichloroacetic acid[6-8] and the relatively facile formation of 1-adamantylcarbenium ion under acidic conditions,[9] we examined the reaction of 1-adamantanol (**1**) with in situ generated hydrazoic acid in various acid–chloroform mixtures. As shown in Table I, azide **2** was obtained in an excellent yield by using 57% H_2SO_4 as the acid and 3 h as the reaction time. However, azide **2** was not stable under the reaction conditions and was converted slowly to a rearranged product **3**, as demonstrated by the data of a 15-h reaction (Table I). **2** was also converted to **3** exclusively on treatment with 95% H_2SO_4–$CHCl_3$ (Scheme I). The rearranged product **3** was identified as 3-hydroxy-4-azatricyclo[4.3.1.1^{3,8}]undecane (4-azahomoadamantan-3-ol) by comparison with an authentic sample.[4,10] **3** was also obtained directly from **1** in 94% yield by using 95% H_2SO_4–$CHCl_3$ and sodium azide (1.25-fold excess to **1**) (The Schmidt reaction). This provides a facile and efficient synthesis of **3**. The reaction of **1** with sodium azide in other acid–$CHCl_3$ mixtures did not give satisfactory results, as summarized in Table I.

Application of this simple azide synthetic method to 1-hydroxy-3,5-dimethyladamantane (**4**) afforded azide **5** in 72% yield which was converted to known amine **6**[11] on lithium aluminum hydride reduction. Azide **5** on treatment with 95% H_2SO_4–$CHCl_3$ afforded a 2:1 mixture of rearranged products **7** and **8**, which was also obtained directly from **4** on treatment with sodium azide in 95% H_2SO_4–$CHCl_3$ in high yields (Scheme I). The major product **7** was isolated after repeated recrystallizations from aqueous methanol and was characterized as 6,8-dimethyl-4-azahomoadamantan-3-ol on the basis of analytical and spectral data. The IR spectrum (KBr)

Scheme I



exhibited strong bands at 3300 and 3170 cm^{-1} (OH and NH) but no carbonyl absorption bands, and the NMR spectrum ($CDCl_3$) revealed characteristic signals at δ 3.47 (s, 1 H) and 3.25 (br s, 1 H) (both signals disappeared on shaking with D_2O and are assignable to OH and NH), 2.63 (s, 2 H, $-CH_2N-$), 2.3–0.9 (m, 11 H), 0.90 (s, 3 H, CH_3), and 0.80 (s, 3 H, CH_3), supporting the assigned structure **7**. The IR spectrum of the mixture of **7** and **8** was quite similar to **7**, and the NMR spectrum exhibited a characteristic doublet at δ 2.90 (J = 4.0 Hz, 0.75 H against 1.25 H of the signal at δ 2.63) and a singlet signal at δ 0.92 (2.3 H against 3.7 H of the two methyl signlets at δ 0.90 and 0.80) besides the signals due to **7**, and hence the rearranged product was analyzed as 2:1 mixture of **7** and **8**, 1,8-dimethyl-4-azahomoadamantan-3-ol. The results indicate that the methyl substituent at C_3 and C_5 in **5** or its protonated form revealed no effect on the migratory aptitude of C_1–C_2 and C_1–C_9 bonds compared to the C_1–C_8 bond because the bond migration occurred in a statistical ratio.

Table I. Reactions of 1 with NaN_3 in Various Acid–$CHCl_3$ Mixtures

Acid[a]	Mol ratio of NaN_3 to 1	React. time, h[b]	Product, %[c] 2	Product, %[c] 3	Unreacted 1, %[d]
CCl_3COOH	1.5	20	1	0	99
CF_3COOH	1.5	20	0.3	40	59
CH_3SO_3H	1.5	20	2.4	65	0.8
30% H_2SO_4	3.0	15	Trace	0	99
47.5% H_2SO_4	3.0	15	68	22	Trace
57% H_2SO_4	2.0	3	96	Trace	4
57% H_2SO_4	2.0	15	67	27	4
95% H_2SO_4	1.25	1	0	94	1.8

[a] A 1:1 (v/v) mixture of the acid and $CHCl_3$ was used. [b] Sodium azide was added little by little during 0.5 h to a stirred and ice-cooled mixture of 1 and acid–$CHCl_3$, and the stirring was continued at 20–25 °C. The reaction time involves the addition time of NaN_3. [c] Isolated yield of the crude product. [d] GLC analysis of the crude product.

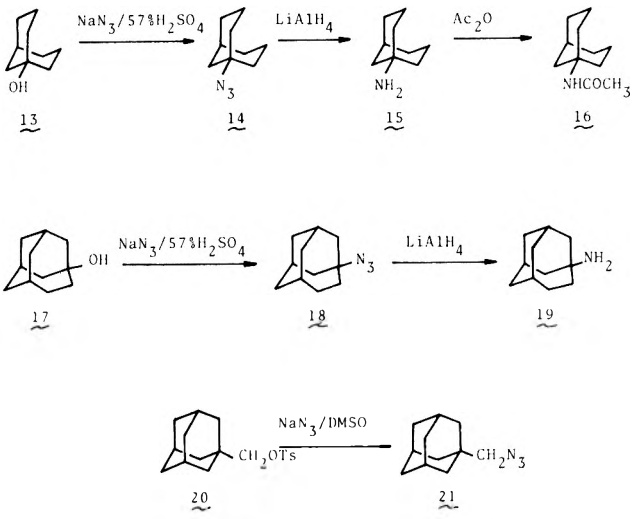
Similarly, 3,5,7-trimethyl-1-adamantyl azide (**10**) was prepared from **9** in 76% yield and was converted to the corresponding amine **11** which was identified with an authentic sample.[12] The acid-catalyzed decomposition of **10** afforded 1,6,8-trimethyl-4-azahomoadamantan-3-ol (**12**) in high yield, which was also obtained from **9** and sodium azide in 95% H_2SO_4 (Scheme I).

Other bridgehead azides such as **14** and **18** were also obtained in good yields (Scheme II). 1-Azidobicyclo[3.3.1]nonane (**14**) was obtained from the corresponding bridgehead alcohol **13**[13] in 70% yield on treatment with sodium azide in 57% H_2SO_4–$CHCl_3$. Lithium aluminum hydride reduction of **14** gave the corresponding amine **15** which was acetylated to the known acetylamino derivative **16**.[14]

3-Homoadamantyl azide (**18**) was obtained in 73% yield from 3-homoadamantanol (**17**) under the similar conditions. Lithium aluminum hydride reduction of **18** gave 3-homoadamantylamine **19**.[15] The skeletal integrity of **18** was evidenced by the spectral data (Table II) and also by comparison with 1-adamantylcarbinyl azide (**21**) which was prepared from the carbinyl tosylate **20** on treatment with sodium azide in dimethyl sulfoxide (Scheme II). All of these results are summarized in Schemes I and II, and Tables I and II.

Although several improved procedures for the synthesis of bridgehead azides have been developed recently,[5,16] the present procedure by using sodium azide in 57% H_2SO_4–$CHCl_3$ may be one of the most simple and efficient methods. However, it should be noted that this method can not be applicable to less-reactive bridgehead alcohols such as nonradamantan-1-ol, since the corresponding bridgehead carbenium ion can not be generated under the reaction conditions (57% H_2SO_4).[17]

Scheme II



Experimental Section[18]

General Procedure for Synthesis of Bridgehead Azides from the Corresponding Alcohol. To an ice-cooled and stirred mixture of an appropriate bridgehead alcohol (10 mmol) in 57% H_2SO_4 (10 mL) and $CHCl_3$ (10 mL) was added little by little solid sodium azide (1.30 g, 20 mmol) (or an appropriate amount depending on the substrate, see Table II) during 0.5 h, and the resulting mixture was stirred for 2–27 h at 20–25 °C (Tables I and II). The mixture was poured onto ice–water and extracted with methylene chloride (four 10 mL portions). The combined extracts were washed with 5% $NaHCO_3$ (10 mL) and water (5 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure (water aspirator) gave the corresponding azides. The solid azides **2** and **18** were purified by recrystallization from aqueous methanol and sublimation. The oily azides **5**, **10**, and **14** were purified on a silica gel column eluting with *n*-hexane–methylene chloride or by Kugelrohr distillation. The acidic aqueous layer was basified with ice–50% NaOH and extracted with $CHCl_3$ (five 10 mL portions). The combined extracts were dried (Na_2SO_4) and evaporated to dryness to afford rearranged products such as **3** in various amounts depending on the reaction conditions.

3-Hydroxy-4-azatricyclo[4.3.1.1^{3,8}]undecane (3). To an ice-cooled and stirred mixture of 95% H_2SO_4 (8 mL) and chloroform (8 mL) was added 1-hydroxyadamantane (**1**) (0.76 g, 5.0 mmol) in one portion and then solid sodium azide (0.41 g, 6.3 mmol) little by little during 0.5 h. After the stirring was continued for a further 0.5 h at 20–25 °C, the mixture was poured onto ice–water (ca. 20 mL), and the aqueous layer was separated from the chloroform layer, washed with methylene chloride (two 10-mL portions), and basified with ice–50% NaOH, and extracted with chloroform (seven 10-mL portions). The

Table II. Synthesis of Bridgehead Azides 5, 10, 14 and 18, and Their Physical Data[a,b]

Alcohol	Mol ratio of NaN_3 to alcohol	React. time, h[c]	Azide (yield, %)	n_D (mp, °C)	IR,[d] cm^{-1}	NMR chemical shift,[e] δ
4	3.0	2.0	**5** (72)	1.5038 (27)	2100	2.4–2.0 (m, 2 H), 1.8–1.0 (m, 12 H), 0.89 (s, 6 H)
9	3.0	24.0	**10** (76)	1.5045 (15)	2090	1.35 (s, 6 H), 1.10 (s, 6 H), 0.89 (s, 9 H)
13	4.3	2.0	**14** (70)	1.5092 (20)	2100	2.2 (br s, 1 H), 2.1–1.1 (m, 14 H)
17	4.0	27.0	**18** (73)	97–98	2100	2.7–1.2 (m)

[a] Solid NaN_3 was added to a stirred and ice-cooled mixture of alcohol and 57% H_2SO_4–$CHCl_3$ (1:1, v/v, ratio) during 0.3–0.5 h, and the mixture was stirred at 20–25 °C. [b] Satisfactory elemental analytical data were reported for all compounds listed in the table. [c] The reaction time involves the addition time of NaN_3. [d] Neat film for oily azides and KBr for solid azides. [e] In $CDCl_3$.

combined extracts were dried (Na_2SO_4) and evaporated to afford **3** as colorless crystals (0.785 g, 94.0%) which the IR spectrum was superimposahle with an authentic sample.[10] One recrystallization from methanol afforded **3** of mp 163–165 °C (lit.[10] 164–165 °C)(0.668 g, 85.0%).

Azide **2** (50 mg, 0.28 mmol) was stirred in 95% H_2SO_4 (1 mL) and $CHCl_3$ (1 mL) for 1 h at 20–25 °C and the usual workup as above afforded **3** (38 mg, 81%).

1-Amino-3,5-dimethyladamantane (6). A mixture of azide **5** (62 mg, 0.30 mmol) and lithium aluminum hydride (38 mg, 1.0 mmol) in anhydrous ether (2 mL) was stirred for 12 h at room temperature and refluxed for 1 h. The cooled reaction mixture was treated with water, and the mixture was extracted with ether (ten 2-mL portions). The combined extracts were dried (Na_2SO_4) and saturated with dry hydrogen chloride gas to precipitate the hydrochloride of the amine **6** (40 mg, 61.4%), mp >300 °C, which the IR spectrum was superimposable with an authentic sample, mp >300 °C, which was prepared by hydrolysis of 1-acetylamino-3,5-dimethyladamantane.[11]

3-Hydroxy-6,8-dimethyl-(7) and 3-Hydroxy-1,8-dimethyl-4-azatricyclo[4.3.1.1^{3,8}]undecane (8). To an ice-cooled and stirred mixture of 1-hydroxy-3,5-dimethyladamantane (**4**) (1.08 g, 6.0 mmol), $CHCl_3$ (8 mL), was added solid sodium azide (0.65 g, 10 mmol) during 0.5 h, and the stirring was continued for a further 3 h at 20–25 °C. The mixture was poured onto ice–water and the chloroform layer was separated. The aqueous layer was basified with ice–50% NaOH and extracted with chloroform (seven 10-mL portions), and the combined extracts were dried (Na_2SO_4). Removal of the solvent gave crude rearranged products which were recrystallyzed from aqueous methanol to afford a 2:1 mixture of **7** and **8** (1.08 g, 92%): mp 78–88 °C; IR (KBr) 3300, 3170, 1455, and 1050 cm^{-1}; NMR see the text.

Anal. Calcd for $C_{12}H_{21}ON$: C, 73.79; H, 10.84; N, 7.17. Found: C, 73.79; H, 10.58; N, 7.20.

Recrystallization of the mixture five times from aqueous methanol afforded pure **7** (105 mg, 9%): mp 105–107 °C; IR (KBr) 3300, 3170, 1456, and 1050 cm^{-1}; NMR see the text.

Anal. Calcd for $C_{12}H_{21}ON$: C, 73.79; H, 10.84; N, 7.17. Found: C, 73.76; H, 10.60; N, 7.19.

Azide **5** (19 mg, 0.093 mmol) was decomposed in 95% H_2SO_4 (0.5 mL) and $CHCl_3$ (0.5 mL) for 0.5 h at 20 °C, and workup as above gave also a 2:1 mixture of **7** and **8** (15 mg, 82.6%).

1-Amino-3,5,7-trimethyladamantane (11). A mixture of azide **10** (170 mg, 0.78 mmol) and lithium aluminum hydride (170 mg, 4.5 mmol) in anhydrous ether (15 mL) was refluxed for 6 h, and the usual workup afforded amine **11** as the hydrochloride (150 mg, 90%), mp >300 °C, which the IR spectrum was superimposable with an authentic sample, mp >300 °C.[12]

1,6,8-Trimethyl-3-hydroxy-4-azahomoadamantane (12). To an ice-cooled and stirred mixture of the alcohol **9** (389 mg, 2.00 mmol) in 95% H_2SO_4 (6 mL) and $CHCl_3$ (6 mL) was added sodium azide (260 mg, 4.0 mmol). After the stirring was continued for 1 h, the mixture was poured onto ice–water and workup as above afforded the rearranged product **12** as colorless crystals after recrystallization from methanol (345 mg, 82.4%): mp 153–154 °C; IR (KBr) 3300, 3130, 1455, 1040 cm^{-1}; NMR ($CDCl_3$) δ 3.6–2.7 (br m, 2 H, disappeared on shaking with D_2O), 2.65 (s, 2 H, CH_2N–), 1.75–1.1 (m, 10 H, other ring protons), 0.92 (s, 6 H, two CH_3 at C_1 and C_8), and 0.98 (s 3 H, C_6-CH_3).

Anal. Calcd for $C_{13}H_{23}ON$: C, 74.59; H, 11.08; N, 6.69. Found: C, 74.64; H, 10.80; N, 6.92.

Azide **10** (52 mg, 0.24 mmol) was decomposed in 95% H_2SO_4 (2 mL) and $CHCl_3$ (2 mL) for 0.5 h at 20–25 °C. Workup as above afforded the rearranged product **12** as colorless crystals (42 mg, 84.7%).

1-Aminobicyclo[3.3.1]nonane (15). A mixture of azide **14** (48 mg, 0.29 mmol) and lithium aluminum hydride (100 mg, 2.6 mmol) in anhydrous ether (10 mL) was refluxed for 5 h. The usual workup and treatment of the crude product with dry hydrogen chloride gas afforded the hydrochloride of the amine **15** as colorless solids (50 mg, 98%): mp >300 °C; IR (KBr) 3300–2400, 1600, 1510, and 1375 cm^{-1}; NMR ($CDCl_3$) δ 8.25 (br s, 3 H, disappeared on shaking with D_2O) and 2.8–1.3 (m, 15 H).

Anal. Calcd for $C_9H_{18}NCl$: C, 61.52; H, 10.33; N, 7.97. Found: C, 61.78; H, 10.10; N, 7.95.

The amine **15** hydrochloride (25 mg, 0.14 mmol) was acetylated with acetic anhydride (0.21 g, 2.0 mmol) in pyridine (2.5 mL) at 50 °C for 2 h and the usual workup, followed by recrystallization from *n*-hexane–CH_2Cl_2, afforded the acetylamino derivative **16** as colorless crystals (22 mg, 86.7%), mp 87.5–88.5 °C (lit.[14] mp 85–86 °C), which the IR and NMR spectra were superimposable with an authentic sample.[14]

3-Aminohomoadamantane (19). A mixture of azide **18** (90 mg, 0.47 mmol) and lithium aluminum hydride (90 mg, 2.4 mmol) in anhydrous ether (4 mL) was stirred for 15 h at room temperature. The usual workup and two sublimations afforded the amine **19** as colorless solids (62 mg, 79.8%), mp 193–195 °C (lit.[15] mp 193–194 °C), which the IR and NMR spectra were superimposable with an authentic sample.[15]

1-Azidomethyladamantane (21). A mixture of 1-adamantylcarbinyl tosylate (**20**)[19] (0.32 g, 1.0 mmol) and sodium azide (0.65 g, 10 mmol) in dimethyl sulfoxide (10 mL) was stirred at 60 °C for 1 week. The mixture was diluted with water (50 mL) and extracted with methylene chloride (three 10-mL portions). The combined extracts were washed with water and dried (Na_2SO_4). Removal of the solvent gave crude azide which was purified on a silica gel column eluting with *n*-hexane to afford azide **21** as an oil (50 mg, 26.1%): $n^{25}D$ 1.5205; IR (neat) 2100, 1455, 1275, 980, and 930 cm^{-1}; NMR ($CDCl_3$) δ 2.91 (s, 2 H, CH_2N), 1.97 (br s, 3 H, bridgehead protons), and 1.8–1.35 (m, 12 H, ring methylene protons).

Anal. Calcd for $C_{11}H_{17}N_3$: C, 69.07; H, 8.96; N, 21.97. Found: C, 69.33; H, 8.84; N, 21.83.

Registry No.—**1**, 768-95-6; **2**, 24886-73-5; **3**, 55086-02-7; **4**, 707-37-9; **5**, 63534-29-2; **7**, 63534-30-5; **8**, 63534-31-6; **9**, 13987-76-3; **10**, 63534-32-7; **12**, 63534-33-8; **13**, 15158-56-2; **14**, 63534-34-9; **15** HCl, 19388-60-4; **17**, 14504-80-4; **18**, 63534-35-0; **20**, 795-63-1; **21**, 63534-36-1.

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(17) In fact, 1-noradamantanol was recovered on treatment with NaN_3 (2.5 mol excess) in 57% H_2SO_4–$CHCl_3$ for 2 h, but the reaction in 95% H_2SO_4–$CHCl_3$ gave rearranged products which were not completely characterized yet. The alcohol **13** and **17** gave also rearranged products on treatment with NaN_3 in 95% H_2SO_4–$CHCl_3$ and these results will be reported in future publications.
(18) Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. Melting points were determined with a Yanagimoto micromelting point apparatus (hot-stage type) and are uncorrected. IR spectra were obtained with a Jasco IRA-1 spectrometer. NMR spectra were taken with a Jeol-C-60HL spectrometer using Me_4Si as internal standard.
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Pentacyclic Triterpene Synthesis. Synthesis and Reactions of *cis*- and *trans*-7,7,10-Trimethyl-$\Delta^{3,4}$-octalin-2-one—Preparation of DE Synthon[1a]

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Synthesis of the *cis*- and *trans*-octalones **9a** from the corresponding cis and trans dicarboxylic acids **4** and studies on the base-catalyzed alkylation of the above octalones **9a** and their α-formyl **9d** and α-cyano **9e** derivatives are described. A novel case of predominant O-methylation of a homocyclic β-keto nitrile has been observed.

In connection with our work on the synthesis of pentacyclic triterpenoids, we explored methods for the synthesis of tetracyclic intermediates comprising the ABDE rings by coupling of two fragments corresponding to the AB and DE units. To this end, we synthesized the *cis*- and *trans*-trimethyloctalones **9a** to serve as the DE unit of the projected synthetic plan. The choice of the above octalones for this scheme was dictated by the consideration that the octalones possessing a single reactive methylene group at the desired position could be alkylated directly, without taking recourse to protecting groups, to give the required tetracyclic intermediates which can be employed for the construction of the pentacyclic units.

Synthesis of the above *cis*- and *trans*-trimethyloctalones **9a** was readily achieved from the corresponding cis and trans dicarboxylic acids **4** by the steps outlined in Chart I. Catalytic reduction of the unsaturated cyanoacetate **2** gave by stereospecific reduction only the cis isomer, whereas reduction with aluminum amalgam in moist ether[2] gave a mixture of cis and trans isomers in the ratio of 1:1.

The decalindiones **7** being unsymmetrically substituted can theoretically give rise to the two isomeric enol ethers **8** and **10** and hence to the two isomeric octalones **9a** and **11** (Chart I). In the trans series, the structure of the octalone obtained by the above procedure was settled by an unambiguous synthesis of the *trans*-decalone **14** from the trans dicarboxylic acid ester **5** by two successive homologations of the acetic acid chain followed by ring closure of the resulting pimelate[4] (Chart II). This *trans*-decalone **14** was different in all respects from the *trans*-decalone **15a** obtained through the enol ether procedure. Finally, the 2 position of carbonyl group and the stereochemistry of the octalones **9a** were settled unambiguously by catalytic hydrogenation to the corresponding known *cis*- and *trans*-decalones **15a** prepared earlier by Halsall and Thomas.[3]

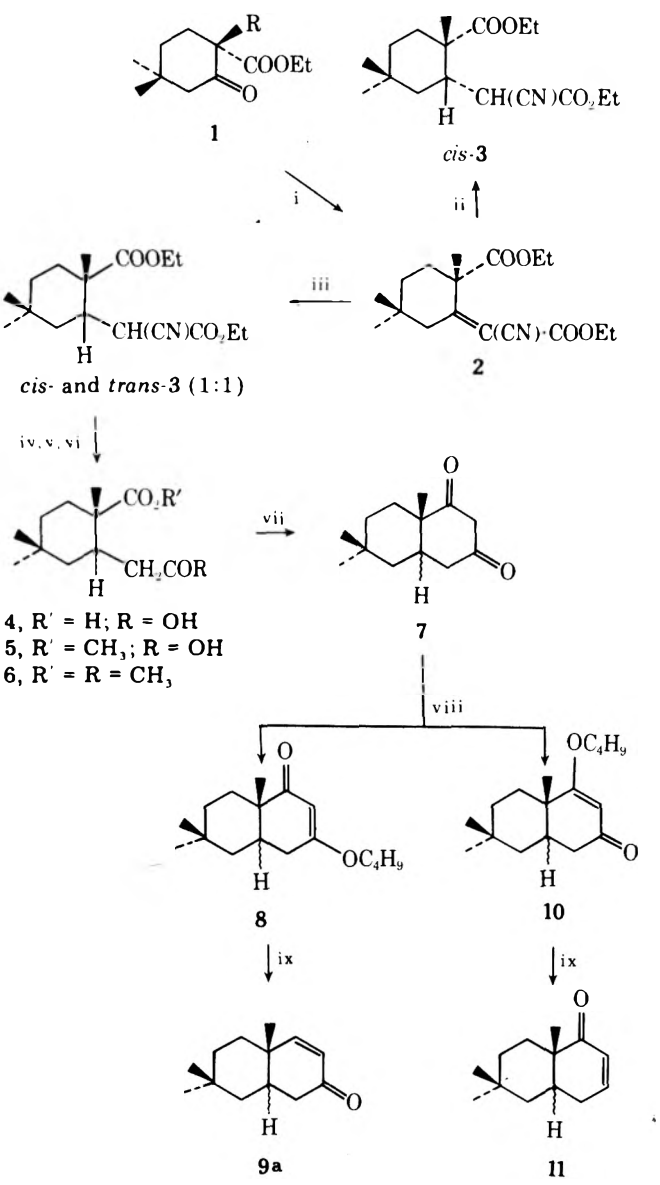
The *cis*- and *trans*-octalones **9a** possessing only one reactive center at the desired position were ideally constituted for direct base-catalyzed alkylation with appropriate alkyl halides to give the required tetracyclic intermediates. Unfortunately, attempted alkylation of either isomer in the presence of KOBu^t in Bu^{t}OH or NaH in C_6H_6–DMF mixture with different alkyl halides was always unsuccessful.

In view of this, we examined the alkylation of the corresponding *cis*- and *trans*-β-keto aldehydes **9d** and β-keto nitriles **9e**.

Methylation of the *trans*-β-keto aldehyde **9d** gave after usual separation of O- and C-methylated products[5] the *trans*-tetramethyloctalone (*trans*-**9b**) in moderate yield. This, on catalytic hydrogenation, gave the *trans*-tetramethyldecalone (*trans*-**15b**). Attempted alkylation of the *trans*-β-keto aldehyde **9d** with ethyl bromoacetate[6] was unsuccessful. The *cis*-β-keto aldehyde **9d** however reacted under identical conditions to give exclusively the O-alkylated products.

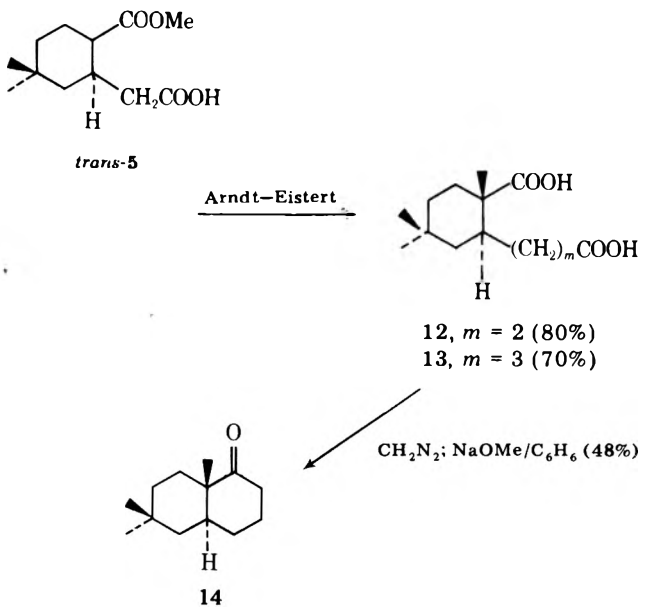
The *trans*-β-keto nitrile **9e** reacted with ethyl bromoacetate in the presence of KOBu^t in Bu^{t}OH to give the desired C-

Chart I



i, $CH_2(CN)CO_2Et$, AcOH, NH_4OAc, C_6H_6 (53%)
ii, 10% Pd–C (90%)
iii, Al–Hg–moist ether (86%)
iv, conc HCl and aq NaOH (90%)
v, MeOH–H_2SO_4 or CH_2N_2; 1 equiv of NaOH (86%)
vi, $SOCl_2$, CH_2N_2–HI, or $CdMe_2$, or $CH_2(CO_2Et)_2$–H_2O (68%)
vii, NaOEt (94%)
viii, *i*-BuOH–H+/C_6H_6 (82%)
ix, LAH–H_2SO_4 (81%)

Chart II



alkylated product in very low yield. Much unreacted keto nitrile was recovered. Hydrolysis and esterification of the above condensation product gave the *trans*-octalone ester **9c** which on successive catalytic hydrogenation and hydrolysis afforded the *trans*-decaloneacetic acid[7] **15c**. Attempted alkylation of the *trans*-octalonenitrile **9e** with the ethylene ketal of 2-(2-oxocyclohexyl)ethyl bromide (**20**) was however less promising.

The *cis*-octalonenitrile **9e** under identical conditions however reacted with ethyl bromoacetate as well as with the bromide **20** to give in quantitative yield the corresponding O-alkylated products. No evidence of any C alkylation could be obtained in either case.

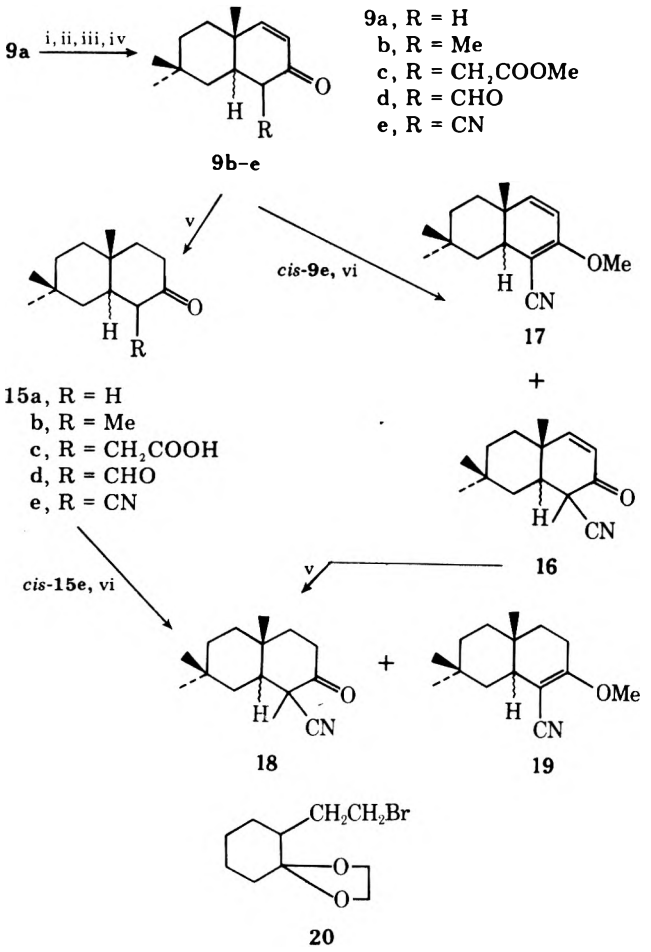
Base-catalyzed alkylation of β-keto esters and β-keto nitriles have been known to give essentially the corresponding C-alkylated products except with highly reactive alkyl halides which are known to promote O alkylation.[8] The observed exclusive O alkylation of the *cis*-β-keto nitrile **9e** with ethyl bromoacetate provided an exception to the general behavior of such β-keto nitriles[9] and encouraged us to investigate the methylation of the β-keto nitriles *cis*- and *trans*-**9e**.

Methylation of the *cis*-octalonenitrile **9e** with methyl iodide in the presence of KOBu^t in Bu^{t}OH gave a mixture of O- and C-methylated products **16** and **17** from which the C-methylated product *cis*-**16** was obtained in ca. 30% yield. Catalytic hydrogenation of the *cis*-octalonenitrile **16** gave the corresponding decalone **18**. The predominant O methylation observed in this system thus provided an exception to the general behavior[10] of homocyclic β-keto nitriles so far reported.[11]

The *cis*-decalonenitrile **15e** was methylated under identical conditions to yield again a mixture of O- and C-methylated products, from which the C-methylated product *cis*-**18** was isolated in ca. 40% yield. It was interesting and significant to note that the methylation of *cis*-octalone **9e** and *cis*-decalone **15e** was highly stereoselective and gave only one stereoselective product, though the sense of stereoelectivity[12] remained unknown from these studies. Alkylation of the *cis*-decalonenitrile **15e** with ethyl bromoacetate followed by vigorous hydrolysis ultimately gave the *cis*-decaloneacetic acid **15c** in an extremely poor yield. Attempted alkylation of *cis*-decalonenitrile **15e** with the bromide **20** gave the C-alkylated product in an insignificant yield.

In the cis series, O alkylation is favored in all cases due to severe steric hindrance to alkylation of C-1 from both faces of the *cis*-decalone moiety. The predominant O alkylation can presumably be due to a high equilibrium concentration of the enol form and the formation of a product in which considerable 1,3-diaxial interactions are eliminated.

Our work in this direction was abandoned following the publication of Barltrop's synthesis[13] of a pentacyclic structure along similar lines.



i, HCO_2Et, NaOEt (85%)
ii, MeI, K_2CO_3, Me_2CO (26%)
iii, NH_2OH·HCl, AcOH, NaOMe (80%)
iv, $BrCH_2CO_2Et$, KOBu^t, ^{t}BuOH; HCl; CH_2N_2 (10%)
v, H_2–10%-Pd-C (98%)
vi, KOBu^t-MeI (30–40%)

Experimental Section

All melting points are uncorrected. Usual workup means extraction with an organic solvent, washing the extract with water, dilute acid or dilute base where necessary, followed by water again to neutrality, drying over anhydrous Na_2SO_4, and removal of solvent under reduced pressure.

Ethyl 2,5,5-Trimethylcyclohexanone-2-carboxylate (1, R = CH_3). 3,3-Dimethylcyclohexanone[14] (93 g) was condensed with diethyl oxalate (108 g) in the presence of NaOEt (503 g) in EtOH (225 mL) to afford after usual workup the crude glyoxalate which was decarboxylated[15] with soft-glass powder (ca. 4 g) at 170–180 °C until evaluation of carbon monoxide ceased. Conventional workup and distillation gave the β-keto ester (**1**, R = H, 122 g), bp 105–110 °C (10 mm).

Methyl iodide (27 mL) was added to the sodium salt of the above β-keto ester prepared from the keto ester **1** (R = H, 56 g) and Na dust (6.45 g) in benzene (300 mL), and the mixture was refluxed until a negative $FeCl_3$ test was observed (6.5 h). Usual workup gave the methylated keto ester **1** (R = Me, 56 g), bp 110–112 °C (10 mm). The **2,4-dinitrophenylhydrazone** had mp 115 °C (lit.[16] mp 111–111.5 °C). The **semicarbazone** crystallized from EtOH had mp 150 °C.

Anal. Calcd for $C_{13}H_{23}N_3O_3$: N, 15.6. Found: N, 15.4.

Ethyl 6-Ethoxycarbonyl-3,3,6-trimethylcyclohexylidene-1-cyanoacetate (2). A mixture of the above keto ester **1** (R = CH_3;

58.3 g), ethyl cyanoacetate (49.7 g), and glacial acetic acid (18 g) in benzene (145 mL) was heated to reflux with a water separator. Ammonium acetate (23.1 g) was added in four equal portions during 15 h, and the mixture was refluxed for a further 10 h after the last addition. Usual workup and distillation afforded the desired condensation product **2** (30 g) as a pale-yellow oil, bp 150–160 °C (1 mm). The recovered keto ester was recycled to afford an additional quantity (15 g) of the condensation product **2**. Redistillation, bp 155–156 °C (1 mm), gave the analytical sample.

Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.45; H, 8.14. Found: C, 66.70; H, 8.30.

***cis*-2-Carboxy-2,5,5-trimethylcyclohexane-1-acetic Acid (*cis*-4).** The unsaturated cyano ester **2** (6.2 g) in ethanol (15 mL) was stirred in an atmosphere of hydrogen in the presence of 10% Pd-on-charcoal catalyst at atmospheric pressure until the calculated amount of hydrogen was consumed (ca. 10 h). Usual workup and distillation afforded the dihydro derivative **3** (5.5 g), bp 146–147 °C (1 mm).

The compound **3** was refluxed with a mixture of concentrated HCl (50 mL) and glacial acetic acid (10 mL) for 60 h, and the solution was then concentrated under reduced pressure. The precipitated heavy oil was taken up in ether and the ether solution extracted with aqueous $NaHCO_3$ solution. Acidification of the bicarbonate extract precipitated a crystalline solid *cis*-**4** (1.2 g), mp 170–180 °C, which after one crystallization from acetone–petroleum ether had mp 189 °C, unchanged upon further crystallization.

The neutral ether solution was evaporated, and the residue (4 g) was hydrolyzed for 10 h with 10% NaOH solution (40 mL). After removal of neutral matter by extraction with ether, acidification of the alkaline solution gave an acid (*cis*-**4**, 3.5 g), mp 175–185 °C, which after crystallization from acetone–petroleum ether had mp 189 °C and was found identical with the acid described above. An analytical specimen was prepared by crystallization from acetone–petroleum ether.

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.17; H, 8.77. Found: C, 62.85; H, 8.60. Calcd Mol Wt for $C_{12}H_{20}O_4$: 228. Found: 230 by titration.

The cis acid **4** (12 g) was esterified with anhydrous methanol (60 mL) and concentrated H_2SO_4 (3 mL) for 20 h to afford after usual workup the dimethyl ester (7 g), bp 135–140 °C (5 mm), and a crystalline acid ester (5 g), mp 146–150 °C. The latter on esterification with diazomethane gave the dimethyl ester of *cis*-**4**.

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.62; H, 9.37. Found: C, 65.22; H, 9.01.

***cis*- and *trans*-2-Carboxy-2,5,5-trimethylcyclohexane-1-acetic Acid (*cis*- and *trans*-4).** The unsaturated cyano ester **2** (60 g) was added to Al–Hg prepared from Al foil (40 g) covered with moist ether (500 mL) containing ethanol (2 mL), and the mixture was set aside at room temperature for 7 days with addition of water (2 mL) each day.[2] It was then poured into a mixture of ice and concentrated HCl (530 mL) with vigorous stirring. The ether layer was removed, the aqueous layer was extracted with ether, and the combined ether extracts were then processed in the usual way to give the dihydro derivatives *cis*- and *trans*-**3** (52 g), bp 145–150 °C (1 mm).

The crude mixture of *cis*- and *trans*-**3** (29 g) was hydrolyzed with a mixture of concentrated HCl (290 mL) and glacial AcOH (29 mL) for 60 h and then concentrated to a small volume under reduced pressure, and the organic matter was taken up in ether. Extraction of this ether solutions with aqueous $NaHCO_3$ solution and acidification of the bicarbonate extract precipitated the trans acid **4** (12 g), mp 165–170 °C, which after crystallization from acetone–petroleum ether had mp 177–178 °C. The melting point was depressed (155–159 °C) on admixture with the cis acid **4** (mp 189 °C).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.17; H, 8.77. Found: C, 63.36; H, 8.75. Calcd Mol Wt for $C_{12}H_{20}O_4$: 228. Found: 225 by titration.

The neutral ether solution was concentrated and the residue (18 g) was hydrolyzed for 10 h with 10% aqueous NaOH (180 mL). Usual workup as described before gave the cis acid **4** (10 g), mp 170–180 °C, which after crystallization had mp 189 °C.

Esterification of the trans acid **4** (7 g) with methanol (35 mL) and concentrated H_2SO_4 (2.5 mL) for 20 h gave the *trans*-dimethyl ester of **4** (7 g), bp 140–142 °C (8 mm).

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.62; H, 9.37. Found: C, 65.35; H, 9.40.

***cis*- and *trans*-2-Methoxycarbonyl-2,5,5-trimethylcyclohexane-1-acetic Acid (*cis*- and *trans*-5).** (a) The *cis*-dimethyl ester of **4** (3.72 g) was hydrolyzed for 3 h with a solution of NaOH (0.6 g) in methanol (75 mL) and water (15 mL). Methanol was removed under reduced pressure and the residual solution extracted once with ether. Acidification of the aqueous alkaline solution precipitated an oil which was taken up in ether and processed in the usual way to afford the cis acid ester **5** (3.6 g), mp 97–100 °C, which after crystallization from acetone–petroleum ether had mp 104–105 °C.

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.46; H, 9.09. Found: C, 64.52; H, 9.31. Calcd. Mol Wt. for $C_{13}H_{22}O_4$: 242. Found: 242 by titration.

(b) Partial hydrolysis of the *trans*-dimethyl ester of **4** (6.55 g) under identical conditions afforded the trans acid ester **5** (6.3 g), mp 84–90 °C, which after crystallization from petroleum ether had mp 94–95 °C.

Anal. Calcd for $C_{13}H_{22}O_4$; c, 64.46; H, 9.09. Found: C, 63.99; H, 9.08. Calcd Mol. Wt for $C_{13}H_{22}O_4$: 242. Found: 242 by titration.

Methyl *cis*- and *trans*-2-(2-Oxopropyl)-1,4,4-trimethylcyclohexane-1-carboxylate (*cis*- and *trans*-6). The *cis*- and *trans*-methyl ketones **6** were prepared from the cis and trans acid ester **5** by three different methods. (1) A solution of the cis acid ester **5** (3.7 g) in benzene (50 mL) containing a drop of pyridine was treated with freshly distilled thionyl chloride (3.6 g) to afford on usual treatment the corresponding acid chloride as an oil (4.0 g). This was taken up in benzene (10 mL) and was added to an ethereal solution of diazomethane (2.7 g) at 0 °C. After standing 2 h at this temperature, ether was completely removed under reduced pressure. The residual crude diazo ketone was dissolved in chloroform (50 mL) and the solution vigorously shaken (5 min) with freshly distilled hydriodic acid, specific gravity 1.7 (5 mL).[17] The chloroform solution was then washed in succession with water, aqueous sodium thiosulfate, and again with water. Removal of solvent and distillation gave the methyl ketone *cis*-**6** (2.5 g), bp 125–130 °C (4 mm).

(2) The crude diazo ketone obtained from the cis acid ester **5** (4 g) as described before was dissolved in anhydrous ether (50 mL) and cooled to 0 °C, and an excess of HCl (g) was passed. Removal of solvent gave the crude chloromethyl derivative which was dissolved in glacial AcOH (50 mL) and then powdered KI (4 g) was added to it. Zinc dust (20 g) was then added slowly with stirring to the above solution at room temperature during 6 h.[18] Water (10 mL) was added, stirring continued for 1 h more, and the mixture left at room temperature overnight. It was then filtered and the inorganic residue washed with aqueous HOAc (80%). Evaporation of the acetic acid under reduced pressure and usual workup of the organic residue gave the *cis*-methyl ketone **6**, bp 145–150 °C (15 mm).

(3) The acid chloride prepared in the usual way from the cis acid ester **5** (41 g) was added to an ice-cold suspension of sodiomalonic ester [prepared from Na dust (8 g) and diethyl malonate (50 g)] in benzene (400 mL). After stirring for 2 h at 0 °C, the reaction mixture was heated on a steam bath for 2 h, cooled, and decomposed with glacial HOAc. The benzene layer was removed and concentrated under reduced pressure. The residue was heated under reflux with a mixture of concentrated HCl (100 mL), glacial HOAc (100 mL), and water (50 mL) for 9 h.[19] After cooling, the solution was neutralized with 15% NaOH solution and extracted with ether to give after usual workup the *cis*-methyl ketone **6** (30 g), bp 125–130 °C (4 mm). It gave a positive haloform test for the methyl keto group.

2,4-Dinitrophenylhydrazone crystallized from aqueous methanol had mp 114 °C. Anal. Calcd for $C_{20}H_{28}N_4O_6$: C, 57.15; H, 6.69. Found: C, 57.39; H, 6.90. The **semicarbazone** crystallized from aqueous methanol had mp 190 °C. Anal. Calcd for $C_{15}H_{27}N_3O_3$: N, 14.14. Found: N, 14.20.

(b) The trans methyl ketone **6**, bp 125–130 °C (4 mm), was similarly prepared from the trans acid ester **5** by the above methods in comparable yields. It gave a positive haloform test for the methyl keto group.

2,4-Dinitrophenylhydrazone crystallized from aqueous methanol had mp 149 °C. Anal. Calcd for $C_{15}H_{27}N_3O_3$: N, 14.14. Found: N, 14.20.

***cis*- and *trans*-7,7,10-Trimethyldecalin-2,4-dione (*cis*- and *trans*-7).** (a) A solution of cis keto ester **6** (6 g) in ethanol (10 mL) was added to NaOEt (2.03 g) in ethanol (12 mL) and the mixture refluxed under nitrogen for 11 h. Ethanol was then completely removed under pressure, and the residue was dissolved in water and extracted once with ether. Acidification of the aqueous solution precipitated the cis diketone **7** (5.5 g), mp 160–165 °C, which after two crystallizations from acetone–petroleum ether had mp 178 °C.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.99; H, 9.61. Found: C, 75.50; H, 9.78.

(b) The trans keto ester **6** (9.32 g) under identical treatment gave the trans diketone **7** (8.0 g), mp 160–162 °C, which after crystallization from acetone–petroleum ether had mp 166 °C.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.99; H, 9.61. Found: C, 75.16; H, 9.61.

***cis*- and *trans*-7,7,10-Trimethyl-$\Delta^{3,4}$-octalin-2-one (*cis*- and *trans*-9a.)** (a) A mixture of the cis diketone **7** (5 g), 2-butanol (11.5 mL), benzene (60 mL), and *p*-toluenesulfonic acid (0.7 g) was refluxed with a water separator until no more water separated.[20] Usual workup

and distillation afforded the enol ether *cis*-8 (5.2 g), bp 140–145 °C (1 mm), which solidified and after crystallization from petroleum ether had mp 62–63 °C.

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.27; H, 11.36. Found: C, 77.30; H, 11.00.

A solution of the above cis enol ether **8** (26.4 g) in ether (50 mL) was added to LAH (3.7 g) in ether (200 mL). After stirring at room temperature for 3 h, the reaction mixture was decomposed with excess of 10% aqueous H_2SO_4. Usual workup gave the *cis*-octalone **9a** (15.6 g): bp 117–118 °C (5 mm); λ_{max}^{EtOH} 232 nm, log ε 4.0.

The **2,4-dinitrophenylhydrazone** was crystallized from ethanol–ethyl acetate: mp 209 °C[21] (lit.[3] mp 207–209 °C); $\lambda_{max}^{CHCl_3}$ 380 nm, log ε 4.6. Anal. Calcd for $C_{19}H_{24}N_4O_4$: N, 15.0. Found: N, 15.4. The **semicarbazone** crystallized from ethanol, mp 228 °C (dec). Anal. Calcd for $C_{14}H_{23}N_3O$: C, 67.48; H, 9.23. Found: C, 67.38; H, 9.07.

A higher boiling fraction (5 g), bp 140–150 °C (4 mm), which solidified and had mp 62–63 °C after crystallization, was identified as unreacted enol ether *cis*-8.

(b) The trans diketone **7** (8 g) was similarly converted to the oily *trans*-enol ether **8** (8.3 g), bp 140–145 °C (1 mm), which upon hydride reduction and acid hydrolysis gave the *trans*-octalone **9a** (6.7 g): bp 118 °C (5 mm); λ_{max}^{EtOH} 228 nm, log ε 3.99.

The 2,4-dinitrophenylhydrazone crystallized from ethanol–ethyl acetate had mp 178 °C.

Anal. Calcd for $C_{19}H_{24}N_4O_4$: N, 15.0. Found: N, 15.0.

The **semicarbazone** crystallized from ethanol had mp 223 °C (dec). Anal. Calcd for $C_{14}H_{23}N_3O$: C, 67.48; H, 9.23. Found: C, 67.30; H, 9.15.

***cis*- and *trans*-7,7,10-Trimethyldecalin-2-one (*cis*- and *trans*-15a).** The *cis*-octalone **9a** (1 g) in ethanol (25 mL) was stirred in an atmosphere of hydrogen in the presence of 10% Pd-on-charcoal catalyst (0.05 g) when hydrogen uptake was complete in 20 min. Usual workup gave the *cis*-decalone **15a** as a crystalline solid which after crystallization from aqueous methanol had mp 71 °C (lit.[3] mp 67.5–68 °C).

The **2,4-dinitrophenylhydrazone** had mp 193 °C (lit.[3] mp 187–189 °C). Anal. Calcd for $C_{19}H_{26}N_4O_4$: C, 60.95; H, 6.95. Found: C, 61.08; H, 6.84.

The **semicarbazone** had mp 238 °C (dec) (lit.[3] mp 225–227 °C). Anal. Calcd for $C_{14}H_{25}N_3O$: N, 16.73. Found: N, 16.50.

(b) The *trans*-octalone **9a** was similarly hydrogenated to the oily *trans*-decalone **15a**, bp 120 °C (5 mm).

The **2,4-dinitrophenylhydrazone** had mp 202 °C (lit.[3] mp 191 °C). Anal. Calcd for $C_{19}H_{26}N_4O_4$: C, 60.95; H, 6.95. Found: C, 61.44; H, 7.26.

The **semicarbazone** had mp 225 °C (dec). Anal. Calcd for $C_{14}H_{25}N_3O$: C, 66.92; H, 9.96. Found: C, 66.70; H, 9.67.

***trans*-7,7,10-Trimethyldecalin-4-one (14).** The trans acid ester **5** (1.9 g) was converted in the usual way to its acid chloride by treatment with thionyl chloride (2.5 g) in benzene (30 mL), and the crude acid chloride was then treated with diazomethane (1 g) in ether (50 mL) to afford an oily diazo ketone (2 g) which was subjected to Wolff rearrangement[22] by heating with benzyl alcohol (10 mL) and γ-collidine (10 mL) at 170–180 °C. Usual workup and hydrolysis of the resultant crude neutral ester with excess 10% trimethylcyclohexane-1-β-propionic acid (**12**, 1.5 g) which after crystallization from acetone–petroleum ether had mp 213 °C.

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.46; H, 9.09. Found: C, 64.42; H, 8.98. Calcd Mol. Wt. for $C_{13}H_{22}O_4$: 242. Found; 242 by titration.

The above trans acid **12** (1.4 g) was esterified with diazomethane and the dimethyl ester partially hydrolyzed to the corresponding oily acid ester. This was then subjected to a second Arndt–Eistert homologation following the above procedure to give the crystalline *trans*-2-carboxy-2,5,5-trimethylcyclohexane-1-γ-butyric acid (**13**, 0.75 g) which when crystallized from benzene–petroleum ether had mp 186 °C.

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.63; H, 9.38. Found: C, 65.73; H, 9.51.

The above dicarboxylic acid **13** was then esterified with diazomethane, and the resultant dimethyl ester (0.7 g), bp 150 °C (5 mm), was heated in benzene (10 mL) with NaOMe (0.28 g) for 10 h under nitrogen. Hydrolysis of the resultant β-keto ester and usual workup gave the *trans*-octalone **14** (0.2 g), bp 140 °C (7 mm).

The **2,4-dinitrophenylhydrazone** had mp 183 °C. Admixture with the 2,4-dinitrophenylhydrazone of the isomeric *trans*-decalone **15a** depressed the melting point to 160–170 °C.

Anal. Calcd for $C_{19}H_{26}N_4O_4$: N, 14.90. Found: N, 14.82.

The **semicarbazone** had mp 228 °C (dec). Mixture melting point with the semicarbazone of the isomeric *trans*-decalone **15a** (mp 225 °C) was depressed to 170–175 °C.

Anal. Calcd for $C_{14}H_{25}N_3O$: C, 66.92; H, 9.96. Found: C, 66.65; H, 9.58.

***trans*-1,7,7,10-Tetramethyl-Δ^{3,4}-octalin-2-one (*trans*-9b).** A solution of the *trans*-octalone **9a** (2.8 g) in benzene (50 mL) was condensed with ethyl formate (5 g) in the presence of anhydrous NaOMe (2.34 g) in the usual way[5] to afford, after the usual workup, the *trans*-hydroxymethyleneoctalone **9d** (2.8 g), as an oil which responded to $FeCl_3$ test.

A solution of the above hydroxymethyleneoctalone **9d** (2.8 g) in anhydrous acetone (25 mL) containing K_2CO_3 (25 g) and methyl iodide (4 mL) was stirred under reflux for 25 h. Conventional workup gave an oil which was hydrolyzed at room temperature overnight with a mixture of methanol (9 mL), water (1 mL), and concentrated HCl (0.5 mL), and the resulting product was then separated into neutral and acidic fractions by extraction with a 2% KOH solution. Hydrolysis of the neutral oil with 10% KOH solution for 2 h under nitrogen[5] gave after conventional workup the *trans*-tetramethyloctalone *trans*-**9b**, 0.8 g), bp 115 °C (5 mm).

The **2,4-dinitrophenylhydrazone** crystallized from ethanol–ethyl acetate had mp 220 °C. Anal. Calcd for $C_{20}H_{26}N_4O_4$: N, 14.50. Found: N, 14.20.

This *trans*-tetramethyloctalone (*trans*-**9b**) was reduced catalytically in the presence of 10% Pd-on-charcoal catalyst to furnish the *trans*-tetramethyldecalone (*trans*-**15b**).

This **2,4-dinitrophenylhydrazone** crystallized from ethanol–ethyl acetate had mp 218 °C. Anal. Calcd for $C_{20}H_{28}N_4O_4$: N, 14.43. Found: N, 14.73.

The *semicarbazone* after crystallization from ethanol had mp 225 °C (dec). Anal. Calcd for $C_{15}H_{27}N_3O$: N, 15.84. Found: N, 16.09.

Attempted alkylation of the above *trans*-hydroxymethyleneoctalone (*trans*-**9d**) with ethyl bromoacetate[6] was not successful.

Attempted methylation of the corresponding *cis*-hydroxymethyleneoctalone (*cis*-**9d**) under above conditions gave exclusively the O-methyl derivative.

***trans*-7,7,10-Trimethyldecal-2-one-1-acetic Acid (*trans*-15c).** The crude hydroxymethylene derivative of the *trans*-octalone **9d** (2.8 g) prepared by the above procedure in glacial acetic acid (180 mL) containing hydroxylamine hydrochloride (1.7 g) was heated under nitrogen for 2 h at 100 °C and then completely evaporated to dryness under reduced pressure. The residue was dissolved in $CHCl_3$, and the solution was washed in succession with 2% NaOH solution and water and concentrated to give the isoxazole derivative (2.4 g). A benzene solution (120 mL) of the isoxazole was added to a solution of NaOMe (1.41 g) in methanol (25 mL) and stirred for 45 min at room temperature.[9] The benzene solution was extracted twice with ice-cold 0.5% KOH solution, and the combined alkaline extract was acidified and the liberated oil taken up in $CHCl_3$ to give the keto nitrile *trans*-**9e** (1.8 g) as a gummy solid which was directly employed for the next step.

This keto nitrile (*trans*-**9e**) in *tert*-butyl alcohol (30 mL) was added to a solution of $KOBu^t$ (4.1 g) in *tert*-butyl alcohol (30 mL) under nitrogen followed by ethyl bromoacetate (4.5 mL), and the mixture was refluxed for 3 h under nitrogen. After removal of the solvent under reduced pressure and dilution with water, the reaction mixture was extracted with ether and the ether solution washed with 0.5% KOH solution and then with water to neutrality. Concentration of the neutral ether solution left a viscous oil (0.6 g). Acidification of the aqueous alkaline extract gave the unreacted β-keto nitrile *trans*-**9e** (1.0 g).

The condensation product (0.6 g) was hydrolyzed with concentrated HCl (6 mL) for 10 h. Usual workup gave a viscous gummy acid (0.4 g) which was esterfied (diazomethane) to give the octalone methyl ester *trans*-**9c** (bp 160–162 °C (1 mm).

The **2,4-dinitrophenylhydrazone** crystallized from methanol had mp 163 °C. Anal. Calcd for $C_{22}H_{28}N_4O_6$: N, 12.60. Found: N, 12.25.

The *trans*-octalone ester **9c** (0.3 g) in ethanol (20 mL) was reduced catalytically in the presence of 10% Pd-on-charcoal catalyst to afford the *trans*-decalone ester, bp 155–160 (1 mm).

The **2,4-dinitrophenylhydrazone** crystallized from methanol had mp 191 °C (lit.[3] mp 187–189 °C). Anal. Calcd for $C_{22}H_{30}N_4O_6$: C, 59.20; H, 6.73. Found: C, 58.91; H, 6.43.

The above decalone ester (0.2 g) was hydrolyzed with an excess of 10% methanolic KOH to afford the *trans*-decaloneacetic acid (*trans*-**15c**), which after purification through its cyclohexylamine salt, mp 160 °C, and crystallization from an ether–petroleum ether mixture had mp 96–98 °C (lit.[3] mp 92–94 °C).

***cis*-1-Cyano-7,7,10-trimethyl-Δ^{3,4}-octalin-2-one (*cis*-9e).** The crude hydroxymethylene compound[23] **9d**, obtained from the *cis*-octalone **9a** (0.92 (1.92 g), ethyl formate (3.6 g), and anhydrous sodium methoxide (2.0 g) in benzene (30 mL) as described for the *trans*-oc-

talone, was heated with hydroxylamine (1.14 g) in glacial acetic acid (120 mL) for 2 h at 100 °C to yield the isoxazole (1.8 g) which in benzene (12 mL) was treated with a solution of NaOMe (1.1 g) in methanol (10 mL) at room temperature.[9] Usual workup gave *cis*-β-keto nitrile, **9e** (1.7 g), mp 120–124 °C, which upon crystallization from benzene-petroleum ether had mp 128 °C.

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.41; H, 8.76. Found: C, 77.89; H, 8.90.

The **2,4-dinitrophenyl hydrazone** crystallized from ethanol–ethyl acetate, mp 206 °C.

***cis*-1-Cyano-7,7,10-trimethyldecalin-2-one (*cis*-15e).** The above *cis*-octalonenitrile **9e** (1 g) in ethanol (25 mL) was stirred in an atmosphere of hydrogen in the presence of 10% Pd-on-charcoal catalyst (0.05 g) when the calculated amount of hydrogen was taken up in 30 min. Usual workup gave the decalonenitrile, **15e**, which after crystallization from ether–petroleum ether had mp 113–114 °C.

Anal. Calcd for $C_{14}H_{21}NO$: C, 76:72; H, 9.59. Found: C, 76.77; H, 9.78.

The **2,4-dinitrophenylhydrazone** had mp 260 °C (dec).

Methylation of the *cis*-Cyanooctalone 9e: Formation of *cis*-1-Cyano-1,7,7,10-tetramethyl-$\Delta^{3,4}$-octalin-2-one (*cis*-16). The *cis*-cyanooctalone **9e** (1 g) in *tert*-butyl alcohol (10 mL) was added to a solution of KOBu^t (2.2 g) in *tert*-butyl alcohol (20 mL) under nitrogen followed by methyl iodide (2 mL), and the mixture was stirred under reflux for 3 h. Alcohol was then removed under reduced pressure, and the residue was diluted with water and extracted with ether. The unreacted β-keto nitrile **9e** (0.05 g) was removed by extraction of the above ether solution with 0.5% aqueous KOH. Usual workup of the neutral ether extract gave an oil (1 g), bp 135–140 °C (2 mm). This showed λ_{max}^{EtOH} 302 nm, log ε 3.79, indicative of the presence of a homoannular diene derived from predominant O methylation to give **17**.

This oil was left at room temperature for 36 h with a mixture of methanol (7 mL), water (0.5 mL), and concenrated HCl (0.5 mL). It was then diluted with brine and extracted with ether. The ether solution was then washed with 0.5% aqueous KOH until alkaline, and this alkaline solution, upon acidification, gave the *cis*-octalonenitrile **9e** (0.6 g), mp 128 °C.

The neutral ether solution upon usual workup gave the C-methylated product **16** (0.3 g), mp 87–89 °C, which after crystallization from ether–petroleum ether had mp 103 °C.

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.92; H, 9.05. Found: C, 78.27; H, 9.00.

The **2,4-dinitrophenylhydrazone** crystallized from ethanol–ethyl acetate, mp 208 °C.

Anal. Calcd for $C_{21}H_{25}N_5O_4$: N, 17.03. Found: N, 16.75.

Attempted alkylation of the *cis*-cyanooctalone **9e** with ethyl bromoacetate and with the ethylene ketal of 2-(2-oxocyclohexyl)ethyl bromide (**20**) under identical conditions gave in each case exclusively the O-alkylated products in quantitative yield.

Methylation of the *cis*-Decalonenitrile 15e: Formation of *cis*-1-cyano-1,7,7,10-tetramethyldecalin-2-one (*cis*-18). The *cis*-decalonenitrile **15e** (1 g) was reacted with methyl iodide (1.5 mL) in the presence of KOBu^t (0.6 g) and *tert*-butyl alcohol (20 mL) as described above, and the reaction mixture was worked up to yield an oil (1 g), bp 160–162 °C (2 mm), which had λ_{max}^{EtOH} 235 nm, log ε 3.94, indicative of the presence of a *cis*-β-methoxycrotononitrile chromophore derived through O methylation to give **19**. This oil was treated with a mixture of methanol (8 mL), water (0.5 mL), and concentrated HCl (0.5 mL) for 36 h at room temperature and then worked up as described earlier to give the *cis*-decalonenitrile **15e**, (0.6 g), mp 113 °C, and the C-methylated product **18** (0.4 g) which after crystallization from ethanol had mp 133 °C.

Anal. Calcd for $C_{15}H_{23}NO$: C, 77.25; H, 9.87. Found: C, 77.04; H, 9.65.

The **2,4-dinitrophenylhydrazone** had mp 157 °C. Anal. Calcd for $C_{21}H_{27}N_5O_4$: N, 16.94. Found: N, 17.02. Catalytic hydrogenation of the *cis*-tetramethyloctalonenitrile (*cis*-16) gave the above tetramethyldecalonenitrile (*cis*-18), confirming identical stereochemistry at C-1 in both.

***cis*-7,7,10-Trimethyldecalin-2-one-1-acetic acid (*cis*-15c).** The *cis*-decalonenitrile **15e** (13.g) was condensed with ethyl bromoacetate (5 mL) in the presence of KOBu^t (3.0 g) and *tert*-butyl alcohol (30 mL) in the manner described before to yield a neutral condensation product (2 g) which was hydrolyzed by heating on a steam bath for 1 h with a mixture of methanol (8 mL), water (1 mL), and concentrated HCl (1 mL) to give after usual workup the decalonenitrile **15e** (1.1 g) and a neutral viscous oil (0.2 g). Hydrolysis of the latter with an excess of concentrated HCl under reflux for 8 h gave a gummy acid which was taken in ether, and the ether solution was extracted with aqueous $NaHCO_3$. Acidification of the bicarbonate extract precipitated a gummy solid which gradually solidified. This, after crystallization from a ether–petroleum ether mixture, had mp 190 °C.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.42; H, 9.52. Found: C, 71.56; H, 9.65.

Ethylene Ketal of 2-(2-Oxocyclohexyl)ethyl Bromide (20). Ethyl cyclohexanone-2-acetate (42 g), ethylene glycol (18.5 g), and PTSA (100 mg) in benzene (200 mL) were refluxed (6 h) with a Dean–Stark apparatus until no more water separated. Usual workup gave the ketal (48 g), bp 120–122 °C (5 mm), which was reduced with $LiAlH_4$ (5.6 g) in ether (160 mL) in the usual way to give after decomposition with saturated Na_2SO_4 solution and conventional workup the ketal alcohol (36 g), mp 115–118 °C (5 mm).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.51; H, 9.67. Found: C, 64.80; H, 9.79.

The above ketal alcohol (10 g) was added to a solution of *p*-toluenesulfonyl chloride (12 g) in pyridine (36 mL) at 0 °C. After 24 h, it was worked up to give an oily tosyl ester (20 g) which in dry acetone (50 mL) was heated under reflux for 8 h with lithium bromide (6 g) to afford after conventional workup the required bromide **20**, bp 120–122 °C (6 mm).

Anal. Calcd for $C_{10}H_{17}O_2Br$: Br, 32.1. Found: Br, 32.5.

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Registry No.—**1** (R = H), 36168-42-0; **1** (R = Me), 63648-19-6; **1** (R = Me) semicarbazone, 63548-20-9; **2**, 63548-21-0; **3**, 63548-22-1; *cis*-**4**, 63548-23-2; *cis*-**4** dimethyl ester, 63548-24-3; *trans*-**4**, 63548-25-4; *trans*-4 dimethyl ester, 63548-26-5; *cis*-**5**, 63548-27-6; *trans*-**5**, 63548-28-7; *cis*-**6**, 63548-29-8; *cis*-**6** DNPH, 63548-30-1; *cis*-**6** semicarbazone, 63548-31-2; *trans*-**6**, 63548-32-3; *trans*-**6** DNPH, 63548-33-4; *trans*-**6** semicarbazone, 63548-34-5; *cis*-**7**, 63548-35-6; *trans* **7**, 63548-36-7; *cis*-**8**, 63548-37-8; *trans*-**8**, 63548-38-9; *cis*-**9a**, 59270-18-7; *cis*-**9a** DNPH, 59270-19-8; *cis*-**9a** semicarbazone, 63548-39-0; *trans*-**9a**, 63548-40-3; *trans*-**9a** DNPH, 63548-41-4; *trans*-**9a** semicarbazone, 63548-42-5; *trans*-**9b**, 63548-43-6; *trans*-**9b** DNPH, 63548-44-7; *trans*-**9c**, 63548-45-8; *trans*-**9c** DNPH, 63547-91-1; *cis*-**9d**, 63640-21-1; *trans* **9d**, 63547-92-2; *cis*-**9e**, 63547-93-3; *cis*-**9e** DNPH, 63547-94-4; *trans*-**9e**, 63598-04-9; **12**, 63547-95-5; **13**, 63547-96-6; **14**, 63547-97-7; **14** DNPH, 63547-98-8; **14** semicarbazone, 63548-99-9; *cis*-**15a**, 7056-56-6; *cis*-**15a** DNPH, 63548-00-5; *cis*-**5a** semicarbazone, 63548-01-6; *trans*-**15a**, 54699-31-9; *trans*-**15a** DNPH, 63548-02-7; *trans*-**15a** semicarbazone, 63548-03-8; *trans*-**15b**, 63548-04-9; *trans*-**15b** DNPH, 63548-05-0; *trans*-**15b** semicarbazone, 63548-06-1; *cis*-**15c**, 63548-07-2; *trans*-**15c** methyl ester, 93548-08-3; *trans*-**15c** methyl ester DNPH, 63548-09-4; *cis*-**15e**, 63548-10-7; *cis*-**15e** DNPH, 63548-11-8; *cis*-**16**, 63548-12-9; *cis*-**16** DNPH, 63548-13-0; **17**, 63548-14-1; *cis*-**18**, 63548-15-2; *cis*-**18** DNPH, 63548-16-3; **19**, 63548-17-4; **20**, 63548-18-5; 3,3-dimethylcyclohexanone, 2979-19-3; diethyl oxalate, 95-92-1; ethyl cyanoacetate, 105-56-6; ethyl cyclohexanone-2-acetate, 24731-17-7; 2-(2-oxocyclohexyl)ethanol, ethylene ketal, 57133-56-9.

References and Notes

(1) (a) After this paper was written, related results were reported by J. E. Ellis, J. S. Dutcher, and C. H. Heathcock, *J. Org. Chem.*, **41**, 2670 (1976). (b) Address correspondence to: Department of Chemistry, Warner-Lambert/Parke-Davis Research Division, Ann Arbor, Mich. 48105. (c) Abstracted from the thesis of I. S. submitted for the Ph.D. degree of the University of Calcutta, Calcutta, India, Nov., 1963. (d) Council of Scientific and Industrial Research (India) Jr. Fellow, 1959–1962; University Grants Commission Jr. Research Scholar, 1962–1963.
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Potassium Permanganate Oxidations of Terminal Olefins and Acetylenes to Carboxylic Acids of One Less Carbon[1]

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The potassium permanganate cleavages of terminal olefins and acetylenes to prepare carboxylic acids of one less carbon have been studied under a variety of conditions. Overoxidation is a problem if the reaction is performed in an initially neutral or basic aqueous permanganate solution under heterogeneous liquid–liquid conditions or under heterogeneous liquid–liquid conditions using organic solvents and quaternary ammonium salts as phase-transfer agents. The presence of acetic acid in the two-phase liquid–liquid aqueous permanganate oxidations using organic solvents and quaternary ammonium salts leads to good yields of carboxylic acids with small amounts of overoxidized acids. The results of experiments which attempt to elucidate the overoxidation mechanism are described.

The initial goal of the present research was an exploration of the use of the operationally simple heterogeneous liquid–liquid aqueous permanganate oxidations of the commercially available even-numbered continuous chain α-olefins to prepare high purity odd-numbered carboxylic acids of one less carbon.

$$CH_3(CH_2)_nCH{=}CH_2 \rightarrow CH_3(CH_2)_nCOOH$$

It had previously been reported that 1-decene could be oxidized to nonanoic acid (91% yield, 98% purity) in the heterogeneous two-phase water–benzene system by permanganate and the phase-transfer agent Aliquat 336.[4,5] Similarly, the conversion of 1-octene to heptanoic acid (81%) had been reported using tetrabutylammonium bromide as the phase-transfer catalyst.[6]

Oxidation of the 1-decene following the published procedure[4] (a four-times more dilute aqueous permanganate solution was used to permit effective stirring as MnO_2 fills the flask) led to an excellent yield of a crude acid mixture which consisted of nonanoic acid (90%) and octanoic acid (10%). Similarly, permanganate oxidations of 1-octene and 1-dodecene led to the desired carboxylic acids which were contaminated by hexanoic acid (8%) and decanoic acid (9%), respectively. Under these reaction conditions, the desired one-carbon cleavage products are contaminated with the overoxidation product resulting from a loss of two carbons.

It seemed reasonable to speculate that the overoxidation of the α-olefins was related in some manner to the OH^- formed as a permanganate oxidation proceeds. A study of the oxidation was then undertaken.

Numerous studies have been reported in which the products and rates of product formation from oxidations by permanganate of various substrates depend on the reaction conditions and the pH if an aqueous medium is employed.[7] Mechanistic rationalizations have been advanced to account for the products and rates found during oxidations of olefinic substrates.[7a,b,e-g]

Oxidations by permanganate, although quite effective, are usually plagued by the insolubility of the organic substrate in water. Methods for effecting reaction are rapid stirring to facilitate interfacial contact between the reactants or addition of a cosolvent such as acetic acid to the aqueous phase to enhance solubility. Along with phase-transfer agents,[4,5] crown ethers have found use in solubilizing permanganate in organic solvents.[5e,7l] Acetic anhydride has been used as a solvent in permanganate oxidations.[7h-j] Surfactants in two-phase reactions can also operate as emulsion or micellar catalysts.[8]

The stoichiometry for the cleavage of α-olefins is represented by the equation:

$$3RCH{=}CH_2 + 8MnO_4^- \rightarrow 3RCO_2^- + 3HCO_2^- + 8MnO_2 + 2OH^- + 2HOH$$

Manganese(IV) dioxide is the usual product from permanganate oxidations of most organic substrates in alkaline or mildly acidic solutions. In the equation, formate could possibly undergo further oxidation to CO_2 (to produce CO_3^{2-} in a basic medium) with a net consumption of permanganate.[7a]

The permanganate oxidation of 1-octene was studied under a variety of conditions and the results are summarized in Table I.

Let us examine some of the salient features of the data recorded in Table I. The oxidation of 1-octene proceeds in aqueous permanganate under liquid–liquid heterogeneous conditions at a rate which depends on the mode of stirring and the stirring speed (entries 1, 2, and 3). The extent of overoxidation appears to be a function of reaction time (entries 1 and 2). In the presence of acetic acid (3.3 M) the oxidation is rapid and overoxidation is suppressed (entry 4). The use of pentane or benzene in the oxidation with Aliquat 336 or benzylhexa-

Table I. Permanganate Oxidations of 1-Octene[a]

Additives	Reaction time, h	Stirring	Product analysis: 1-Octene	Hexanoic acid	Heptanoic acid
None[b]	4	Mech[c]	6	10	84
None[b]	2	Mech	9	5	86
None[b]	4	Mag[d]	55	10	35
15 mL of acetic acid[e]	2	Mag	1	3	96
100 mL of pentane,[e] 0.2 g of Aliquat 336	10	Mag	9	7	84
300 mL of benzene,[f] 0.2 g of bzl-PTC	6	Mag		10	90[g]
100 mL of pentane,[e] 30 mL of acetic acid, 0.2 g of Aliquat 336	2	Mag	3	2	95
300 mL of benzene,[f] 60 mL of acetic acid, 0.2 g of bzl-PTC	3	Mag		3	97[g]
300 mL of benzene,[f,h] 35 g of 85% H_3PO_4, 0.2 g of bzl-PTC	5	Mag		6	94[g]
100 mL of pentane,[e] 30 mL of acetic acid	3	Mech	20	2	78

[a] Product analysis was done by VPC of the reaction products treated with ethereal diazomethane in most cases; ±2–3% reliability. [b] $KMnO_4$ (0.06 mol) in 75 mL of water treated with 1-octene (0.015 mol) and any listed additives. See Experimental Section for reaction details. [c] Motor-driven shaft and propeller blade (about 400 rpm). [d] One-inch egg-shaped magnet with a Fisher Thermix motor. [e] $KMnO_4$ (0.10 mol) in 150 mL of water to which 1-octene (0.015 mol) containing the acetic acid was added, along with solvent or PTC. [f] $KMnO_4$ (0.20 mol) in 300 mL of water treated with 1-octene (0.06 mol) and any listed additives. [g] Distilled products isolated in 65–75% yields. [h] About 1 M in H_3PO_4.

Table II. Permanganate Oxidations of 1-Decene

Additives	Reaction[a] time, h	1-Decene	Octanoic acid	Nonanoic acid
None[b]	15	78	4	18
None[b]	14[c]	15	8	77
30 mL of acetic acid[d]	2	2	4	94
150 mL of benzene,[d] 0.1 g of bzl-PTC	19	15	8	77
150 mL of benzene,[d,e] 30 mL of acetic acid	7.5	78	2	20
150 mL of benzene,[d] 30 mL of acetic acid, 0.1 g of bzl-PTC	5	10	3	87
150 mL of benzene,[d] 0.1 M KOH, 0.1 g bzl-PTC	17	4	14	82

[a] All done with magnetic stirring, except in the one case where noted. [b] $KMnO_4$ (0.05 mol) in 75 mL of water treated with 1-decene (0.015 mol). [c] Mechanical stirring. [d] $KMnO_4$ (0.095 mol) in 150 mL of water treated with 1-decene (0.03 mol) and any listed additive. [e] Purple permanganate color completely disappeared, indicating that oxidation of acetic acid was also occurring.

Table III. Permanganate Oxidations of Allylbenzene

Additives	Reaction time, h	C_6H_5COOH	$C_6H_5CH_2COOH$[a]
None[b]	5	75	25
0.2 g of bzl-PTC[b]	7	50	50
60 mL of acetic acid,[b] 0.2 g of bzl-PTC	17	20	80
1.1 M of KOH, 0.2 g of bzl-PTC[b]	10	95	5
0.2 g of bzl-PTC[c]	6	80	20
0.2 g of bzl-PTC[d]	1.5		
60 mL of acetic acid[b]	0.5	20	80

[a] Analysis of the crude acid mixture by ^1H NMR using the aromatic protons and the phenylacetic acid singlet to extrapolate the aromatic protons constituting the contribution of this acid to the total proton integral. [b] $KMnO_4$ (0.19 mol) in 300 mL of water and the benzene (300 mL) containing allylbenzene (0.06 mol) and any listed additives were added in one portion. All runs were stirred magnetically. Product recovery was in the range of 60–80% in all cases. [c] As in *b*, except 0.24 mol of $KMnO_4$ was used. [d] As in b, except 0.03 mol of $KMnO_4$ was used. The recovered olefin showed no detectable isomerization to methylstyrene.

decyldimethylammonium chloride (bzl-PTC) as phase-transfer agents, respectively, leads to 7 and 10% overoxidation (entries 5 and 6). The advantageous effect of acetic acid in suppressing overoxidation in the presence of an organic medium and a phase-transfer agent can be seen in entries 7 and 8. Substitution of phosphoric acid for acetic acid under phase-transfer conditions led to more overoxidation (entry 9). The oxidation also proceeds in the two-phase system pentane–water with added acetic acid (entry 10).

Similar studies were also performed using 1-decene as the olefinic substrate and the data are tabulated in Table II.

As can be seen from the data tabulated in Table II, the behavior shown by 1-decene is similar to that seen in Table I for 1-octene. In the heterogeneous benzene–water media the oxidation of 1-decene in the presence of acetic acid proceeds only to the extent of 22% in 7.5 h (entry 5), while the same reaction performed in the presence of the phase-transfer agent affords 90% oxidation in a 5-h period (entry 6). The ability of OH^- in the aqueous medium to increase the amount of overoxidation is shown in entry 7.

The suppression of the amount of overoxidation product when the oxidations are performed in the presence of acetic acid is probably most dramatically illustrated by the oxidation of allylbenzene to produce phenylacetic acid and the overoxidation product benzoic acid. The results of some experiments are summarized in Table III.

The data presented in Table III clearly indicates that in the oxidation of allylbenzene OH^- increases the amount of overoxidation to yield benzoic acid. Acetic acid in all cases suppresses (but does not completely inhibit) the amount of benzoic acid which is produced.

In order to probe into the nature of the reaction pathway which leads to the undesirable overoxidation in allylbenzene, phenylacetic acid (0.015 mol) in benzene (75 mL with 0.1 g of benzyl PTC) was treated with $KMnO_4$ (0.06 mol in 75 mL of water) for 6 h. The isolated acids consisted of phenylacetic acid (35%) and benzoic acid (65%). If the same reaction is performed in the presence of acetic acid (15 mL), the product consisted of about equal amounts of phenylacetic acid and benzoic acid. Thus, phenylacetic acid is quite susceptible to further oxidation and once formed in the allylbenzene oxidation would be further oxidized to benzoic acid.

Treatment of heptanoic acid (0.03 mol) with $KMnO_4$ (0.12 mol in a 0.1 M KOH solution) for 6 h led to recovery of an acid which contained about 4% hexanoic acid. Some of the overoxidation seen in the cases of 1-octene and 1-decene under basic conditions may possibly arise from further oxidation of the carboxylic acid which is initially formed (MnO_2 is also

Table IV. Permanganate Oxidations of α-Olefins

Registry no.	α-Olefin[a]	Product	Isolated yield, %[b]
111-66-0	1-Octene	Heptanoic acid	80
872-05-9	1-Decene	Nonanoic acid	85
821-95-4	1-Undecene	Decanoic acid	86
112-41-4	1-Dodecene	Undecanoic acid	90
1120-36-1	1-Tetradecene	Tridecanoic acid	83
629-73-2	1-Hexadecene	Pentadecanoic acid	84
112-88-9	1-Octadecene	Heptadecanoic acid	80
3452-07-1	1-Eicosene	Nonadecanoic acid	90

[a] See Experimental Section for a typical procedure. [b] Purity of at least 97% in all cases. Less than 3% contamination with the overoxidation product. Products were distilled or crystallized.

present and could exert some surface catalytic effect).

The initial intermediates which are formed during oxidations of alkenes by permanganate[7] are the cyclic manganese(V) or manganese(VI) species. These intermediates could then lead to aldehydes,[7] diols (in cold, dilute alkaline permanganate solutions), or ketols (low hydroxide concentration). Diols would be cleaved to the expected acids but they could also undergo oxidations to ketols, keto aldehydes, or keto acids (sources of overoxidized acids). The aldehydes could be rapidly oxidized to carboxylic acids. Another pathway for the aldehydes is oxidative cleavage via an enol or enolate to yield the carboxylic acid of one less carbon.

In order to probe into the possibility of overoxidation of the aldehyde intermediate, nonanal and valeraldehyde were oxidized under conditions similar to the α-olefins. Treatment of nonanal (0.03 mol) with permanganate (0.03 mol) in a benzene (150 mL)–water (150 mL) medium with Aliquat 336 (0.1 g) led to nonanoic acid which contained less than 3% octanoic acid. If the same reaction is performed with the aqueous phase initially 0.1 M in KOH, a comparable result was seen. Similarly the two-phase oxidation of valeraldehyde under basic conditions led to valeric acid with about 2% butyric acid.

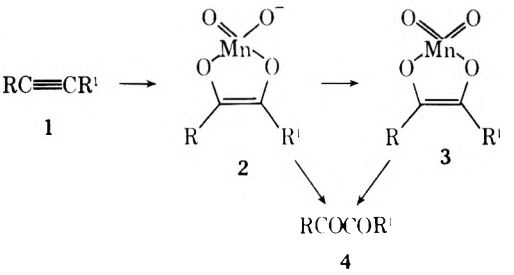
The amount of overoxidation seen in the permanganate oxidations of the α-olefins does not appear to be solely explicable on the premise that the aldehyde initially formed in the cleavage is further oxidatively cleaved.

The function of the acetic acid (soluble in water, benzene, and pentane) in suppressing overoxidation in the reactions conducted under heterogeneous two-phase conditions in the presence of a phase-transfer agent may merely reflect its solubility in the organic phase and rapid destruction of OH^- formed during the disproportionation of manganese(VI) intermediates.[7] Since the acetic acid itself is oxidized at a moderate rate, it might additionally function to destroy any excess permanganate and prevent further oxidation of the initially formed carboxylic acid. In those cases where both the acetic acid and phase-transfer agent are present, it does appear that phase-transfer-type catalysis is occurring.[4]

Since the goal of this research was to produce high-purity carboxylic acids, a series of α-olefins was oxidized using aqueous permanganate and adding solutions of the α-olefins in benzene, acetic acid, and a quaternary ammonium salt. The results of these reactions are tabulated in Table IV. Good yields of reasonably pure carboxylic acids can be obtained in this manner.

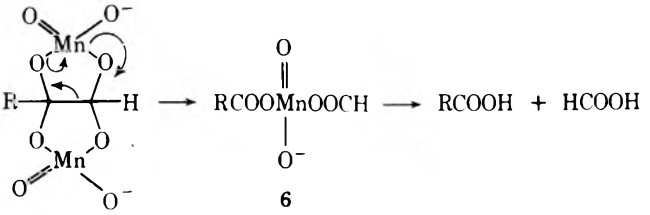
Our attention was next turned to the permanganate oxidations of terminal acetylenes. In Raphael's book[11] several examples of permanganate oxidations of internal alkynes are referenced,[12] and it is stated "As becomes an unsaturated centre the triple bond is very readily attacked by potassium permanganate, the end products being two carboxylic acid molecules". Under controlled conditions α-diketones can be isolated. For example, stearolic acid has been converted into 9,10-diketo stearic acid (92–96%) by performing the oxidation in the pH range 7.0–7.5 (MnO_4^-:acid = 2).[13] The diketo acid is oxidatively cleaved at high (>12) or low (<1) pH.

Scheme I



In mechanistic studies dealing with permanganate oxidations of acetylenes, a cyclic manganese(V) intermediate has been proposed as the first step in the cleavage process.[14] The formation of diones from internal acetylenes 1 (R = R¹ = alkyl) could arise via the pathway depicted in Scheme I.

The α-keto aldehyde 4 (R¹ = H, R = alkyl) which would arise from a terminal acetylene by this route would be expected to undergo further oxidation to the α-keto acid 4 (R¹ = OH, R = alkyl) and then this acid would be oxidized to RCOOH and CO_2.



It is also possible that a bicyclic intermediate such as **5** might be involved in the cleavages of triple bonds [only the manganese(V) state is shown and the manganese(VI) state could also play a role].[14] Breakdown of **5** would lead to **6** which on further reaction would yield the acid fragments.

The stoichiometry for the cleavage of a terminal acetylene (if MnO_2 and CO_2 are the products) under acid and basic conditions is represented in the following equations:

$$3RC{\equiv}CH + 8MnO_4^- + 8H^+ \rightarrow 3RCO_2H + 3CO_2 + 8MnO_2 + 4H_2O$$

$$3RC{\equiv}CH + 8MnO_4^- + OH^- \rightarrow 3RCO_2^- + 3CO_3^{2-} + 8MnO_2 + 2H_2O$$

In studies similar to the olefin oxidations previously discussed, several alkynes were treated with permanganate under a variety of conditions. The results of experiments on 1-hexyne are summarized in Table V.

It can be seen from the data in Table V that 1-hexyne can be oxidized in good yields without too much problem of overoxidation under a variety of reaction conditions.

Permanganate oxidations of 1-octyne are listed in Table VI.

In the oxidations of 1-octyne the amount of overoxidation increases as the basicity of the aqueous phase increases. The reaction can be performed using aqueous permanganate alone. The oxidation proceeds in the two-phase pentane–water system, and phase-transfer catalysis appears to be occurring to some extent (entries 6 and 7).

A few oxidations were performed using 1-decyne, and the results are tabulated in Table VII.

Table V. Permanganate Oxidations of 1-Hexyne

Additive	Reaction time, h	Valeric acid	Butyric acid
None[a]	7	98	2
0.13 M KOH[b]	7	94	6
150 mL of benzene,[c] 0.1 g of bzl-PTC	4	99	1
300 mL of pentane,[d] 60 mL of acetic acid 0.2 g of Aliquat 336	2	99	1

[a] $KMnO_4$ (0.06 mol) in 75 mL of water to which 1-hexyne (0.015 mol) was added. The mixture was stirred magnetically and a 60–70% yield of the crude acid could be isolated. Any 1-hexyne which did not react would have been lost in the concentration process on workup. [b] 0.6 g of KOH (0.01 mol) was added to the aqueous $KMnO_4$ and the reaction was performed as in *a*. [c] $KMnO_4$ (0.10 mol) in 150 mL of water to which 1-hexyne (0.06 mol) and listed PTC were added. A 54% crude yield of acid was obtained. [d] $KMnO_4$ (0.19 mol) in 300 mL of water to which 1-hexyne (0.06 mol) was added containing the listed additives. Isolated crude product in a 60% yield.

Table VI. Permanganate Oxidations of 1-Octyne

Additives[a]	Reaction time, h	1-Octyne	Hexanoic acid	Heptanoic acid
None	5	28	5	66
0.1 M KOH[b]	5	1	14	85
0.5 M KOH[c]	3	2	50	48
150 mL of pentane	5	50	2	48
150 mL of pentane, 30 mL of acetic acid	7.5	21	2	77
150 mL of pentane, 0.2 g of Aliquat 336	5	35	2	64
150 mL of pentane, 0.8 g of Aliquat 336	5	13	3	84
30 mL of acetic acid[d]	2	1	4	95
150 mL of pentane, 30 mL of acetic acid, 0.2 g of Aliquat 336	5	10	2	88

[a] $KMnO_4$ (0.12 mol) was placed in 200 mL of water in a 1-L flask equipped with a mechanical stirrer and blade. The mixture was immersed in an ice bath and 1-octyne (0.03 mol) was added in one portion with any listed additive. Product recovery in all cases was greater than 80%. [b] 1.5 g of KOH was added to the $KMnO_4$ solution. [c] 5.5 g of KOH was added to the $KMnO_4$ solution. [d] Added to the aqueous layer before octyne addition.

Preparative oxidations of 1-hexyne, 1-octyne, and 1-decyne (pentane, aqueous permanganate, acetic acid, and Aliquat 336) yielded the carboxylic acids in 70–80% yields of greater than 97% overall purity. This is an extremely convenient method to effect oxidations of terminal acetylenes.

Comparative oxidations performed in aqueous permanganate showed that 1-octyne oxidized somewhat more rapidly than 1-octene and less overoxidation occurred in the case of 1-octyne. However, 1-decene and 1-decyne oxidize at comparable rates with more overoxidation in the 1-decene case. Both of these substrates proceed much slower than the oxidations of 1-octene and 1-octyne.

The mechanistic pathway leading to the overoxidation which is seen in the case of 1-octyne as the basicity of the aqueous phase increases is unclear. The question of the importance (in some of the oxidations performed with quaternary ammonium salts) of phase-transfer catalysis also is difficult to assess.

Experimental Section

Materials. All α-olefins (99% purity) were obtained from the Humphrey Chemical Co., North Haven, Conn. 06473, and were used as received. 1-Octene (99.9%) and all the acetylenes were obtained from the Chemical Samples Co., Columbus, Ohio. Aliquat 336 (tricaprylylammonium chloride was kindly provided by General Mills Chemical Co., Minneapolis, Minn. 55435) and benzylhexadecyldimethylammonium chloride (J. T. Baker, practical grade) were used as phase-transfer agents. Potassium permanganate (Fisher Certified) was used as received.

Table VII. Permanganate Oxidations of 1-Decyne

Additives	Reaction time, h	1-Decyne	Octanoic acid	Nonanoic acid
None[a]	15	77	2	21
15 mL of acetic acid[a]	3.5	2	6	92
100 mL of pentane,[b] 50 mL of acetic acid 0.2 g of Aliquat 336	8	21	3	76

[a] $KMnO_4$ (0.06 mol) in 75 mL of water and 1-decyne (0.015 mol) were added. [b] $KMnO_4$ (0.15 mol) in 200 mL of water and 1-decyne (0.045 mol) and listed additives were added.

All acids which were prepared had ^1H NMR spectra in agreement with their structures and these data are not listed here. All boiling and melting points of the acids closely corresponded to the literature values.

(A) General Procedure for All Oxidations. The aqueous $KMnO_4$ (0.12 mol) in about 150–200 mL of water was cooled with stirring in an ice bath. The substrate (0.03 mol), and any solvent (100–150 mL), acetic acid (30 mL), or PTC (0.2 g), was added in one portion. The reaction was allowed to proceed for the specified time and recooled. In those runs without solvent, pentane or benzene was added at this point. Sodium sulfite (20 g) was slowly added and then either aqueous HCl (25 mL of concentrated HCl in 50 mL of water) *or* aqueous H_2SO_4 (25 g of concentrated H_2SO_4 in 100 mL of water) was slowly added. Two clear layers form; the organic layer is washed once with cold water and dried over Na_2SO_4. Distillation or concentration on a Buchi rotary evaporator leaves the crude product. The crude product was treated with ethereal CH_2N_2 and the methyl esters were analyzed by GLC (DC-200 column).

(B) α-Olefin Oxidations. Preparative Runs. (1) Typical Procedure. Tridecanoic Acid. A 1-L rb flask is charged with $KMnO_4$ (32 g, 0.20 mol) and 300 mL of water. The flask is immersed in an ice bath and stirred vigorously via an egg-shaped magnet (1 in.). A solution of 1-tetradecene (11.8 g, 0.06 mol), 300 mL of benzene, 60 mL of glacial acetic acid, and benzylhexadecyldimethylammonium chloride (0.2 g, 0.5 mmol) is added in one portion. Stirring is continued without any further addition of ice to the bath for about 4 hr. A total of 35 g of Na_2SO_3 is added to the cooled reaction mixture followed by the slow addition of a solution of 35 mL of concentrated HCl in 35 mL of water. Two clear layers result. The layers are separated and the benzene layer is washed once with a 100-mL portion of cold water. The benzene layer is dried over anhydrous sodium sulfate, the drying agent is removed by filtration, and the bulk of the benzene is removed by distillation. The residual benzene is removed on a rotary evaporator to yield 12.7 g (99%) of crude solid. The crude acid is dissolved in pentane (60 mL), filtered to remove traces of insoluble material, and placed in the freezer overnight. Filtration yields 10.6 g (83%) of tridecanoic acid of mp 43–44 °C (lit. mp 44–45 °C).[16] Treatment of a sample of the crude or crystallized acid with CH_2N_2 followed by GLC analysis showed about 2% contamination by dodecanoic acid and a trace amount of a short retention time impurity.

(2) Pentadecanoic acid was prepared as in the typical procedure, except 1-hexadecene (13.4 g, 0.06 mol) and 1 g of Aliquat 336 were used. The reaction was allowed to proceed overnight (10 h). The crude solid weighed 14.4 g (99%). Crystallization from ligroin (35–60 °C) gave 12.2 g (84%) of mp 52–53 °C (lit. mp 53–54 °C).[16] GLC of the methyl esters showed 2% contamination by tetradecanoic acid.

(3) Heptadecanoic acid was prepared as in the typical procedure, except 1-octadecene (15.4 g, 0.06 mol) and 0.1 g of bzl-PTC were used and the reaction was allowed to proceed for 6 h. Workup yielded 13.0 g (80%) of acid after crystallization from ligroin. GLC analysis of the methyl esters showed about 3% contamination by hexadecanoic acid and 0.5% of an unidentified peak of short retention time.

(4) Nonadecanoic acid was prepared as in the typical procedure, except 1-eicosene (16.8 g, 0.06 mol) and 1 g of Aliquat 336 were used and the reaction was allowed to proceed for 3 h. The crude white solid was placed in cold ethanol and filtered to yield 15.5 g (86%) of acid of mp 65–67 °C (lit. mp 69 °C).[16] Crystallization from CH_3CN raised

the melting point to 67–68 °C. GLC of the methyl esters showed 3% contamination by stearic acid.

(5) Decanoic acid was prepared as in the typical procedure, except 1-undecene (9.2 g, 0.06 mol) was used. The reaction was allowed to proceed overnight and on workup the crude acid (10.2 g, 99%) was obtained. Distillation, 105–107 °C/0.5 mm, yielded 8.6 g (84%) of decanoic acid which solidified. GLC of the methyl esters showed about 3% contamination by nonanoic acid.

(6) Undecanoic acid was prepared as in the typical procedure, except 1-dodecene (0.06 mol) and a reaction time of 4 h was used. The crude acid, 11.1 g (99%), was distilled at 110–115 °C/0.1 mm to yield 9.9 g (90%) of undecanoic acid. GLC of the methyl esters showed about 3% contamination by decanoic acid and less than 0.5% of a short retention time impurity.

(7) Nonanoic acid was prepared as above, except 1-decene (0.06 mol) and 0.1 g of bzl-PTC were used and the reaction was allowed to proceed for 4 h. The crude acid was distilled, bp 89–90 °C/0.1 mm, to yield 8.0 g (85%) of 97% pure nonanoic acid (GLC of esters).

(8) Heptanoic acid was prepared as above, except 1-octene (6.7 g, 0.06 mol) was used and the reaction was allowed to proceed for 3 h. Distillation at 83–84 °C/1.5 mm gave 6.2 g (80%) of acid of 98% purity (GLC of methyl esters).

(C) Acetylene Oxidations. Preparative Runs. (1) Typical Procedure: 1-Octyne → Heptanoic Acid. In a 1-L rb flask fitted with a 1-in. egg-shaped spinbar is placed $KMnO_4$ (28 g, 0.18 mol) and 200 mL of tap water. The mixture is stirred and immersed in an ice bath. A solution of 1-octyne (5.0 g, 0.045 mol), 120 mL of pentane, 60 mL of acetic acid, and 0.2 g of Aliquat 336 is added in one portion. The mess is stirred for 5 h without replenishing the ice. The black-brown mixture is cooled in an ice bath and Na_2SO_3 (30 g) is added in several portions. A solution of 60 mL of concentrated HCl in 60 mL of water is then cautiously added. The top pentane layer is separated and the acidic layer is extracted once with 50 mL of pentane. The combined pentane extracts are washed with 50 mL of cold water, dried over Na_2SO_4, decanted from the drying agent, and concentrated on a Buchi rotary evaporator to yield 5.4 g of crude product (90% recovery). Vacuum distillation yields 4.1 g (70%) of heptanoic acid (98% pure by GLC of the methyl esters, trace amounts of short retention time impurities were also present).

(2) Nonanoic acid was prepared as above, except 1-decyne (0.045 mol) was used and the reaction was run for 8 h. On distillation, 4.6 g (70%) of acid was obtained of 98% purity (GLC of methyl esters).

(3) Pentanoic acid was prepared as above, except $KMnO_4$ (0.24 mol), 300 mL of water, 1-hexyne (0.06 mol), 250 mL of pentane, and 0.3 g of Aliquat 336 were used, and the reaction was run for 3 h to yield 4.0 g (66%) of acid of 98% purity (GLC of methyl esters).

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Registry No.—$KMnO_4$, 7722-64-7; decanoic acid, 334-48-5; undecanoic acid, 112-37-8; nonanoic acid, 112-05-0; heptanoic acid, 11-14-8; allylbenzene, 300-57-2; 1-hexyne, 693-02-7; 1-octyne, 629-05-0; 1-decyne, 764-93-2.

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Novel Carbon Catalysis: Oxidation in Basic Solution

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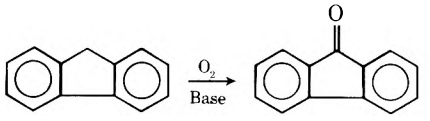
Catalytic oxidations of hydrocarbons by molecular oxygen are of considerable biological and industrial importance. One hydrocarbon oxidation which has been extensively investigated is the oxidation of fluorene to fluorenone in basic solution[1] (eq 1). Fluorene is oxidized by molecular oxygen in the



(1)

presence of potassium *tert*-butoxide in *tert*-butyl alcohol solution. The reaction is improved by the presence of benzene, dioxane, morpholine, piperidine, pyridine, hexamethylphosphoramide, dimethylformamide, or dimethyl sulfoxide (Me_2SO).[1] Also, the oxidation of solid fluorene is known to be catalyzed by ordinary or sodium methoxide treated alumina.[2]

The present note describes the strong catalysis by carbon of the fluorene oxidation in basic solutions of *tert*-butyl alcohol and ethanol. The addition of 5% charcoal in *tert*-butyl alcohol 0.2 M in potassium *tert*-butoxide increases initial reaction rate tenfold (see Figure 1). In refluxing ethanolic sodium hydroxide, autoxidation proceeds to the extent of <1% in 2 h. With the addition of 5% charcoal, reaction is virtually complete in 2 h.

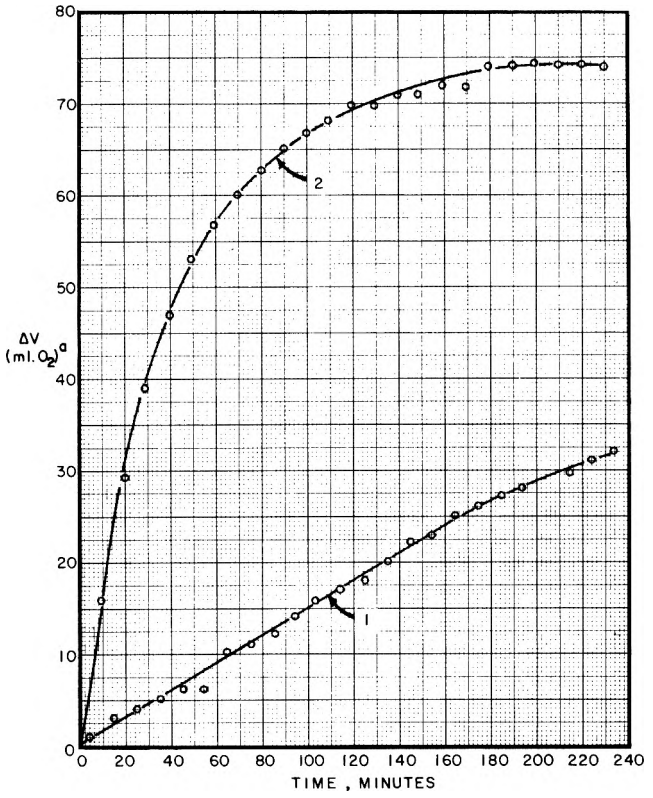


Figure 1. Autoxidation of fluorene (0.14 M) in the presence of 0.2 M potassium *tert*-butoxide: (1) *tert*-butyl alcohol; (2) with 5% by weight activated charcoal.[b] (a) No correction made for vapor pressure of water. (b) Theoretical consumption of O_2 is 75 mL.

The present catalysis may be due to the fact that OH^- ions adsorbed on carbon are more basic than OH^- in solution. The adsorption of OH^- has been postulated before to explain the catalysis of H_2O_2 decomposition.[3] Carbon is known to catalyze exchange reactions of the type:[4,5]

$$BrC_2H_4Br + C_2H_5Cl \rightleftharpoons ClC_2H_4Br + C_2H_5Br$$

$$C_2H_5Br + CH_3OH \rightleftharpoons C_2H_5OH + CH_3Br$$

Here again, the occurrence of some interaction between negatively charged groups and the carbon surface is indicated. The OH^- activation may also occur through the adsorption of cations, similar to the case of anion activation by cation complexing observed in the crown ether–potassium hydroxide system.[6] In the catalysis by alumina mentioned earlier, an important role is played by adsorbed oxygen.[2] This may also be the case here. It is evident that the elucidation of mechanistic detail requires further investigation.

Reaction with charcoal in the common solvents has several advantages over reactions using catalysts previously described: (1) Charcoal is a relatively cheap material. (2) It is stable to acid, base, heat, and chemical reaction. In autoxidation it is not oxidized, as are some of the aprotic dipolar solvents.[7] It is not consumed in the reaction by complex formation as is, for example, Me_2SO.[1] (3) As a solid it can be used in a bed reactor for continuous flow processes.[8] (4) Finally, we have shown that charcoal catalyzes basic oxidation of fluorene in a solvent system not useful for oxidation without charcoal. Sodium hydroxide as base is superior to potassium *tert*-butoxide, pyridine,[9] or other common bases on economic grounds, as well as in simplicity of the chemical process, i.e., there is less chance for side products.

Experimental Section

Potassium *tert*-Butoxide–Butyl Alcohol. To a round-bottom flask fitted through a $CaCl_2$ drying tube[9] with oxygen inlet connected to a gas buret was added 25 mL of *tert*-butyl alcohol, 0.55 g of potassium *tert*-butoxide (5 mmol), and 0.56 g of fluorene (3.4 mmol). The flask was thoroughly flushed with oxygen, and reaction was allowed to proceed with vigorous stirring. The reactor was kept in a water bath at 27–30 °C. Oxygen pressure was maintained at the prevailing atmospheric pressure by means of a leveling bulb. After 4 h reaction time, the reaction mixture was quenched with water, products were extracted with carbon tetrachloride, and the organic solution was thoroughly washed with water, dried over Na_2SO_4, and then evaporated. The solid residue was analyzed by GC and NMR. Product conversion was 38% fluorenone (see Figure 1).

The above experiment was repeated with the addition of 1.0 g of Burrell charcoal (1135 m^2/g; 95%, 50 mesh) to the solution. Product conversion was 94% fluorene (see Figure 1).

Sodium Hydroxide-Ethanol. The reactor described above was fitted with a reflux condenser; 25 mL of ethanol, 0.45 g of fluorene (2.7 mmol), and 0.20 g of sodium hydroxide (5 mequiv) were stirred at reflux temperature under an oxygen atmosphere for 2 h. Analysis by GC and NMR indicated <1% conversion to fluorenone.

The above procedure, with the addition of 1.0 g of charcoal, gave a bright yellow product which was pure fluorenone by GC analysis; NMR analysis indicated mostly fluorenone with some polymeric materials as impurity, but no fluorene.

Registry No.—Fluorene, 86-73-7; fluorenone, 486-25-9.

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Direct Synthesis of Anilides from Nitroarenes

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Nitroaromatic compounds are readily reduced to arylamines by a number of reagents [e.g., Fe, Sn, Sn(II), Zn, Ti(III)]. However, only a few methods are available for their direct conversion to the anilides, e.g., catalytic hydrogenation in the presence of acid anhydrides, and reaction with acyl tetracarbonylferrates.[1] We wish to report a new method for this latter transformation.

Despite conspicuousness of the reducing ability of low-valent molybdenum, the property has, until recently, rarely been exploited in organic synthesis. Aside from our own effort,[2] we are aware of only one report[3] on the use of complex salts of molybdenum for deoxygenation of sulfoxides. As molybdenum(II) species[4] are conveniently prepared by heating $Mo(CO)_6$ with carboxylic acids, we considered it worthwhile to examine the synthetic utility of the system. From various experiments performed, it has been shown that nitroarenes are converted to anilides directly.

$$ArNO_2 \xrightarrow{Mo(CO)_6,\ RCOOH} RCONHAr$$

Since arylamines undergo acylation on heating with carboxylic acids, it can be inferred that the amines, either in the free or metalated state, are the intermediates of our reaction. Dimeric products such as azoarenes have neither been detected nor isolated. In fact, these compounds are convertible to anilides also.[5]

It should be emphasized that the reagent combination is a rather mild reducing system. For example, it can be used to reduce a nitro group in the presence of an olefinic linkage which cannot be achieved by catalytic hydrogenation. To illustrate this point, 4-nitrostilbene was subjected to our experimental conditions. 4-Acetaminostilbene[6] was isolated. Most other functional groups such as alcohols, ketones, esters, acids, amides, nitriles, and sulfones are stable toward the Mo(II) reagents.

Table I. Reductive Acylation of Nitroarenes

Nitroarene	Anilide	Yield, %
$PhNO_2$ 98-95-3	PhNHAc 103-84-4	55
	PhNHCOEt 620-71-3	62
	$PhNHCOPr^n$ 1129-50-6	63
m-$MeC_6H_4NO_2$ 99-08-1	m-MeC_6H_4NHAc 537-92-8	68
p-$MeOC_6H_4NO_2$ 100-17-4	p-$MeOC_6H_4NHAc$ 57-66-1	85
p-$AcC_6H_4NO_2$ 100-19-6	p-AcC_6H_4NHAc 2719-21-3	46
p-$O_2NC_6H_4CH{=}CHPh$ 4003-94-5	p-$AcNHC_6H_4CH{=}CHPh$ 18559-97-2	50

Experimental Section

General Procedure for Reductive Acylation of Nitroarenes. A mixture of a nitroarene (5 mmol) and molybdenum hexacarbonyl (2.64 g, 10 mmol) in a carboxylic acid (5 mL) was heated under nitrogen at 120 °C for 20 h. The sublimed $Mo(CO)_6$ was returned to the liquid phase during reaction by occasional swirling. The cooled reaction mixture was neutralized with dilute ammonia and extracted with ether (three 50-mL portions), and the extracts were dried and evaporated to give a solid product, which was recrystallized and identified by comparison with an authentic sample.

Registry No.—$Mo(CO)_6$, 13939-06-5; acetic acid, 64-19-7; propionic acid, 79-09-4; butyric acid, 107-92-6.

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Alkylation of 1,5-Dimethoxy-1,4-cyclohexadiene. A Convenient Synthesis of 2-Alkyl- and 2-Alkenyl-1,3-cyclohexanediones

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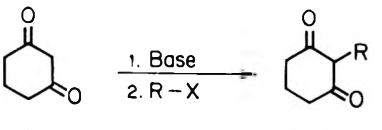
In connection with another research problem in our laboratory, we required a series of 2-alkyl- and 2-alkenyl-1,3-cyclohexanediones (**2**). The preparation of this type of compound via direct alkylation of the parent 1,3-cyclohexanedione (**1**) is reasonably efficient with reactive alkylating reagents

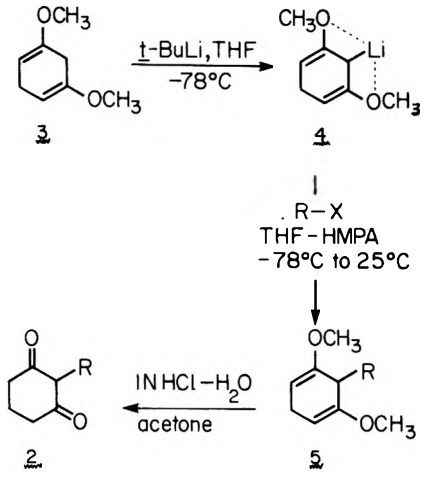


1 **2**

such as methyl iodide[1] and allylic[2,3] or benzylic halides.[2] However, with less reactive alkylating agents, the reaction is generally sluggish. For example, alkylation of **1** with 1-bromobutane[3] and 4-iodo-1-butene[4] afforded the corresponding alkylated products **2** [R = $(CH_2)_3CH_3$ and $(CH_2)_2CH{=}CH_2$, respectively] in very poor yield (<11%).[5] We report herein an efficient and experimentally convenient method which avoids this problem. The method involves two simple steps: the alkylation of 1,5-dimethoxy-1,4-cyclohexadiene (**3**)[7,8] and the acid-catalyzed hydrolysis of the resultant products **5**.

The dimethoxy compound **3** was converted into the corresponding organolithium derivative by treatment with t-BuLi in THF at −78 °C. On the basis of competing inductive and

resonance effects associated with the two methoxy groups in **3**, one might expect the allylic protons at C-6 to be more acidic than those at C-3. Furthermore, lithiation at C-6 would undoubtedly be facilitated by initial association of the lithium of *t*-BuLi with the oxygen atoms of the two methoxy groups, and it thus seems reasonable to propose that the lithiated

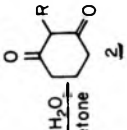


species can be conveniently represented by structure **4**.[9] In any case, successive addition of HMPA (slightly more than 1 equiv) and alkylating agent to the solution of the lithiated intermediate resulted in smooth and efficient formation of the corresponding alkylated compounds **5**. In each case, it was clear from GLC and spectral analyses of the product that the alkylation was very highly regioselective, since no isomeric products could be detected.

A number of different reagents and procedures were investigated in connection with the conversion of the alkylated products **5** into the corresponding 1,3-cyclohexanediones **2**. Eventually it was found that this hydrolysis could be conveniently and efficiently accomplished by treatment of **5** with dilute hydrochloric acid in acetone. However, the reaction was clean and high yielding only if precautions were taken to carefully exclude oxygen from the reaction mixture. Thus, prior to use, both the acetone and dilute hydrochloric acid were thoroughly purged with a stream of nitrogen, and the hydrolyses were carried out under an atmosphere of nitrogen. If these precautions were not followed, the products obtained were seriously discolored and the yields were considerably diminished.

A summary of the results appears in Table I.

Table I. Synthesis of 2-Alkyl- and 2-Alkenyl-1,3-cyclohexanediones[a]



t-BuLi, equiv	Alkylating agent (Equiv)	Registry no.	HMPA, equiv	Yield of 5, %[b]	Registry no.	Distillation temp[c] of 5, °C (Torr)	Yield of 2, %[d]	Registry no.	Mp of 2, °C Obsd[e]	Lit.
1.09	$CH_3(CH_2)_3I$ (1.30)	542-69-8	1.33	99	63588-95-4	80–85 (0.4)	96	18456-90-1	116–117	115–116[f] 112–113[g]
1.11	$CH_2{=}CH(CH_2)_2Br$ (1.31)	5162-44-7	1.17	99	63588-96-5	55–60 (0.1)	95	56459-16-6	95–96	95–97.5[h] 92.5–93.5[g]
1.09	$CH_3(CH_2)_4I$ (1.09)	628-17-1	1.02	96	63588-97-6	60–67 (0.25)	95	63589-01-5	91–95	
1.11	$C_6H_5CH_2CH_2Br$ (1.11)	103-63-9	1.33	99	63588-98-7	110–117 (0.25)[i]	93	62264-41-9	149–150	147–148[j]
1.09	$(CH_3)_2C{=}CH(CH_2)_2Br$[k] (1.10)	2270-59-9	1.04	98	63588-99-8	60–65 (0.25)	93	63589-02-6	117–120	
1.08	$(CH_3)_2C{=}CH(CH_2)_3I$[l] (1.04)	63588-94-3	1.04	88	63589-00-4	65–70 (0.08)	94	63589-03-7	87–89	
1.11	CH_3I (1.08)	74-88-4	1.08	98	25435-93-2	40–45 (0.2)[m]	65	1193-55-1	205–208 dec	208–210[n] dec

[a] All products reported in the table showed expected spectral properties. All new compounds gave satisfactory C, H analyses (within ± 0.3% of calculated values). [b] Isolated yield, based on **3**. [c] Air-bath temperature (uncorrected) of bulb-to-bulb distillation. [d] Isolated yield based on **5**. [e] Melting points are uncorrected and were measured on a Fischer–Johns melting point apparatus. [f] Reference 3. [g] Reference 6. [h] Reference 4. [i] Lit.[8] bp 163–164 °C (2 Torr). [j] Reference 8. [k] M. Julia, S. Julia, and R. Guegan, *Bull. Soc. Chim. Fr.*, 1072 (1960). [l] M. F. Ansell and S. S. Brown, *J. Chem. Soc.*, 1789 (1957). [m] Lit. bp 65–67 °C (3 Torr): A. J. Birch and R. A. Russell, *Aust. J. Chem.*, 24, 1975 (1971). See also I. Alfaro, W. Ashton, L. D. McManus, R. C. Newstead, K. L. Rabone, N. A. J. Rogers, and W. Kernick, *Tetrahedron*, 26, 201 (1970). [n] Reference 1.

Experimental Section

1,5-Dimethoxy-1,4-cyclohexadiene (3). Ammonia (700 mL, freshly distilled from sodium metal) was collected in a three-necked, 1-L flask equipped with a dry-ice condenser, an all-glass mechanical stirrer, and an addition funnel. Sodium metal (30.0 g, 1.3 mol) was added over a period of about 30 min while the ammonia was vigorously stirred, and the resultant dark blue solution was stirred for an additional 30 min. A solution of *m*-dimethoxybenzene (32.7 g, 0.237 mol) in a mixture of anhydrous ether (100 mL) and anhydrous ethanol (62.5 g, 1.36 mol) was added slowly over a period of 2 h. The mixture was stirred for an additional 1.5 h. The reaction mixture was quenched by careful addition of 75 mL of 1:1 ethanol–water, followed by water until a colorless mixture was obtained. The condenser and addition funnel were removed from the flask and the ammonia was allowed to evaporate. The remaining mixture was diluted with brine (700 mL) and thoroughly extracted with a 1:1 mixture of ether and petroleum ether (bp 30–60 °C). The combined extracts were washed with brine and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure, followed by distillation of the remaining oil, afforded 31.5 g (95%) of 1,5-dimethoxy-1,4-cyclohexadiene (**3**) as a clear colorless oil: bp 56 °C (0.55 Torr) [lit. bp 95 °C at (18 Torr)[7]]; IR (film) ν_{max} 3090, 3010, 2960, 2925, 2850, 1690, 1665, 1590, 1440, 1390, 1360, 1230, 1200, 1140, 1005, 920, 885, 760 cm^{-1}; ^1H NMR

($CDCl_3$) δ 2.66–2.86 (unresolved m, 4 H, allylic protons), 3.47 (s, 6 H, methoxy protons), 4.58 (br t, 2 H, vinylic protons, $J \approx 3$ Hz).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.74; H, 8.80.

The following procedures, describing the preparation of compounds **5** (R = $CH_2CH_2CH{=}CH_2$) and **2** (R = $CH_2CH_2CH{=}CH_2$), are typical.

3-(Δ^3-Butenyl)-2,4-dimethoxy-1,4-cyclohexadiene (5, R = $CH_2CH_2CH{=}CH_2$). To a solution of *t*-BuLi[10] (1.11 equiv) in cold (−78 °C) THF (80 mL) was added 1.98 g of 1,5-dimethoxy-1,4-cyclohexadiene (**3**) and the resultant solution was stirred at −78 °C for 1 h. HMPA (1.17 equiv, freshly distilled from $LiAlH_4$) was added and stirring was continued for an additional 10 min. Addition of 4-bromo-1-butene (1.31 equiv, freshly filtered through a short column of neutral alumina) resulted in an immediate change in the color of the reaction mixture (maroon to light brown). The reaction mixture was allowed to warm to room temperature, diluted with 50 mL of brine, and then trice extracted with 50-mL portions of pentane. The combined pentane extracts were washed twice with brine and dried over anhydrous $MgSO_4$. Removal of the solvent, followed by distillation (air-bath temperature 55–60 °C, 0.1 Torr) of the resultant light brown oil, afforded 1.71 g (99%) of 3-(Δ^3-butenyl)-2,4-dimethoxy-1,4-cyclohexadiene: IR (film) ν_{max} 3090, 3020, 2950, 2925, 2850, 1690, 1660, 1640, 1610, 1450, 1390, 1320, 1300, 1140, 1020, 985, 955, 900, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70–2.02 (unresolved m, 4 H, $-CH_2CH_2CH{=}CH_2$), 2.66–3.04 (unresolved m, 3 H, C-3 and C-6 protons), 3.50 (s, 6 H, methoxy protons), 4.68 (t, 2 H, C-1 and C-5 protons, J = 4 Hz), 4.76–5.06 (unresolved m, 2 H, $-CH{=}CH_2$), 5.56–6.02 (unresolved m, 1 H, $-CH{=}CH_2$).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.00; H, 9.38.

2-(Δ^3-Butenyl)-1,3-cyclohexanedione (2, R = $CH_2CH_2CH{=}CH_2$). To a solution of compound **5** (R = $CH_2CH_2CH{=}CH_2$) (0.52 g) in acetone (12 mL, spectrograde, previously purged with a stream of N_2 for 15 min) was added, with vigorous stirring, 1 N hydrochloric acid (4 mL, previously purged with a stream of N_2 for 15 min). The resultant solution was stirred for 1 h. The acetone was removed under reduced pressure, the residue was diluted with 10 mL of brine, and the mixture was then extracted four times with 10-mL portions of CH_2Cl_2. The combined extracts were dried over anhydrous magnesium sulfate. Removal of the solvent afforded 0.42 g (95%) of 2-(Δ^3-butenyl)-1,3-cyclohexanedione as a white crystalline solid. This material was shown by GLC analysis to be >98% pure,and exhibited IR and ^1H NMR spectra which were essentially identical with those of an analytical sample obtained by recrystallization from benzene–heptane: mp 95–96 °C (lit. mp 95–97.5 °C[4], 92.5–93.5 °C[6]); UV (C_2H_5OH) λ_{max} 262 mm (ε 1.56 × 10^4); IR ($CHCl_3$) ν_{max} 3570, 3500–2600 (broad), 1715, 1695, 1615, 1370, 1170, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74–2.28 (m, 4 H), 2.28–2.76 (m, 6 H), 3.45 (t, ⅙ H, C-2 proton of diketo tautomer, J = 5 Hz), 4.84–5.16 (unresolved m, 2 H, $-CH{=}CH_2$), 5.62–6.12 (unresolved m, 1 H, $-CH{=}CH_2$).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.27; H, 8.45.

Acknowledgments. Financial support from the National Research Council of Canada is gratefully acknowledged.

Registry No.—**3**, 37567-78-5; *m*-dimethoxybenzene, 151-10-0.

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(10) A commercially available (Ventron) solution of *t*-BuLi in *n*-pentane was employed.

Aliphatic Diazo Ketones. A Modified Synthesis Requiring Minimal Diazomethane

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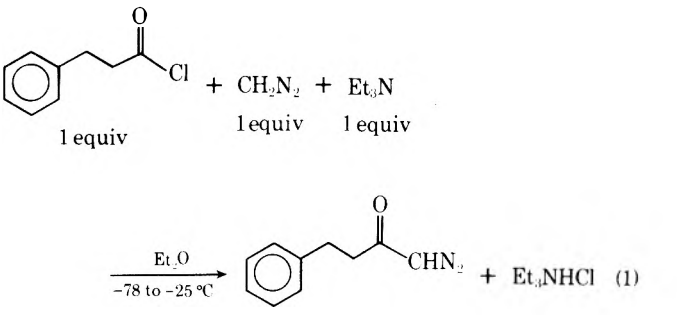
The common practice of employing excess diazomethane to scavenge HCl during the preparation of α-diazo ketones from acid chlorides and diazomethane[1] works extremely well in most instances but does not lend itself to the efficient use of isotopically labeled diazomethane or of other diazoalkanes. To circumvent this problem, Newman[2] and Berenbom[3] independently developed an alternative procedure for preparing α-diazo ketones from aromatic acid chlorides using 1 molar equiv of diazomethane in the presence of triethylamine at 0 °C. Under the same conditions, however, aliphatic acid chlorides bearing α-hydrogen atoms give only low yields of impure products,[2] presumably as a consequence of competing ketene formation and subsequent side reactions.[4]

In connection with a ^{13}C-labeling study, we had need to prepare the diazo ketone derived from 3-phenylpropanoyl chloride using minimal diazomethane and found that this can be accomplished simply by carrying out the reaction with triethylamine present at lower temperatures than usual (eq 1). A stoichiometric ratio of reagents gives optimal yields of



the diazo ketone based on diazomethane (see Table I). By comparison, the conventional procedure,[1] using 2 equiv of diazomethane, gives a much lower yield of product based on diazomethane (49.6%), albeit in a somewhat higher state of purity (95.2% by N_2 evolution, 90.1% by NMR). Chromatography on silica gel provides a means of separating and identifying the minor by-products formed during the reaction in eq 1 (see Experimental Section); however, the crude product proved satisfactory for subsequent copper-catalyzed cyclization.[5]

Table I lists several other aliphatic diazo ketones prepared by this method. Ketene formation competes successfully only in those cases with especially acidic α-hydrogens; phenylacetyl chloride, for example, gives an 85% yield of 2- and 3- phenylcyclobutanone under these reaction conditions,[6] presumably via phenyl ketene and phenylcyclopropanone.[7]

Experimental Section

1-Diazo-4-phenyl-2-butanone. Dry triethylamine[8] (11.1 mL, 0.08 mol) was added to 350 mL of an anhydrous ethereal solution of diazomethane[9] (0.08 mol) under nitrogen in a baked-out 1-L Morton flask fitted with a mechanical stirrer, a dropping funnel, and a low-temperature thermometer. The solution was cooled to − 78 °C (dry ice/acetone), and 11.8 mL of 3-phenylpropanoyl chloride[10] (0.08 mol) in 40 mL of anhydrous ether[8] was added dropwise with vigorous stirring over 25 min. A thick slurry formed during the addition.[11] The reaction mixture was stirred an additional 15 min at −78 °C and then for 1 h at −25 to −20 °C (dry ice/H_2O/$CaCl_2$).[12] During the course of the

Table I. Aliphatic Diazo Ketones Prepared by the Method [a] of eq 1

Registry no.	Diazo ketone	Yield, %	Purity, % N_2 evol (NMR)
10290-42-3	$C_6H_5CH_2CH_2C(=O)$-CHN_2	96	82 (83)
31151-40-3	c-$C_6H_{11}C(=O)CHN_2$	96	85 (77)
58697-26-0	$CH_3(CH_2)_7C(=O)CHN_2$	96	87 (85)
14088-55-2	$(CH_3)_2CHC(=O)CHN_2$	86[b]	85 (76)
	$C_6H_5CH_2C(=O)CHN_2$		(<10%)

[a] Optimized only for the first entry. [b] Lower yield due to partial solubility of the product in water.

reaction, the mixture grew more viscous and then thinned out again. After warming to room temperature, the reaction mixture was diluted with water. The organic layer was separated and washed successively with 10% aqueous acetic acid, water, saturated sodium bicarbonate solution, water, and saturated sodium chloride solution. The resulting solution was dried over calcium sulfate[13] and concentrated under vacuum to a deep yellow oil: 12.8–13.9 g, 92–100% yield.

A weighed aliquot of the crude product was dissolved in ethanol and treated with concentrated hydrochloric acid;[2,3] the nitrogen evolved corresponded to 76–87% of that expected for pure diazo ketone. NMR analysis of the crude product revealed 1-diazo-4-phenyl-2-butanone (76–90%), 1-chloro-4-phenyl-2-butanone (4–5%), methyl 3-phenylpropanoate (2–3%), 3-phenylpropanoic anhydride, and benzylcyclobutanone (both isomers), all of which were isolated by chromatography on silica gel (15% ethyl acetate/petroleum ether) for identification purposes.

Acknowledgment. We thank the National Science Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University of Nevada Research Advisory Board for financial support of this work.

Registry No.—Diazomethane, 334-88-3; 3-phenylpropanoyl chloride, 645-45-4; 1-chloro-4-phenyl-2-butanone, 20845-80-1; methyl 3-phenylpropanoate, 103-25-3; cyclohexylcarbonyl chloride, 2719-27-9; nonanoyl chloride, 764-85-2; 2-methylpropanoyl chloride, 79-30-1.

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(8) Distilled under nitrogen from sodium/benzophenone.
(9) Caution Explosive. Diazomethane was prepared according to the procedure of J. A. Moore and D. E. Reed, "Organic Syntheses", Collect. Vol. V, 1973, 351, and standardized by duplicate titrations according to the procedure of F. Arndt, "Organic Syntheses," Collect. Vol. II, 1943, p 165. Reagent grade ether (ethanol free) must be used to avoid contamination of the final product by ethyl ester. After distillation, the diazomethane solution still contains at least 1% water which can be removed by drying over potassium hydroxide pellets for 30 min at 0 °C. Omission of this drying step leads to a considerable amount of methyl ester in the final product. When properly dried, no cloudiness (ice crystals) developes in the ethereal diazomethane on cooling to −78 °C; further drying over sodium wire proved unnecessary.
(10) Prepared from hydrocinnamic acid and thionyl chloride in 95% yield after distillation.
(11) Even in the absence of diazomethane, a thick white precipitate forms instantly. Hydrolysis of the resulting mixture gives hydrocinnamic anhydride, the expected product from an acylammonium salt. [See J. V. Paukstelis and M.-g. Kim, *J. Org. Chem.*, 39, 1503 (1974)]. The reactive species may actually be this acylammonium salt, although formation of the diazo ketone does not occur at −78 °C.
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(13) Magnesium sulfate should be avoided, as it slowly decomposes diazo ketones.

A Convenient Large-Scale Preparation of Benzobarrelene

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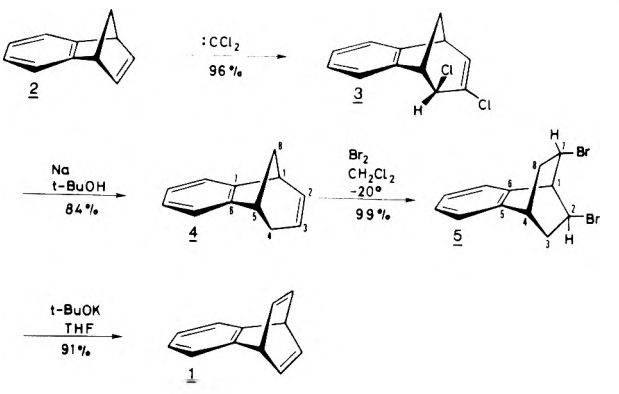
Benzobarrelene (**1**) is a molecule of considerable potential mechanistic interest, but studies of its chemistry have been few on account of its relative unavailability. Neither of the existing synthetic routes, the addition of benzyne to benzene,[1] nor the cycloaddition of maleic anhydride to β-naphthol,[2] is suitable for large-scale preparation. However, Heaney and co-workers have recently reported[3] a high-yield preparation which consists of the reductive dechlorination of tetrachlorobenzobarrelene, obtained from the cycloaddition of tetrachlorobenzyne to benzene. We now present here an alternative large-scale preparation of benzobarrelene which has considerable flexibility and should allow efficient isotopic labeling of the bicyclic skeleton, as well as preparation of aromatic substituted derivatives.

The addition of dichlorocarbene to the readily available benzonorbornadiene (**2**)[4] gives a rearranged adduct which on reductive dechlorination affords benzo[6,7]bicyclo[3.2.1]-octa-2,6-diene (**4**).[5] In the present work, the method of Parham and Schweizer[6] was used for generating dichlorocarbene. Dechlorination of the adduct was effected with sodium and *tert*-butyl alcohol (Scheme I) and **4** was obtained in an overall yield of 80% for the two steps.

Bromination of hydrocarbon **4** in dichloromethane at −20 °C proceeded with rearrangement to give di-*anti*-bromo adduct **5** in essentially quantitative yield. This key step serves both to bring about the requisite skeletal rearrangement and to provide the functionality which permits the easy introduction of two double bonds. The structure of adduct **5** was securely assigned from its ^1H and ^{13}C NMR spectra (see Experimental Section) which unambiguously provide evidence for the symmetry of the molecule. Analogous stereospecific bromination rearrangements have been observed for the homologues, benzonorbornadiene (**2**)[7] and benzo[7,8]bicyclo[4.2.1]nona-2,7-diene,[8] and present no particular mechanistic problems.

In the final step, the double dehydrobromination of **5** was achieved with surprising efficiency using the classical method of potassium *tert*-butoxide in tetrahydrofuran. Essentially pure benzobarrelene was isolated in yields greater than 90%, after sublimation. Benzobarrelene (**1**) may thus be prepared

Scheme I



from benzonorbornadiene (2) in four steps with an overall yield of ca. 70%.

The presently described synthesis offers several advantages over previous methods. Although relatively lengthy, it begins with a readily available starting material (2), and the subsequent steps are all efficient and readily amenable to large scale-up, since there are no troublesome purifications necessary. However, in addition to simply offering a means of preparing large quantities of the parent 1, this route offers several possibilities for isotopically labeling the bicyclic skeleton. For example, the use of ^{13}C- or ^{12}C-labeled chloroform in the phase-transfer method[9] for carbene generation would lead to 1 selectively labeled at C(2). Alternatively, several deuterated benzonorbornadienes are known,[10] which could serve as precursors to deuterated 1. Finally, this route allows straightforward synthesis of aromatic-substituted benzobarrelenes.[11]

Experimental Section

Addition of Dichlorocarbene to Benzonorbornadiene (2). A mixture of benzonorbornadiene (19.0 g, 0.133 mol), sodium methoxide (32.3 g, 0.597 mol), and dry hexane (150 mL) was cooled in an ice bath and vigorously stirred while ethyl trichloroacetate (100.4 g, 0.545 mol) was added dropwise during 3 h. The reaction temperature was maintained below 5 °C throughout the addition. After an additional 4 h at 0 °C, the mixture was allowed to warm gradually to ambient temperature and was stirred overnight, before being poured into ice water (500 mL). The organic layer was separated and the water layer was extracted with ether (3 × 100 mL). Combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated at reduced pressure to afford a brown oil. Distillation at reduced pressure, then under vacuum, yielded adduct 3 (29.02 g, 96.5%) as a viscous yellow oil (bp 98–105 °C at 0.7 mm), which crystallized on standing.

Recrystallization of a small sample from pentane afforded slightly yellow crystals: mp 75–75.5 °C (lit.[5b] 68–69 °C). The ^1H NMR spectrum was as reported.

Benzo[6,7]bicyclo[3.2.1]octa-2,6-diene (4). Metallic sodium (28.5 g, 1.24 mol) was cut into small pieces and combined with 300 mL of anhydrous ether. This was mechanically stirred at gentle reflux under a nitrogen atmosphere while a mixture of dichloride 3 (29.02 g, 0.129 mol), *tert*-butyl alcohol (74.0 g, 1.0 mol), and ether (50 mL) was added dropwise during 3 h. After stirring at reflux overnight, heating was discontinued and methanol (50 mL) and then water (100 mL) were added dropwise. The mixture was poured into water (200 mL), the organic layer was separated, and the water layer was extracted with ether (3× 100 mL). Combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. Distillation afforded alkene 4 (16.42 g, 83.5%) as a colorless oil: bp 45 °C (0.1 mm); ^1H NMR was as reported;[5b] ^{13}C NMR ($CDCl_3$) 151.8, 146.2, 134.2, 126.0, 125.9, 123.4, 123.3, 120.3, 41.2, 40.7, 40.3, 32.3 ppm.

***anti,anti*-2,7-Dibromobenzo[5,6]bicyclo[2.2.2]oct-5-ene (5).** A solution of alkene 4 (7.58 g, 48.6 mmol) in dichloromethane (20 mL) was stirred at −20 °C while a solution of bromine in dichloromethane (ca. 10% solution) was added dropwise until no further reaction was noted. Warming to ambient temperature and solvent removal at reduced pressure yielded dibromide 5 (15.22 g, 99.2%) as slightly orange crystals.

Recrystallization of a small sample from hexane afforded white crystals: mp 133.5–134.5 °C; IR (KBr) prominent maxima at 2900, 1470, 1322, 1267, 1235, 951, 835, 767 and 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20–2.60 (apparent d of d, 2 H_3, 2 H_8), 3.04 (quint J = 3.0 Hz, H_4), 3.69 (t, J = 2.4 Hz, H_1), 4.12 (t of d, J = 8.0, 2.4 Hz, H_2, H_7), 7.25 (s, four aromatics); ^{13}C NMR ($CDCl_3$) 140.8, 139.8, 128.1, 127.0, 124.7, 123.9, 48.2 (C(1)), 44.8 (C(2), C(7), 38.7 (C(3), C(8)), 35.6 (C(4)).

Anal. Calcd for $C_{12}H_{12}Br_2$: C, 45.61; H, 3.82; Br, 50.57. Found: C, 45.66; H, 3.98; Br, 50,47.

Benzobarrelene (1). The crude dibromide 5 from above (15.22 g, 0.048 mol) was dissolved in dry tetrahydrofuran (60 mL) and added dropwise during 30 min to a stirring ambient temperature solution of potassium *tert*-butoxide (27.2 g, 0.243 mol) in dry tetrahdyrofuran (200 mL), maintained under a nitrogen atmosphere. After 3 h more, the mixture was heated at gentle reflux for 1.5 h, then cooled, quenched by dropwise water addition (100 mL), and poured into cold water (600 mL). The mixture was extracted with pentane (4× 125 mL) and combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated at reduced pressure to afford 7.48 g of off-white crystals. Sublimation at 80 °C (0.7 mm) yielded benzobarrelene (6.77 g, 91.1%) as white needles: mp 63–65 °C. Recrystallization from pentane and resublimation gave material with mp 65–66 °C (lit.[1] 65.5–66 °C). The ^1H NMR spectrum was as reported.[1]

Registry No.—**1**, 7322-47-6; **2**, 4453-90-1; **3**, 54647-00-6; **4**, 2409-43-1; **5**, 63216-61-5; dichlorocarbene, 1605-72-7.

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(11) For example, nitration of dibromide **5** with Ac_2O/HNO_3 afforded a 94% yield of mixed β and β′-NO_2 derivatives. Treatment of this isomeric mixture with potassium *tert*-butoxide in THF gave β-nitrobenzobarrelene. Classical transformations of this nitro derivative and use of an appropriate base for dehydrohalogenation should allow preparation of a variety of aromatic substituted benzobarrelenes.

The First Observation of Splitting by a "Peripheral" Substituent in a Radical Cation Containing a Tetravalent Phosphorus Atom

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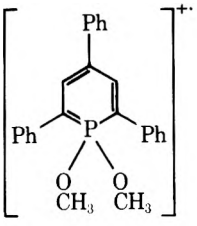
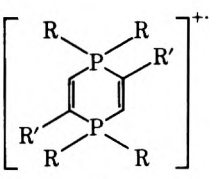
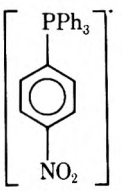
Recently, a number of stable radicals containing tetravalent phosphorus have been reported.[2-6] In all of these cases, coupling was not observed from groups attached to phosphorus which were not part of the delocalized π system containing the unpaired electron. This is best illustrated through examples. In I hyperfine splittings are observed from the phenyl substituents on the hetrocyclic ring and from the two protons on the ring, but no splittings are observed from the methoxy substituents.[4] Similarly, in the spectrum of II there are splittings from R′ and the ring protons, but no evidence is



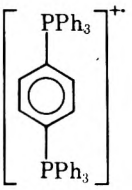
I



II



III



IV

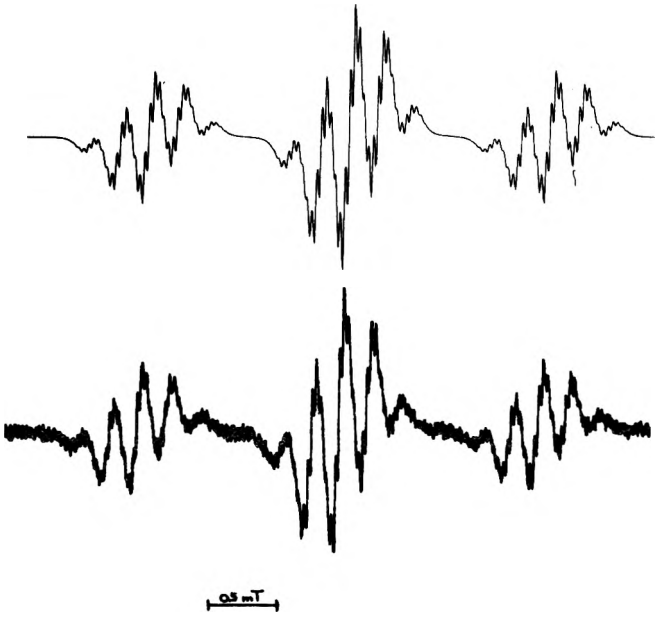
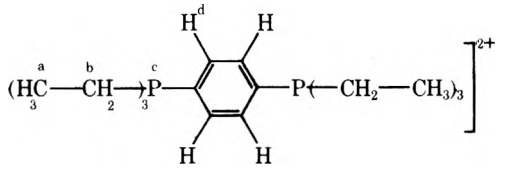


Figure 1. ESR spectrum of the radical cation of V. Upper, calculated spectrum using a line width of 0.030 mT; lower, experimental spectrum in DMF at −47 °C.

observed for couplings from R whether it is alkyl or aryl.[2,7] In fact, if R is *p*-fluorophenyl no coupling is observed from the fluorine atom.[2,7] In III and IV there are no couplings from the "peripheral" phenyl substituents of phosphorus.[3,6] All these radicals have large (0.5–1.8 mT) phosphorus hyperfine splitting constants. We wish to report the first observation of coupling by a group not directly attached to the unpaired-electron-bearing moiety of a stable radical containing tetravalent phosphorus.

Results

Reduction of V in the electron paramagnetic resonance (EPR) cavity at potentials corresponding to the first reduction



V

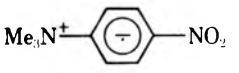
wave results in the EPR spectrum shown in Figure 1. Along with this spectrum is the computer simulation using the hyperfine splitting constants (hfsc) given in Table I. The line width used in the simulation was 0.030 mT.

Hückel molecular orbital (HMO) calculations were carried out on the molecule and the results are given in Table II. The parameters used for the phosphorus atoms assume a conjugative interaction as well as inductive effects on the α-carbon atom rather than just inductive effects alone. These parameters have been shown to correlate EPR and electrochemical data for a large number of phosphorus-containing radicals.[6]

Discussion

The question of whether the phosphorus atom of a phosphonium group can interact with a π system in a combined conjugative and inductive manner or just in an inductive manner has received considerable attention. Recently, convincing evidence has been presented that in certain cases conjugative interaction is, in fact, important.[2-7,11] In this paper, we have presented the first example of an observed hyperfine splitting of a peripheral methylene group attached to a tetravalent phosphorus atom. It is likely that coupling is, in fact, occurring in radicals I–IV as the line widths are typically large (>0.1 mT).[2-8] Only in the case of $IV^{+\cdot}$ is the line width relatively small (0.035 mT);[6] however, in $V^{+\cdot}$ the line width is only 0.030 mT. Computer simulation of the EPR spectrum of $V^{+\cdot}$ using a line width of 0.035 mT showed no signs of coupling of the methylene protons other than the broad line width. Thus, the experimental line width is just small enough to allow observation of the methylene hfsc.

The relatively large coupling of the methylene protons (0.035 mT) represents additional evidence of the conjugative interaction of the phosphorus atom. It is doubtful that such a large coupling could be observed via a spin-polarization mechanism through the phosphorus atom. Also, one would have expected to see coupling in radicals such as II where R is either an ethyl or methyl group. Thus, it would seem that the odd electron is delocalized onto the phosphorus atoms. Further evidence against a spin-polarization mechanism is the observation that the methyl groups of VI do not couple.[3] In



VI

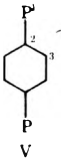
this case, only a spin-polarization mechanism could be involved. Thus, we feel that the observed splittings of the methylene groups of $V^{+\cdot}$ are strong evidence for the conjugative interaction of a tetravalent phosphorus atom.

Table I. Hyperfine Splitting Constants of $V^{+\cdot}$

Atom	hfsc[b] (mT[a])
Phosphorus (c)	1.508
Phenyl protons (d)	0.213
Methylene (b)	0.035
Methyl (a)	0.000

[a] 1 mT = 10 G. [b] ±0.001 mT.

Table II. Hückel Molecular Orbital Calculations[b] of the Odd Electron Density in $V^{+\cdot}$



V

Atom	C^2	hfsc(calcd)[a]	hfsc(obsd)
1	0.2040		
2	0.161		
3	0.0675	0.160	0.213

[a] $a^H = Q\rho$, where Q = 2.37 mT. [b] Parameters from ref 6: $\alpha' = \alpha^0 + h|\beta|\beta' = k\beta^0$; $h_d = +0.6$ $h\alpha_c = -0.6$; $h_{\beta c} = -0.3k_{dp} = 0.5$.

Experimental Section

Melting points were taken with a Thomas-Hoover oil-bath melting-point apparatus and were corrected. Infrared spectra were obtained with a Perkin-Elmer 257 spectrometer. NMR spectra were recorded on a Varian XL-100 instrument. EPR spectra were recorded on a JEOL JES-ME instrument with temperatures determined with a copper–constantan thermocouple. Computer simulation of theoretical EPR spectra was done using a Fortran IV program for mixtures employing Lorentzian line shapes written by R. G. Griffin.[9] The program used for the Hückel MO calculations was written by Munch and Rieke[10] and modified by T. H. Ridgeway for simplified input. Elemental analyses were obtained from Galbraith Laboratories (Knoxville, Tenn.). The electrochemical and EPR equipment and techniques used in this study have been previously described.[3,6]

1,4-Bis(triethylphosphonium)benzene (V). Triethylphosphine (pressure chemical, 8.4 g) and *p*-dibromobenzene (Aldrich, 8.25 g) were heated in a sealed tube for 185 h at 190–210 °C. The mixture was

allowed to cool and the solid triturated with anhydrous ethyl ether, filtered, and washed with ethyl ether. The residue was dissolved in the minimum amount of water and the salt precipitated by the addition of a copious quantity of acetone. This suspension was filtered and dried to yield crude light-brown V (8.25 g, 50%). Crude V was decolorized with activated carbon and recrystallized from isopropyl alcohol to give colorless needles: mp >330; NMR (F_3CCO_2H) δ 8.24 (AA'BB' system, 4 H), 2.70 (oct, 12 H, J = 12.8 Hz), 1.36 (hex, 18 H, J = 19 Hz); IR (KBr) 1450, 1115 cm^{-1}, characteristic of a phosphonium salt. Anal. ($C_{18}H_{34}P_2Br_2$) P, Br.

Acknowledgment. Financial support of this investigation by the National Science Foundation (MPS7506421) is gratefully acknowledged. Also we thank the Ethyl Corp. for financial support for C.K.W.

Registry No.—V dibromide, 63216-62-6; V^{+}-, 63216-63-7; triethylphosphine, 554-70-1; *p*-dibromobenzene, 106-37-6.

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Quantitative Dealkylation of Alkyl Ethers via Treatment with Trimethylsilyl Iodide. A New Method for Ether Hydrolysis

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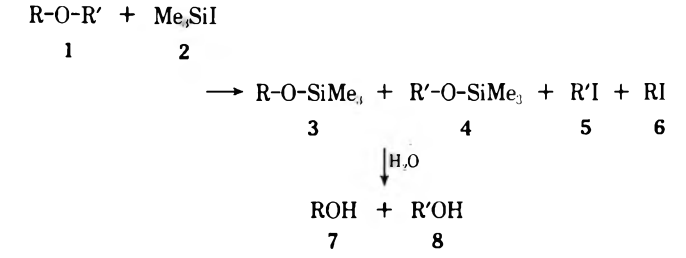
Many alkyl ethers have found extensive use in organic chemistry as protecting groups for alcohols.[1] Foremost among these are *tert*-butyl, triphenylmethyl (trityl), and benzyl ethers, all of which can be removed under relatively mild conditions, i.e., nonaqueous acid, mild aqueous acid, and hydrogenation, respectively.[2] Certain other alkyl ethers have also been employed to advantage on occasion, e.g., allyl,[3] tritylone,[4] *p*-halophenyl,[5] and similar systems.[6] However, simple methyl ethers have found little use in the protection of aliphatic hydroxyl groups (although they are quite extensively utilized for the protection of phenols) due to the difficulties associated with their removal. This fact has promoted the following statement which appeared in a recent review[1a] on protecting groups for aliphatic alcohols: "the methyl group is too stable to be used for the routine protection of alcohols". We report now observations which are contrary to the above statement, namely, the simple and efficient dealkylation of methyl and other alkyl ethers by trimethylsilyl iodide in both aliphatic and aromatic systems, the overall process affording ether hydrolysis in high yields.

Recently, several new modifications of long-standing procedures have been published which increase somewhat the usefulness of aliphatic alkyl ethers as protecting groups. These include the generation of HI in situ[7] and the use of acetic anhydride–Lewis acid media.[8] Boron trihalides have been used occasionally to cleave aliphatic methyl ethers,[9] although the yields in these cases are somewhat lower than with aromatic methyl ethers.[10] However, these methods do not solve the problem of clean and efficient demethylation of alkyl methyl ethers, since they often result in mixtures of dealkylated products.

We have very recently reported the simple and quantitative dealkylation of alkyl carboxylic esters by treatment with trimethylsilyl iodide to afford trimethylsilyl carboxylates, which upon addition of water furnish carboxylic acids.[11] We find that alkyl methyl ethers **1** (R′ = Me) also react with trimethylsilyl iodide **2** to afford mixtures of dealkylated products, the trimethylsilyl ethers **3** and **4** and the alkyl iodides **5** and **6**, in

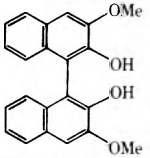


which, in general, the demethylation products **3** and **5** (methyl iodide) greatly predominate.[12] For example, cyclohexyl methyl ether **1a** when treated with 1.1 equiv of trimethylsilyl iodide **2** at 25 °C for 6 h affords 95% of the demethylation products, cyclohexyl trimethylsilyl ether **3a** and methyl iodide **5**, with only 5% of cyclohexyl iodide **6a** and methyl trimethylsilyl ether **4** being formed. It is interesting that at a somewhat higher temperature (50 °C) the reaction is complete in only 2 h, but now affords a 90:10 mixture of cyclohexyl silyl ether and methyl silyl ether. Aryl alkyl ethers (**1q–z**) are all cleaved unidirectionally when treated with trimethylsilyl iodide to afford only the aromatic trimethylsilyl ethers (**3q–z**) and the alkyl iodides (**5q–z**) in very high yields. In all cases, the silyl ethers **3** and **4** can be easily converted into the alcohols or phenols **7** and **8** in high yield upon simple hydrolysis.

The results with a series of methyl ethers and other alkyl ethers **1a–z** are listed in Table I. Several conclusions can be made from this data: (1) trityl, benzyl, and *tert*-butyl ethers are cleaved at a very much faster rate than the other alkyl ethers (methyl, ethyl, isopropyl, cyclohexyl, etc.), thus permitting the former to be selectively hydrolyzed in the presence of the latter; (2) aryl alkyl ethers (e.g., anisole) react with trimethylsilyl iodide at a significantly slower rate than dialkyl ethers (e.g., cyclohexyl methyl ether), so that dialkyl ethers can, in general, be cleaved completely under conditions which cause only 5–10% clevage of phenolic ethers; (3) the rates of dealkylation are such that alkyl methyl ethers can be cleaved cleanly in the presence of methyl esters[11] by conducting the reaction with just slightly more than 1 equiv of the silyl iodide at room temperature or below; (4) as was the case with alkyl esters,[11] many functional groups are stable to the conditions for ether hydrolysis, including acetylenes, olefins, ketones, amines, aromatic halides; (5) by careful variation of solvent, one can cleanly demethylate methyl ethers of straight-chain secondary alcohols, e.g., methyl 2-octyl ether **1g**, since the use of a propene–acetonitrile solution permitted the production of predominately 2-octanol.

As in the case of dealkylation of esters,[11] the possibility that the observed reactions are due entirely to catalytic amounts of HI present in the trimethylsilyl iodide cannot be totally discounted. However, we believe that trimethylsilyl iodide itself is causing dealkylation because, in the presence of 15 mol % pyridine or 2,6-di-*tert*-butyl-4-methylpyridine,[15] ether

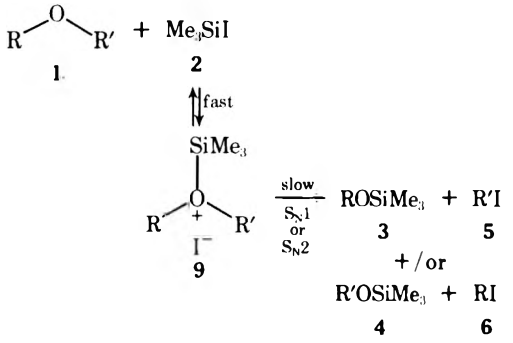
Table I. Dealkylation of Ethers by Trimethylsilyl Iodide:[a] $ROR' + Me_3SiI \rightarrow ROSiMe_3 + R'OSiMe_3 + R'I + RI$ (1, 2, 3, 4, 5, 6)

Ethers							Products and Yields[c]							
Registry no.	Compd 1	R	R'	Temp (°C)	Solvent	Time (h)[b]	3	Registry no.	4	Registry no.	5	Registry no.	6	Registry no.
931-56-6	a	C_6H_{11}	Me	25	$CDCl_3$	6	95[d]	13871-89-1	5	1825-61-2	95	74-88-4	5	626-62-0
	a	C_6H_{11}	Me	50	CCl_4	2	90		10		90		10	
932-92-3	b	C_6H_{11}	Et	25	$CDCl_3$	12	48.7[e]		22.5	1865-62-3	77.5	75-03-6	51.3	
	b	C_6H_{11}	Et	25	$CDCl_3$	16	0		0		100		100	
1860-29-3	c	C_6H_{11}	*i*-Pr	25	CH_2Cl_2	48	0[e]		0		100	75-30-9	100	
25246-83-7	d	C_6H_{11}	*t*-Bu	25	CCl_4	<0.1	100		0		100	558-17-8	0	
16224-09-2	e	C_6H_{11}	CH_2Ph	25	$CDCl_3$	<0.1	100		0		100		0	
20705-40-2	f	C_6H_{11}	CPh_3	25	$CDCl_3$	<0.1	100		0		100	2206-53-3	0	
1541-09-9	g	$CH_3(CH_2)_5CHCH_3$	Me	25	CD_3CN	8.5	86[f]	18023-52-4	0		100		7	557-36-8
1981-90-4	h	3β-cholestanyl	Me	25	$CHCl_3$	12	100[g]	18880-51-8	0		100		0	
13482-23-0	i	4-oxocyclohexyl	Me	25	$CDCl_3$	2.5	100	23510-94-3	0		100		0	
110-71-4	j	CH_2CH_2 (glyme)	2Me	25	$CDCl_3$	9	67[h]	7381-30-8	33[h]	26305-99-7	100[h]		0	
63250-84-0	k	$HC{\equiv}CC(Me)_2$-$C{\equiv}CCH_2$	Me	25	$CDCl_3$	1.3	0		0		100		100	63250-91-9
61478-24-8	l	$PrCOCHEtCH_2$[i]	*t*-Bu	25	$CDCl_3$	<0.1	100	63250-87-3	0		100		0	
61478-23-7	m	*i*-$PrCOC(Me)_2CH_2$[i]	*t*-Bu	25	$CDCl_3$	<0.1	100	63250-88-4	0		100		0	
63250-85-1	n	$Ph_3CCH_2CO(CH_2)_5$	CPh_3	25	$CDCl_3$	<0.1	100	63250-89-5	0		100		0	
60-29-7	o	C_2H_5	Et	25	$CDCl_3$	70	0		0		100		100	
109-99-9	p	$-CH_2(CH_2)_2CH_2-$		25	$CDCl_3$	<0.1	100	18001-91-7	0		100		0	
	p	$-CH_2(CH_2)_2CH_2-$		25	$CDCl_3$	75	0		0		100		100	628-21-7
100-66-3	q	C_6H_5	Me	25	$CDCl_3$	48	100	1529-17-5	0		100		0	
	q	C_6H_5	Me	50	$CDCl_3$	21	100		0		100		0	
104-93-8	r	*p*-C_6H_4	2Me	25	$CDCl_3$	30	100	17902-32-8	0		100		0	
578-57-4	s	*o*-BrC_6H_4	Me	25	$CDCl_3$	125	100	36601-47-5	0		100		0	
2398-37-0	t	*m*-BrC_6H_4	Me	25	$CDCl_3$	120	30[j]	36971-28-5	0		30		0	
104-92-7	u	*p*-BrC_6H_4	Me	25	$CDCl_3$	120	100	17871-44-3	0		100		0	
90-04-0	v	*o*-$NH_2C_6H_4$	Me	50	$(CH_2)_4SO_2$	12	100	36309-44-1	0		100		0	
536-90-3	w	*m*-$NH_2C_6H_4$	Me	50	$(CH_2)_4SO_2$	22	100	36309-43-0	0		100		0	
104-94-9	x	*p*-$NH_2C_6H_4$	Me	50	$(CH_2)_4SO_2$	22	100	36309-42-9	0		100		0	
621-32-9	y	*m*-$CH_3C_6H_4$	Et	50	CCl_4	140	100	17902-31-7	0		100		0	
63250-86-2	z			60	$CDCl_3$	26	100[k]	63250-90-8	0		100		0	63250-92-0

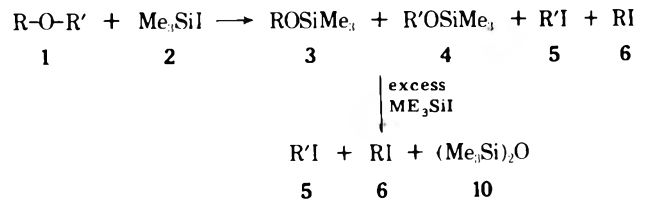
[a] Approximately 1.3 equiv of trimethylsilyl iodide was used in all simple dealkylation experiments. When converting the ethers completely into the two alkyl iodides, approximately 2.5 equiv was employed. [b] The times required for the transformations listed could all be decreased by utilizing a large excess of trimethylsilyl iodide or by using higher temperatures. [c] The yields listed were determined by NMR integration of the pertinent peaks. [d] Starting with 1.5 g of the ether, 1.00 g of cyclohexanol was isolated (column chromatography on silica gel), implying a 76% yield. [e] Examination of the NMR spectra at intermediate times indicates that the ethyl and isopropyl groups are dealkylated at a faster rate than the cyclohexyl group. [f] In this experiment there was still starting material present (7%), due to the insufficient amount of trimethylsilyl iodide employed. Starting with 216 mg of the ether, 119 mg of 2-octanol was isolated (column chromatography on silica gel), implying a 61% yield. See Experimental Section. [g] Starting with 300 mg of the ether, 232 mg of 3β-cholestanol was isolated (column chromatography on silica gel) and indentified as pure by comparison to an authentic sample, implying a yield of 80%. [h] The bis(trimethylsilyl ether) of ethylene glycol is designated 3j, the trimethylsilyl ether of 2-iodoethanol 4j, and methyl iodide 5j. [i] Prepared from the corresponding bis(*tert*-butyl) or bis(trityl) ether by trityl salt oxidation.[18] [j] In this experiment after 5 days there was still a large amount of starting material left (70%), even though a slight excess of trimethylsilyl iodide was still present. [k] The product of dealkylation of the optically active (*R*)-ether was the optically active tetrol, isolated in 95% yield with no loss in optical purity. See Experimental Section.

dealkylation does occur albeit at a slower rate. Furthermore, dealkylation occurs facilely in a propene-saturated carbon tetrachloride solution, in which even trace amounts of HI are trapped out as isopropyl iodide.

We suggest a rather straightforward mechanism for this process: the ether 1 reacts with trimethylsilyl iodide 2 in a fast and reversible step to produce the silylated oxonium iodide 9 which can then go on to products in a slow, irreversible process by either an S_N2 mechanism or an S_N1 (S_Ni) mechanism.



If the alkyl trimethylsilyl ethers, 3 and 4, are allowed to react with excess trimethylsilyl iodide at 50 °C for longer periods of time, they are efficiently converted into the corresponding alkyl iodides, 5 and 6, respectively, and hexamethyldisiloxane (10). Thus, if desired one can easily convert both alkyl residues in a dialkyl ether into the two corresponding



alkyl iodides. For example, compounds **1b, 1c, 1k, 1o,** and **1p** in Table I have been converted totally into the two alkyl iodides in good yields as shown. This then provides a convenient synthesis of iodides directly from ethers.

Trimethylsilyl iodide 2 can be conveniently synthesized in two steps from the readily available trimethylsilyl chloride.[11] This procedure is readily applicable for the preparation of fairly large amounts of this compound[16] (see Experimental Section). We believe that the simplicity and high yields of this method will cause it to be quite useful to chemists interested in synthesis.[17]

Experimental Section

Trimethylsilyl Iodide. A variation of Vornokov's original procedure was used.[19] Aluminum powder (5.6 g, 0.21 mol) and hexamethyldisiloxane[20] (16.2 g, 0.1 mol) are placed in a 250-mL round-bottom flask equipped with a solid addition funnel, reflux condenser, magnetic stirrer, and nitrogen inlet. The flask is warmed in an oil bath to 60 °C. Iodine (50.8 g, 0.2 mol) is added piecewise over a period of 55 min via the solid addition funnel. The mixture is refluxed for 90 min (bath temperature 140 °C). The reflux condenser is then replaced by a distilling head. Distillation at atmospheric pressure (bath temperature 140–210 °C) with collection at 0 °C gives 35.0 g (87.5%) of trimethylsilyl iodide (2), a clear colorless liquid, bp 106 °C: NMR ($CDCl_3$) δ 0.8 (s, 9 H).

General Experimental Procedure. Reactions were normally conducted on a 1 mmol scale in an NMR tube with a tightly sealed cap or on a 20–30 mmol scale in a round-bottom flask under nitrogen as follows. To a 2 M solution containing 1 equiv of the ether 1 in the indicated solvent (see Table I) was added 1.3 equiv of neat trimethylsilyl iodide 2 via a dry syringe. The reaction was maintained at the indicated temperature (see Table I) and monitored by NMR analysis for the given period of time (see Table I). Yields were calculated by NMR integration of the pertinent peaks. For isolation of the alcohols, at the completion of the reaction, the excess trimethylsilyl iodide was destroyed and the intermediate trimethylsilyl ethers 3 formed during the reaction were hydrolyzed to the alcohols 7 by pouring the reaction mixture into 4 equiv of methanol. The volatile components were removed at reduced pressure and the residue was taken up in diethyl ether, washed with aqueous sodium bisulfite, aqueous sodium bicarbonate, and brine, and dried. The residue left after evaporation of solvent was further purified (if necessary) by column chromatography on silica gel. In the case of the alkyl cyclohexyl ethers, the extraction and washings were omitted and the residue after evaporation of the methanol was chromatographed directly.

The following are specific experimental procedures.

1,1′-Binaphthalene-2,2′,3,3′-tetrol. To 52.0 mg (0.15 mmol) of (+)-(*R*)-diol **1z** in an NMR tube was added 0.5 mL of $CDCl_3$ to give a clear solution. Then 0.1 mL (0.75 mmol) of trimethylsilyl iodide was added. The solution was maintained at 60 °C by an oil bath, and the reaction was monitored by NMR periodically. The reaction was apparently complete after 26 h as indicated by the absence of a signal for the OCH_3 protons in the NMR spectrum and the presence of a signal at 2.15 for protons of CH_3I. The brown-purple solution was filtered and ≃0.25 mL of MeOH was added to the filtrate. After 1 day, the solvent was removed by rotary evaporation to give 45.4 mg (95%) of a pink solid, which was identified as (+)-(*R*)-tetrol by its NMR spectrum and its specific rotations, which were identical to those of an authentic sample.

2-Octanol. Methyl 2-octyl ether **1g** (0.216 g, 1.5 mmol) was placed in an NMR tube and ≃0.2 mL of propene was condensed into the tube at −78 °C. To this at −78 °C was added the supernatant liquid from the centrifugation of 1.0 mL CD_3CN and 0.65 mL (5.0 mmol) of trimethylsilyl iodide (all transfers performed with clean dried syringes). After addition of the Me_3SiI/CD_3CN solution, the NMR tube was allowed to warm to room temperature (allowing excess propene to evaporate). The reaction was monitored by NMR. After 8.5 h, the reaction was quenched by pouring the contents of the NMR tube into 1 mL of MeOH through which gaseous HCl had been passed for 5 s. The volatiles were removed on the rotary evaporator. NMR analysis of the residue indicated 86% 2-octanol, 7% 2-octyl iodide, and 7% methyl 2-octyl ether. Chromatography on 30 g of silica gel, elution with anhydrous diethyl ether, and evaporation of the solvent from the combined alcohol-containing fractions afforded 0.119 g (61%) of 2-octanol, identical with an authentic sample.

Acknowledgment. We thank Mr. Paul Ornstein for performing several preparative and dealkylative experiments and Dr. Thomas Tarnowski for performing the reaction involving the binaphthol **1z**.[21]

Registry No.—Trimethylsilyl iodide, 16029-98-4; cyclohexanol, 108-93-0; 2-octanol, 123-96-6; 3β-cholesterol, 80-97-7; hexamethyldisiloxane, 63250-9301; (+)-(*R*)-1,1′-dinaphthalone-2,2′,3,3′-tetrol, 63323-58-0.

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(21) This work was presented in part at the 173rd National Meeting of the American Chemical Society, New Orleans, La., March 1977, abstract ORGN89.

Monohalogenation of Primary Nitroparaffins

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Treatment of the salts of primary nitroparaffins with halogens generally gives the monohalonitro compound contaminated with greater or lesser amounts of the dihalonitro compound and the starting nitroparaffin. In 1960 Trippett and Walker[1] reported that pure 1-bromo-1-nitroalkanes could be prepared by addition of the dry, finely powdered, sodium or ammonium salt of the nitro compound to bromine at 0 °C; they obtained 65–70% yields of pure products. Several years later, Levering[2] devised a procedure for chlorinating the sodium salt of nitroethane, which gives excellent yields of pure 1-chloronitroethane. Unfortunately, his procedure depends on density differences between the monochloronitro compound and the solution of nitroparaffin salt; these differences quickly become relatively small as the molecular weight increases, so that even the preparation of pure 1-chloro-1-nitrobutane is no longer a simple matter. And still more recently, Novikov et al.[3] proposed the use of *N*-halo-*N*-nitroamines or *N*-halosuccinimides as reagents for monohalogenating the salts of primary nitroparaffins, but the purity of their products cannot be regarded as established.

We now report a simple, convenient procedure for chlorinating, brominating, and iodinating primary nitroparaffins; the yields of pure products range from 82 to 94%. All that is required is addition of a methylene chloride solution of the halogen, precooled to −78 °C, to a slurry of the nitroparaffin salt and ice. The reaction is complete in 1–2 min, the methylene chloride phase is dried, the solvent is removed, and the residue is subjected to a simple distillation. This gives analytically pure monohalonitro compound in the yields shown in Table I.

Experimental Section

Chlorination is exemplified by the preparation of 1-chloro-1-nitropropane.

1-Chloro-1-nitropropane. A solution of 22.2 g (337 mmol) of 85% potassium hydroxide in 120 mL of water is prepared under nitrogen in a 500-mL flask fitted with an efficient stirrer.[4] When this solution comes to room temperature 30.0 g (337 mmol) of 1-nitropropane is added all at once and the mixture is stirred under nitrogen until the nitro compound dissolves (ca. 15 min). Following this, the solution is cooled until it just starts to freeze (ca. −15°C), at which point ca. 300 mL of crushed ice is added, and then a solution of 20 mL (ca. 60 g) of liquid chlorine in 100 mL of methylene chloride, which has been cooled to −78 °C, is added all at once with vigorous stirring.[4] In about 1 min the reaction is over. After separation of the two layers, the aqueous phase is extracted with 50 mL of methylene chloride; the combined methylene chloride solutions are washed once with 50 mL of a saturated sodium chloride solution, and then dried over anhydrous magnesium sulfate. The methylene chloride and excess chlorine are removed by distillation through a short column, the column is removed, and the residue is distilled in vacuo. This gives 37.8 g (93% yield) of 1-chloro-1-nitropropane, bp 55 °C (26 mm). On VPC analysis only a single peak is obtained and elemental analysis (Table I) confirms the purity of this material.

Bromination may be carried out as for chlorination. Alternatively, a slightly modified procedure also works well, especially when small batches are being prepared. Instead of adding ice, it suffices to cool a larger volume of methylene chloride than would otherwise be used. The following procedure is illustrative.

1-Bromo-1-nitrooctane. In a 100-mL flask fitted with an efficient stirrer[4] a solution of 2.08 g (31.4 mmol) of 85% potassium hydroxide in 40 mL of 25% aqueous methanol[5] is prepared under nitrogen. At room temperature 5 g (31.4 mmol) of 1-nitrooctane is added, and the mixture is stirred under nitrogen until the nitro compound dissolves (ca. 40 min). The resulting solution is cooled until it just starts to freeze, and then 4.93 g (30.8 mmol) of bromine in 50 mL of methylene chloride (precooled to −78 °C) is added, all at once, with vigorous stirring.[4] After about 1 min the reaction is over; the layers are separated and the aqueous phase is extracted with 20 mL of methylene chloride. The combined methylene chloride solutions are washed with 20 mL of H_2O and dried over anhydrous magnesium sulfate, and then the solvent is removed. Distillation of the residue gives 6.64 g (89% yield) of analytically pure 1-bromo-1-nitrooctane; bp 75 °C (0.4 mm).

1-Iodo-1-nitroethane. To a solution of 4.40 g (66.7 mmol) of 85% KOH in 40 mL of water at 20–25 °C is added 5 g (66.7 mmol) of nitroethane all at once; the mixture is stirred under nitrogen until the nitro compound dissolves (ca. 10 min). With minimal exposure to light, the aqueous solution is cooled until freezing begins, and then 50 mL of CH_2Cl_2 (cooled to −78 °C) is added followed by 16.6 g (65.3 mmol) of powdered iodine (nitrogen atmosphere; vigorous stirring). In about 3 min the reaction is complete. After separating the layers, the aqueous phase is extracted with 20 mL of CH_2Cl_2, the combined methylene chloride solutions are dried (anhydrous $MgSO_4$), and then the solvent is removed by distillation through a short Vigreux column, first at atmospheric pressure and, finally, at 50 mm. The column is removed and the residue is distilled at 0.4 mm, whereupon 10.95 g (82% yield) of analytically pure 1-iodo-1-nitroethane is obtained (bp 42 °C). This compound soon develops a pink color.

Acknowledgment. We are grateful to the National Science Foundation for support of this work.

Table I. Monohalonitroparaffins

Compd	Registry no.	Yield, %	Bp, °C (mm)	Anal. Calcd	Anal. Found
1-Chloro-1-nitroethane	598-92-5	92	52 (45)	C, 21.94; H, 3.66; Cl, 32.36	C, 21.86; H, 3.73; Cl, 32.42
1-Chloro-1-nitropropane	600-25-9	94	55 (26)	C, 29.17; H, 4.86; Cl, 28.69	C, 29.38; H, 4.89; Cl, 29.00
1-Chloro-1-nitrooctane	63599-45-1	92	60 (0.4)	C, 49.74; H, 8.29; Cl, 18.34	C, 50.00; H, 8.25; Cl, 18.19
1-Bromo-1-nitroethane	563-97-3	89	48 (11)	C, 15.59; H, 2.60; Br, 51.92	C, 15.63; H, 2.68; Br, 51.79
1-Bromo-1-nitropropane	5447-96-1	92	50 (4)	C, 21.44; H, 3.57: Br, 47.59	C, 21.61; H, 3.65; Br, 47.39
1-Bromo-1-nitrooctane	63569-74-4	89	75 (0.4)	C, 40.35; H, 6.72; Br, 33.59	C, 40.48; H, 6.86; Br, 33.80
1-Iodo-1-nitroethane	51771-09-6	82	42 (0.4)	C, 11.94; H, 1.99; I, 63.18	C, 11.87; H, 1.87; I, 63.03

Registry No.—1-Nitropropane, 10903-2; methylene chloride, 75-09-2; 1-nitrooctane, 629-37-8; nitroethane, 79-24-3.

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(4) A mechanical stirrer is required.
(5) With the higher nitroparaffins it is advantageous to employ 25% methanol–75% water to achieve rapid solution.

Bicyclo[3.3.0]octane-2,6-dione and Bicyclo[3.3.0]octa-3,7-diene-2,6-dione

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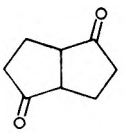
Several projects in this laboratory[1] have required substantial quantities of bicyclo[3.3.0]octane-2,6-dione (**1**) and the related dienedione **2**. Although these compounds have been known since 1934[2] and 1953,[3] respectively, the original



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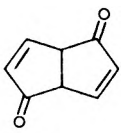
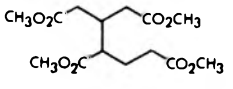


2

preparations, as well as some more recent procedures,[4] are unwieldy for large-scale operation. Therefore, we present here the details of our modified preparation of these versatile intermediates in molar quantities.

The synthetic sequence is outlined in Figure 1, and, as mentioned above, is based on the methods worked out by the Dauben group.[3,4] The free-radical induced coupling of dimethyl glutarate (**3**) to give tetraester **4** proceeds in only modest yield (ca. 50% based on recovered **3**), but is well suited for large (ca. 1 mol) runs. It is advisable to recrystallize the tetraester after distillation to remove some 15% of an impurity (presumably the isomeric ester **6**) which otherwise interferes in Dieckmann cyclization.



6

The cyclization of **4** is best carried out with sodium methoxide in dimethyl sulfoxide (Me_2SO). Provided that all sources of hydroxide ion are excluded, this combination gives yields superior to those obtained previously with potassium *tert*-butoxide in *tert*-butyl alcohol.[4] Hydrolysis and decarboxylation of the resulting bisketo ester **5** are accomplished by heating with aqueous acid followed by extraction; because of an unfavorable partition coefficient, ether is a very poor solvent for this extraction, but the dione **1** is readily recovered using chloroform. If necessary, the dione may be purified by sublimation in vacuo; recrystallization is not recommended, as **1** tends to oil out, even when very pure.

The conversion of the saturated dione **1** into dienedione **2** was originally[3] carried out by chlorination, ketalization with ethylene glycol, double dehydrochlorination, and deketalization. The last procedure of the Dauben group[4b] paralleled this, employing the bromoketal. We experienced considerable difficulty with this route, finding bromination of the bisenol acetate capricious, and the ketalization and elimination steps

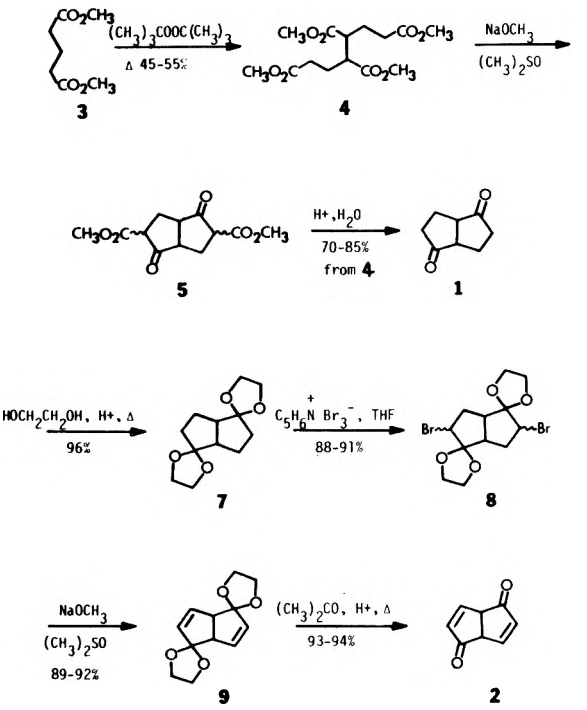


Figure 1. Improved synthesis of bicyclo[3.3.0]octa-3,7-diene-2,6-dione (**2**).

very slow. We have employed instead the sequence used by Eaton in some related systems,[5] and found it very satisfactory.

Ketalization of dione **1** with ethylene glycol proceeds smoothly and in nearly quantitative yield. The oily diketal is then brominated with pyridinium tribromide in tetrahydrofuran at low temperature (if the reaction is carried out at or near room temperature considerable polymer is formed, and the product can be purified only with difficulty). The dibromo diketal **8** may also be obtained directly by brominating **1** in ethylene glycol,[6] but this method is suitable for small-scale runs only. Although double dehydrobromination of **8** with ethanolic potassium hydroxide[4] requires refluxing for several days for complete reaction, the elimination may be effected in several hours with sodium methoxide in Me_2SO. Finally, ketal exchange with acetone afforded dienedione **2**.

By means of these procedures we have obtained quantities of both diketones sufficient to permit their use as starting materials for other syntheses. The preparations are reasonably rapid and efficient and, provided the usual precautions are taken, free from hazard. There is no reason to suppose that they could not be scaled up several fold over the amounts specified in the Experimental Section, provided suitably sized equipment is at hand.

Experimental Section

General. All melting points were measured in open capillaries with a Thomas-Hoover apparatus and are uncorrected; boiling points are also uncorrected. Combustion analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Unless noted otherwise, reagents and solvents were reagent-grade materials used as received.

Proton nuclear magnetic resonance (NMR) spectra were run on Varian A-60, A-56/60, and T-60 instruments (60 MHz). Chemical shifts are reported in parts per million downfield of internal tetramethylsilane (δ 0.0). Infrared spectra were measured on a Perkin-Elmer Model 137 spectrophotometer. Liquid samples were examined as neat films, and solids as Nujol mulls. All gas chromatographic separations were achieved using an F and M Model 700 chromatograph equipped with a thermal conductivity detector. Helium was used as the carrier gas at flow rates of 70–80 mL/min; an injector temperature of 240 °C and a detector temperature of 270 °C were used

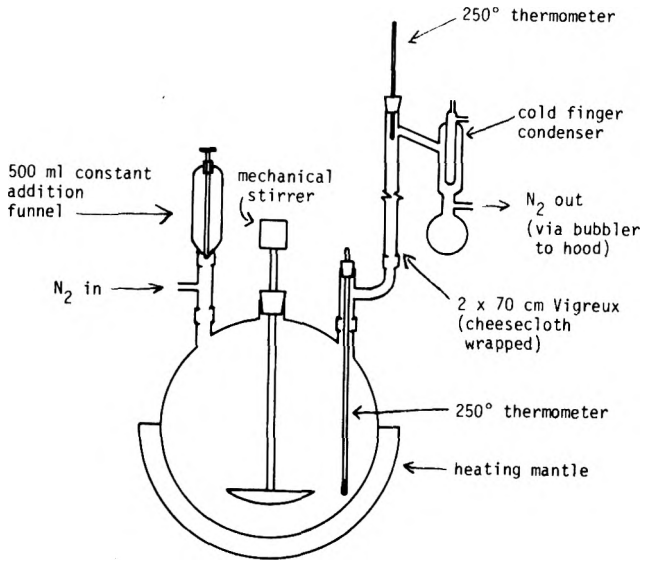


Figure 2. Apparatus for preparation of tetraester 4.

in all cases. The compositions reported were calculated from the peak areas (determined by triangulation) without corrections for differing detector responses. The columns employed were 6 ft × 1/4 in. aluminum columns packed with the following materials: column A, 4% QF on 60–80 mesh Chromosorb G, acid and base washed and silanized; column B, 5% Carbowax 20M on 60–80 mesh Chromosorb G, acid and base washed and silanized; column C, 4% OV-17 on 60–80 mesh Chromosorb G, acid and base washed and silanized; column D, 1% SE-30 on 60–80 mesh Chromosorb G (untreated).

Dimethyl Glutarate (3). A mixture of glutaric anhydride (Aldrich, technical grade, 70% stated purity, 2.5 kg), methanol (2 L), and *p*-toluenesulfonic acid (1–2 g) was refluxed for 20–30 h. The reaction mixture was cooled, diluted with 1 L of water, made slightly basic by the addition of 10% sodium hydroxide solution, and extracted with ether (4 × 1 L). The combined ether layers were washed with water and saturated aqueous sodium chloride solution, dried over Drierite, and freed from solvent on the rotary evaporator. Distillation of the residue afforded impure dimethyl glutarate, bp 90–110 °C (17 mm). This material was redistilled through a 1-m Vigreux column, and the fraction boiling at 99–101 °C (17 mm) was collected. This product, a water-white oily liquid, was ca. 99.5% pure by GC (column A, 150 °C); yields were in the range 45–55%.

The aqueous solution from the above extraction was acidified with hydrochloric acid. Extraction of this mixture with ether afforded, after removal of the solvent, very crude momomethyl glutarate, which was combined with the glutaric anhydride for reuse.

Tetramethyl Hexane-1,3,4,6-tetracarboxylate (4). Free Radical Induced Coupling of Dimethyl Glutarate. This procedure is a slight modification of those of Osborne[4a] and Simpson.[4b] The reaction vessel was a 5-L three-necked flask equipped as shown in Figure 2. The flask was charged with 2500 mL of dimethyl glutarate (DMG), which was heated to boiling, with stirring, while nitrogen was passed through the apparatus. After 15 min of boiling, the DMG was cooled to 175 °C, and the nitrogen flow was adjusted to 45–50 mL/min. A mixture of di-*tert*-butyl peroxide (Columbia, 400 mL, ca. 2.17 mol) and DMG (160 mL) was then added to the vigorously stirred DMG, maintaining the liquid temperature at 170–175 °C; the addition rate was 1 mL/min. After addition was completed, heating was continued until gas evolution ceased (this was determined by temporarily stopping the nitrogen flow and inspecting the gas bubbler at the outlet of the system); this typically required an additional hour. When no more gas was evolved, the contents of the flask were rapidly heated to vigorous boiling until DMG (bp 214 °C) began to distill over.

The flask and contents were allowed to cool overnight, and the reaction mixture was transferred to a 5-L round-bottom flask. Unreacted DMG was then removed by vacuum distillation through a 50-cm Vigreux column; everything boiling up to 140 °C (17 mm) was collected in one fraction. The volume of recovered DMG was 2180 mL, so 480 mL (ca. 520 g, 3.23 mol) of DMG had been consumed.

The residue in the pot was cooled to around 80 °C, and transferred while hot to a 1-L round-bottom flask. Distillation was then continued through the 50-cm Vigreux; three fractions were collected: fraction 1, 20 g, bp 80–135 °C (0.02 mm); fraction 2, 290 g, bp 135 (0.02 mm)–155 °C (0.03 mm) [most of this material boiled at 140–143 °C (0.02 mm)], and fraction 3, 20 g, bp 155–180 °C (0.03 mm). The dark pot residue was discarded.

All of these fractions eventually solidified to give mushy white crystals. Fraction 2 contained about 85% of the desired product and about 15% of an additional compound (two barely separated peaks by GC on column A, 210 °C). Solution of fraction 2 in an equal volume of warm methanol and cooling to 10 °C afforded 165 g of white crystals (a mixture of needles and tablets). Two more crops, 54 and 6.5 g, were obtained by cooling the mother liquor to −10 °C and then to −60 °C. Fractions 1 and 3 were combined and crystallized in the same manner to give 11 g more (two crops, 10 and −60 °C). Thus, the total recrystallized product came to 236.5 g (0.745 mol). This corresponds to a yield of ca. 46% based on the DMG consumed, or 34% based on the di-*tert*-butyl peroxide.

Subsequent runs were made in the same manner, using the recovered DMG; after four or five batches, the DMG was refractionated, as described previously, to remove the impurities which had accumulated. The apparatus and still were not cleaned between runs, so as to minimize losses due to holdup. A number of preparations afforded recrystallized 4 in yields of 42–55% based on reacted DMG.

The mother liquors from the recrystallization of several preparations could be combined and processed as above to obtain an additional amount of pure tetraester 4. The broad melting range of the recrystallized tetraester (48–59 °C) is undoubtedly due to the presence of a mixture of the meso and *dl* diastereomers. The other data on this mixture are in complete agreement with structure 4: IR (neat melted) 5.75 μm; NMR (δ, CCl_4) 3.70 (6 H, s), 3.65 (6, H, s), 2.68 (2 H, br t, J = 4 Hz), 2.50–2.06 (4 H, m), 1.84 (4 H, br m).

Bicyclo[3.3.0]octane-2,6-dione (1). Dieckmann Cyclization of Tetraester 4, and Hydrolysis–Decarboxylation of the Product, Keto Ester 5. NB. The success of this procedure depends crucially upon the strict exclusion of water and other sources of hydroxide ion. The use of dry glassware, dry dimethyl sulfoxide (Me_2SO), and fresh sodium methoxide is essential; if these precautions are not taken, the yield drops substantially, even to the point of no product being formed. It should be noted that even freshly opened bottles of commercial reagent grade Me_2SO usually gave unsatisfactory results. Me_2SO was purified by stirring with calcium hydride for several days, then vacuum distillation from the same drying agent: bp 77–78 °C (15 mm).

A 1-L three-necked flask was fitted with a mechanical stirrer, addition funnel, thermometer, and provision for an inert atmosphere. The apparatus was then flame dried while it was evacuated. Sodium methoxide, *freshly opened* (60 g, 1.1 mol), and dry Me_2SO (ca. 300 mL) were then added, and a nitrogen atmosphere was established by repeated cycles of evacuation and bleeding in nitrogen. Tetraester 4 (159 g, 0.50 mol), dissolved in ca. 150 mL of warm Me_2SO, was then added to the stirred slurry of sodium methoxide. Addition took 15 min, during which the internal temperature rose to 50–60 °C. An additional portion of sodium methoxide (40 g, 0.74 mol) was then added. The reaction mixture, which had become deep orange during the ester addition, was then heated at 70–80 °C for 1.5 h. The nearly black mixture was then cooled to 20–25 °C with an ice bath, and *ice-cold* 6 M hydrochloric acid (320 mL) was added slowly, with continued stirring. Ice bath cooling was used to keep the temperature below 30 °C. As the acid was added, the mixture lightened in color, becoming yellow-brown and finally pink with a finely divided solid precipitate. The final slurry was poured into 2.5 L of ice water, and the pH was checked to make certain it was acidic. When the temperature of this mixture reached 10 °C the solid was collected by filtration through a *large* Buchner funnel, washed several times with cold water, washed once with cold methanol–water (1:1), and sucked as dry as possible. The crude bisketo ester was then dried, first at room temperature and finally in an oven at 85–90 °C. The oven drying led to considerable sintering and some darkening of the initially yellow or pink, powdery product, but did no harm; the sintering was in fact beneficial in the next step. The crude keto ester 5 weighed 109.5 g (86.3% crude) and showed mp 91–98 °C dec. Further purification was not necessary, but could be achieved by crystallization from methanol (5 mL/g) in 80% recovery. The recrystallized product melted at 93–96 °C; a second recrystallization, this time from acetone–hexane, gave colorless prisms, mp 92–93 °C (lit.[4a] 90.4–92.4 °C).

The entire crude product from the above Dieckmann cyclization was added to 300–400 mL of 6 M hydrochloric acid, containing one small drop of Dow-Corning "Antifoam C" defoamer, in a 2-L Erlenmeyer flask. Several Carborundum boiling stones were added, and the mixture was heated on the steam bath with frequent swirling (gas evolution and foaming!); the temperature was kept below 70 °C, as considerable darkening occurred at higher temperatures, and the foaming became inconveniently vigorous. When gas evolution had ceased (typically, after about 1 h of heating), the solution was cooled

and filtered with suction through two thicknesses of filter paper. The filtrate was then extracted six times with 200-mL portions of chloroform. The chloroform layers were combined and washed with 5 M aqueous sodium hydroxide solution (2 × 25 mL), and concentrated to ca. 500 mL by distillation; this also effected azeotropic drying of the solution. The chloroform solution was filtered through a Dierite cone (to catch the fine particles). Removal of the solvent on the rotary evaporator gave a golden yellow oil, which slowly solidified to a pale yellow mass. The yield of crude dione 1 was 56.1 g (96.1% based on the crude keto ester; 82.9% from tetraester 4), yellowish granules, mp 43–46 °C. Again, further purification was not necessary. If desired, purer material could be obtained by sublimation [35–40 °C (0.01 mm)] onto a cold finger kept at 0 °C. Recovery was about 97%. The sublimed product was in the form of blocky crystals, mp 45.1–46.3 ° (lit.[4b] 46–46.5 °C) with the expected spectral properties: IR (Nujol) 5.73 μm; NMR (δ, CCl_4) 2.90 (2 H, br s), 2.20 (8 H, br s).

2,2,6,6-Bis(ethylenedioxy)bicyclo[3.3.0]octane (7). Ketalization of Bicyclooctanedione 1. The crude dione (209 g, 1.5 mol) was added to a mixture of ethylene glycol (200 mL, ca. 3.95 mol, 32% excess), *p*-toluenesulfonic acid hydrate (3.8 g, 0.02 mol), and benzene (1.5 L). This mixture was refluxed with separation of water (Dean–Stark trap, 64 mL, 118%) and magnetic stirring for 44 h. Nearly all of the water distilled over during the first 12 h. The brownish solution was cooled and washed as follows: 1 × 100 × 200 mL of saturated aqueous sodium bicarbonate, 2 × 200 mL of water, and 2 × 100 mL of saturated aqueous sodium chloride solution. The combined aqueous washings were extracted four times with 200-mL portions of ether, which were combined and washed once with saturated sodium chloride solution. This ether extract, combined with the original benzene layer, was filtered through a Drierite cone. Removal of the solvent on the rotary evaporator gave a brownish, oily liquid, which was distilled in vacuum. The fraction, bp 93–95 °C (0.15 mm), homogeneous by GC (column A, 170 °C; column B, 190 °C), was collected to give 327 g (96.5%) of a colorless, oily liquid. Repeated fractional freezing of this liquid in an ice–acetone bath gave an analytical sample. The spectra of this purified material, which were superimposable on those obtained from the distillate, were as follows: IR (neat) 3.41, 3.49, 6.82, 7.47, 8.24, 8.6–9.15, 9.64, 10.53 μm; NMR (δ, CCl_4) 3.87 (8 H, s), 2.37 (2 H, br m), 1.62 (8 H, br m).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.67; H, 8.02.

Other preparations, on 0.2–0.6-mol scales, gave yields of 96.1–96.4%. In view of the ca. 97% purity of the crude dione 1, the yield must be close to quantitative. Other boiling points observed were 100 °C (0.2 mm), 88 °C (0.05 mm), and 84 °C (0.015 mm).

2,2,6,6-Bis(ethylenedioxy)-3,7-dibromobicyclo[3.3.0]octane (8). Bromination of Ketal 7. Pyridinium tribromide was prepared according to Fieser and Fieser,[7] starting with approximately 1 lb of bromine and scaling the other reactants accordingly. During the recrystallization of the product from acetic acid, the mixture was stirred frequently to keep the crystals small. We and others[8] have found that finely divided tribromide gives better results than coarse material. Yields of the purified tribromide were in the range 72–78%.

The diketal 7 (45.2 g, 0.2 mol) was dissolved in dry tetrahydrofuran (400 mL, distilled from CaH_2) in a 1-L three-necked flask equipped with a mechanical stirrer, a drying tube, and a stopper. This solution was cooled, with stirring, to ca. −70 °C in a dry ice–acetone bath, and pyridinium tribromide (140 g, 0.438 mol) was added in one portion. The mixture, which rapidly decolorized, was stirred at ca. −70 °C for 1 h, then allowed to warm to room temperature. The pale yellow suspension was then poured slowly into 2.5–3 L of vigorously stirred cold water, whereupon the product precipitated. After 5 min more stirring, the solid was collected by filtration, washed repeatedly with water, and sucked fairly dry. This yellowish product was then covered with methanol (ca. 200 mL), the lumps were broken up, and the stirred mixture was gently boiled for a few minutes. It was then cooled to −10 °C for several hours, and the white product was collected, washed once with cold methanol, and air dried to give 69 g (90%) of white crystals (needles and granules), mp 152–156 °C (sinters 128 °C, further softens 142–145 °C, with gradual darkening from 128 °C on). Other runs on a similar scale (0.2–0.25 mol) gave yields in the range 88–91%.

2,2,6,6-Bis(ethylenedioxy)bicyclo[3.3.0]octa-3,7-diene (9). Dehydrobromination of Bromoketal 8. The methanol-washed mixture of isomeric bromo ketals (87 g, 0.227 mol) prepared from 7 was added in one portion to a stirred slurry of sodium methoxide (73.5 g, 200% excess) in dimethyl sulfoxide (400 mL) in a 1 L, three-necked flask equipped with a mechanical stirrer, a thermometer, and a gas bubbler. Occasional cooling (ice bath) was used to keep the reaction temperature below 60 °C. After the exothermic reaction had ceased (ca. 30 min) the mixture was heated to 70 °C for 2 h. It was then cooled to room temperature and poured into 2.5 L of stirred water and ice and the flask was rinsed with an additional 100 mL of water. Solid sodium chloride was added to nearly saturate the solution, and the crude solid product was collected by filtration. The filtrate was then extracted eight times with 500-mL portions of ether, each of which was roughly dried by washing with 50 mL of saturated sodium chloride, and evaporated as it was obtained. The residue from these extracts was combined with the original solid product, dissolved in cyclohexane (ca. 1200 mL), and refluxed with water separation (Dean–Stark trap). When water ceased to distill over, the hot cyclohexane solution was filtered, concentrated by distillation to a volume of about 500 mL, and allowed to cool. The product, 44.8 g (89%) of fine colorless needles, mp 101–102 °C, was then collected. Concentration of the mother liquor afforded an additional crop (1.5 g, 3%) of slightly yellowish needles, mp 97–100 °C. Other runs on the same scale gave total yields of 89–93%.

Bicyclo[3.3.0]octa-3,7-diene-2,6-dione (2). Deketalization of Ketal 9. The diene diketal 9 (44.5 g, 0.2 mol) and sulfosalicylic acid (0.3 g) were dissolved in acetone (500 mL) with gentle warming, and the solution was allowed to stand at room temperature for several hours. The acetone and its ethylene ketal were removed on the rotary evaporator. The residue was taken up in acetone, allowed to stand for 30 min, and the volatile material again removed. After a third acetone treatment, the solid residue was sublimed at 70 °C (0.01 mm) onto a carbon tetrachloride–slush cooled condenser, yielding 25.2 g (94%) of white, blocky crystals, mp 76.5–78.5 °C. Recrystallization of this material, although not necessary, could be achieved using cyclohexane as solvent. This gave colorless or white needles, mp 78–79 °C (lit.[3] 78–79.5 °C), in nearly quantitative recovery (three crops): IR (Nujol) 5.88 (strong and broad), 6.35 μm; NMR (δ, CCl_4) 7.66 (2 H, d of m, J = 5.6 Hz), 6.08 (2 H, d of d with additional fine structure, J = 5.6 Hz, J' = 1.4 Hz), 3.67 (2 H, m).

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Registry No.—1, 17572-87-1; 2, 4945-71-5; 3, 1119-40-0; *meso*-4, 63569-68-6; *dl*-4, 63569-69-7; 5, 63569-70-0; 7, 63569-71-1; 8, 63569-72-2; 9, 63569-73-3; glutaric anhydride, 108-55-4.

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Persistent Free Radicals from the Reaction of Sulfenamides with Tetracyanoethylene

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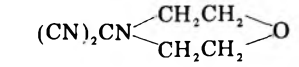
It was reported earlier that tetracyanoethylene reacts with sulfenamides but no identification of the products of the reaction was given.[1] This note reports the observation of persistent radicals in these reaction mixtures. The radicals were observed when degassed benzene, dichloromethane, or tetrahydrofuran solutions of the sulfenamides[2] were mixed with

Table I. Hyperfine Coupling Constants for Aminodicyanomethyl Radicals in Benzene

Registry no.	Radical	a^N	$a^N_{C=N}$	a^H_β	Comments
62681-10-1	$(CN)_2CN(CH_3)_2$	9.55	2.05	8.60	
63533-57-3	$(CN)_2CN(C_2H_5)_2$	9.84	2.12	5.36	a^H_γ = 0.21 g
63533-58-4	$(CN)_2CN(CH_3)Ph$	7.70	2.15	7.88	$a_{o,p}$ = 1.28; a_m = 0.69[4]
63533-59-5		10.42	2.17	17.66	Coupling to only 2β hydrogen atoms
63533-60-8	$(CN)_2CN(CH_2)_4$	9.88	2.10	13.87	Coupling to four equivalent β hydrogen atoms; g value 2.003
63533-61-9	$(CN)_2CN(CH_2)_5$	10.72	2.15	13.24, 0.05	Coupling to two sets of two equivalent β hydrogen atoms

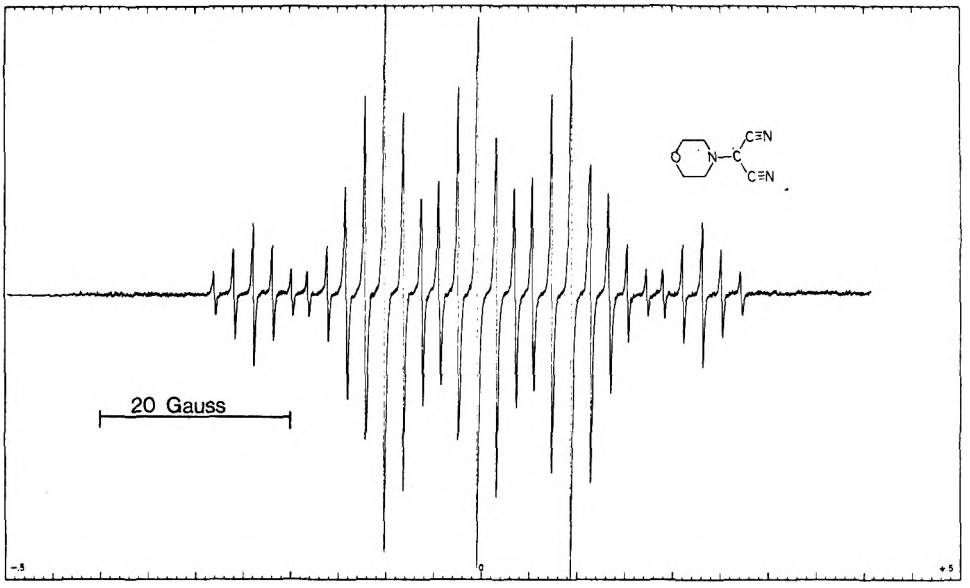
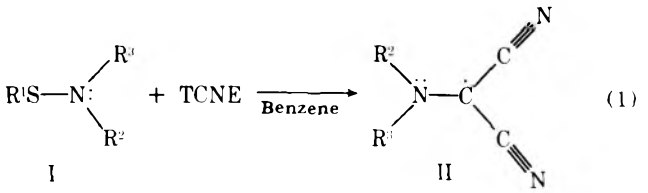


Figure 1. EPR spectrum of morpholinodicyanomethyl radical in benzene solution at room temperature. The width of the central line is 0.4 G.

saturated solutions of tetracyanoethylene in the same solvent. Immediately after mixing the dichloromethane solution a blue color was observed which rapidly disappeared, and an EPR spectrum of the resulting pale-yellow solution was obtained.[3] The reaction occurring is presumed to be that shown in reaction 1.



I II (1)

a, R^1 = Ph; R^2 = R^3 = CH_3
b, R^1 = Ph; R^2 = R^3 = C_2H_5
c, R^1 = C_2H_5; R^2 = CH_3; R^3 = Ph
d, R^1 = i-C_3H_7; R^2 = CH_3; R^3 = Ph
e, R^1 = t-C_4H_9; R^2 = CH_3; R^3 = Ph
f, R^1 = Ph; R^2, R^3 = $(CH_2CH_2)_2O$
g, R^1 = n-Bu; R^2, R^3 = $(CH_2CH_2)_2O$
h, R^1 = n-Pr; R^2, R^3 = $(CH_2)_4$
i, R^1 = Ph; R^2, R^3 = $(CH_2)_5$
j, R^1 = p-nitrophenyl; R^2 = R^3 = CH_3
k, R^1 = 4-chloro-2-nitrophenyl; R^2 = R^3 = CH_3

The spectrum observed is independent of the group initially attached to the sulfur atom in the sulfenamide; however, that group apparently can control whether an observable radical is formed. This can be seen in the series of compounds where R^2 = CH_3–, R^3 = C_6H_5–, and R^1 is either ethyl, isopropyl, or *tert*-butyl. The same radical was observed from the first two compounds; however, when R^1 was t-C_4H_9 no radical was detected. Similarly, the same spectrum was obtained from both morpholine derivatives, R^1 = phenyl and n-butyl. In the *N,N*-dimethylamino series, radicals were not observed when the *S*-aryl group contained a nitro group. Apparently, the reaction does not yield observable radicals when either the sulfur substituent is sterically bulky (t-butyl) or contains electron-withdrawing groups (p-nitrophenyl or 2-nitro-4-chlorophenyl).

All of the spectra observed were characterized by one large hyperfine coupling constant from a single nitrogen atom of between 7.70 and 10.72 G, a smaller hyperfine coupling constant from two equivalent nitrogen atoms of 2.10 to 2.54 G, and proton coupling constants from the protons on carbon atoms attached to the aminonitrogen atom. The observed coupling constants and proposed structures are shown in Table I. The *N,N*-dimethylaminodicyanomethyl radical has recently been reported to have been observed in solutions of dimethylaminomalononitrile.[5] The reported spectrum agrees well with the spectrum obtained from IIa and TCNE in benzene.

The radicals derived from the morpholine and piperidine derivatives are apparently conformationally frozen on the EPR time scale, since there is a large coupling constant to only two of the possible four β protons. This would be expected if the six-membered heterocyclic ring existed in a chair conformation with the dicyanomethyl group occupying an

equatorial position at nitrogen. This would allow one proton on each β carbon atom to be in the axial position for which a large coupling constant would be expected, and the remaining β protons would be equatorial and would be expected to show a small coupling constant.[6] The spectrum of the morpholine derivative is shown in Figure 1 and shows a coupling to only two of the four possible β protons. In the pyrrolidine derivative, conformational interconversion at room temperature is apparently rapid enough to average the β-proton coupling constants, and as a result four equivalent β protons are seen. Evidence for a preferred tetrahedral geometry at nitrogen is found in the results of INDO calculations.[7] These calculations predict an amino nitrogen coupling constant of 12.01 G for the tetrahedral conformation of *N,N*-dimethylaminodicyanomethyl radical as compared with a 4.10-G coupling constant for the planar conformation. The cyano nitrogen coupling constants are predicted to be nearly the same for the tetrahedral model, 2.42 G, as for the planar model, 2.59 G. The calculation did not predict the proton coupling constants well (2.40 G predicted vs. 8.60 G observed). The tetrahedral model is calculated to be lower in energy than the planar conformation. MINDO/3 calculation allowing full optimization of the geometry predicts that the planar conformation should be more stable; however, the MINDO/3 method is known to predict incorrectly the geometry of tertiary amines.[7c]

The amino nitrogen hyperfine coupling constants are lower than those observed for other nitrogen centered radicals, CH_3N–O–t-Bu (a^N = 14.47 g),[8] $(CH_3)_2N\cdot$ (a^N = 14.78 g),[9] and $(CH_3)_2NO$ (a^N = 16.1 g).[10] This may result from the unpaired electron being delocalized over the dicyanomethyl system. The cyano nitrogen coupling constant observed here is slightly larger than that in tetracyanoethylene anion, 1.61 G,[11] suggesting that slightly more than half the electron density is in the dicyanomethyl portion of the molecule, and as a result the spin density on the amino nitrogen is smaller than in the nitrogen-centered radicals.

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Supplementary Material Available: The EPR spectra of the radicals for which coupling constants are given in Table I, except for the morpholine derivative (5 pages). Ordering information is given on any current masthead page.

Registry No.—Ia, 24380-79-8; Ib, 6667-19-2; Ic, 63533-62-0; Id, 63533-63-1; If, 4837-31-4; Ig, 19117-36-3; Ih, 63533-64-2; Ii, 29959-86-2; TCNE, 670-54-2.

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(3) EPR spectra were obtained on a Varian E-4 spectrometer and were still observable 1 day after formation. The hyperfine coupling constants are reported relative to the constants for anthracene cation which was taken as having hyperfine complex constants of 6.53, 3.06, and 1.38 G; J. R. Bolton and G. K. Fraenkel, *J. Chem. Phys.*, **40**, 3307 (1964).
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Acid-Catalyzed Deuterium Exchange of the Indole Ring Protons in Tryptamine Derivatives

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Indole ring hydrogens, like those of other aromatic rings, undergo acid- and base-catalyzed proton exchanges. The rate of the acid-catalyzed proton exchange depends on basicity or nucleophilicity, which is reflected in the ground-state electronic structure of the molecule,[2] as well as on the stability of the protonated transition state,[3] a conjugated acid in terms of Brønsted.

Both acid- and base-catalyzed deuterium exchanges of hydroxyindole derivates have been observed,[4] but the results are qualitative and limited to the hydroxy derivatives. Furthermore, slow deuterium exchanges were not observed. In order to quantitatively assess the electronic structures of tryptamine derivatives and their ring-protonated conjugate acids, we have investigated acid-catalyzed deuterium ex-

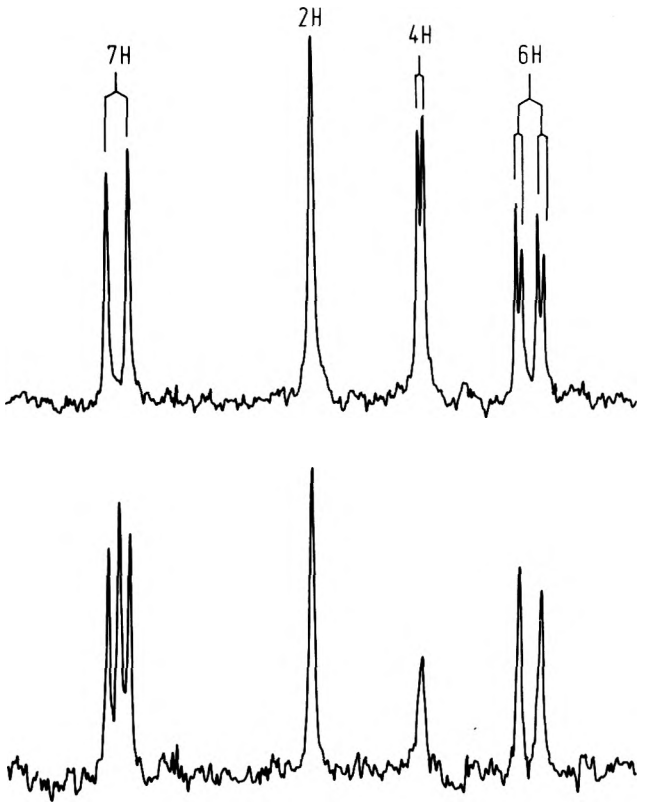

Figure 1. NMR spectra of the aromatic protons of 5-hydroxytryptamine in DCl solution. The upper spectrum is for t_0, and the lower one for t_x (see Table II). Total scanning is 1640–1563 Hz.

Table I. Chemical Shifts (ppm) of Aromatic Proton of Tryptamine Derivatives Relative to TSP as Zero at 220 MHz

Registry no.	Ring substitution	Solvent	Temp, °C	H-2	H-4	H-5	H-6	H-7
50-67-9	5-OH	1.0 N DCl	23	7.284	7.091		6.852	7.405
		D_2O/NaOD pD 9.9	23	7.222	7.045		6.835	7.372
1821-47-2	5-CH_3	1.0 N DCl	52	7.288	7.491		7.123	7.440
		Acetone/H_2O (5:1)	23	7.268	7.412		6.967	7.326
443-31-2	6-OH	0.4 N DCl	23	7.173	7.524	6.778		6.975
		D_2O/NaOH pD 10.5	23	6.926	7.370	6.547		6.617
61-54-1	H	1.0 N DCl	55	7.334	7.695	7.195	7.287	7.553

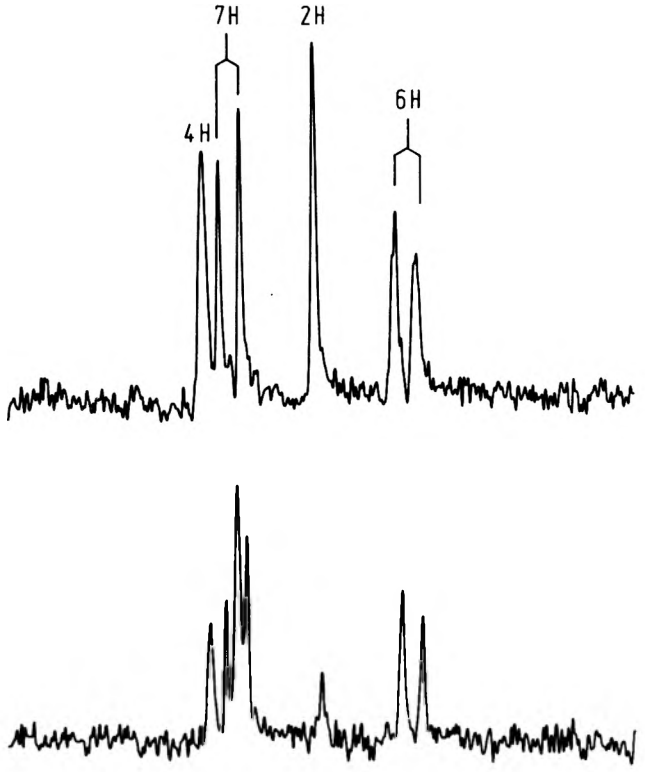

Figure 2. NMR spectra of the aromatic protons of 5-methyltryptamine in DCl solution. The upper spectrum is for t_0, and the lower one for t_x (see Table II). Total scanning is 1710–1491 Hz.

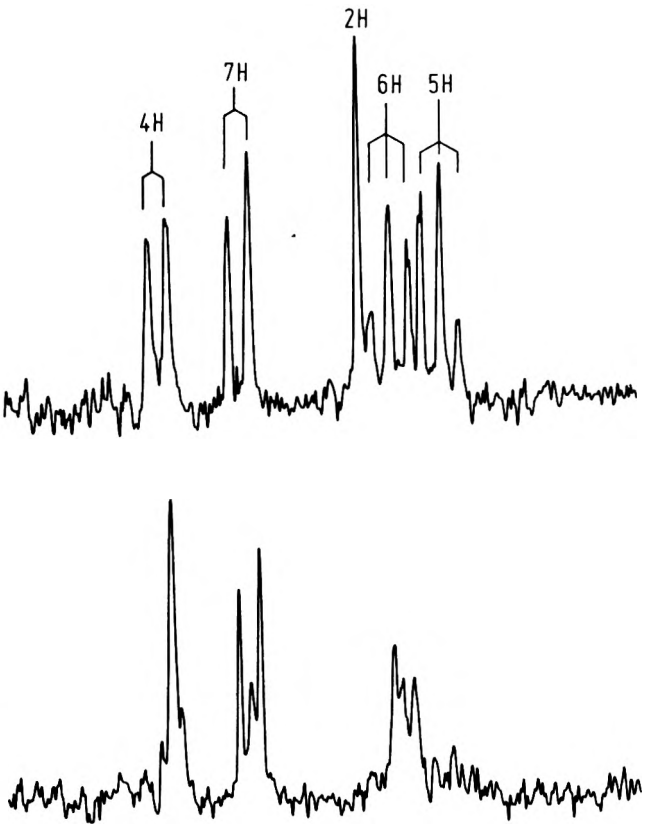

Figure 3. NMR spectra of the aromatic protons of tryptamine in DCl solution. The upper spectrum is for t_0, and the lower one for t_x (see Table II). Total scanning is 1755–1504 Hz.

change of 5-hydroxytryptamine, 6-hydroxytryptamine, 5-methyltryptamine, and tryptamine. Because these compounds exhibit widely different solubilities and exchange rates, comparison of exchange rate constants under identical experimental conditions is difficult. Only evaluation of thermodynamic parameters and acidity function dependence permit such a comparison through an extrapolation.

Chemical Shift Assignments. The benzenoid protons of 5- and 6-substituted tryptamines constitute an AMX spin system at 220 MHz, and their peak assignments are straightforward. In the case of 5-hydroxytryptamine (Figure 1), H-6 appears as a doublet of doublets, being ortho coupled to H-7 ($J_{6,7}$ = 8.0 Hz), and meta coupled to H-4 ($J_{4,6}$ = 2.3 Hz) (Table I). Additional couplings are not observed, so both H-4 and H-7 appear as doublets and H-2 is a singlet.

The proton splitting pattern of 6-hydroxytryptamine is identical with that of 5-hydroxytryptamine, with H-5 being ortho coupled to H-4 ($J_{4,5}$ = 8.6 Hz) and meta coupled to H-7 ($J_{5,7}$ = 2.1 Hz). Again H-2 is a singlet and long-range couplings are not observed. Proton chemical shifts for 5- and 6-hydroxytryptamine are in the same order as previously reported.[4]

The NMR spectrum of 5-methyltryptamine is similar to that of the 5-hydroxy derivative, except that the meta coupling is smaller and poorly resolved ($J_{4,6} \approx 1$ Hz) (Figure 2).

The benzenoid protons of tryptamine constitute an ABCD system, and their assignments are more complicated. Both H-4 and H-7 appear as doublets ($J_{4,5} = J_{6,7}$ = 7.0 Hz), but H-5 and H-6 further split each other ($J_{5,6}$ = 7.0 Hz) and appear as pseudo triplets (i.e., overlapping double doublets). Smaller coupling constants (meta) are <1 Hz, and could not be measured with accuracy. From the analysis of 5-methyltryptamine (Figure 2) and 7-methyltryptamine,[5] the downfield doublet can be assigned to H-4, and the remaining doublet to H-7. This agrees with the previous reports[6,7] that H-4 always appeared at lower field than H-7 in ring-substituted indoles, and is further confirmed by a recent NMR study of tryptophan.[8] Assignment of the H-4 and H-7 doublets (and the H-2 singlet) permits straightforward identification of the remaining resonances. Assignment of H-5 is based upon the observation that coalescence of the H-4 doublet is associated with deuterium exchange of the upfield "triplet" (Figure 3); the re-

Table II. First-Order Rate Constant (k) of Deuterium Exchange of Indole Ring Hydrogens of Tryptamine Derivatives as a Function of Temperature and Acid Concentration[a]

Ring substitution	DCl Concn, N	Temp, °C	H-2	H-4	H-5	H-6	H-7
5-OH	0.05	32.0		5.4×10^{-3}			
	0.10	32.0		1.0×10^{-2}			
	0.15	32.0		1.7×10^{-2}			
	0.50	32.0	9.6×10^{-4}			2.7×10^{-3}	
	1.0	20.5		3.5×10^{-2}			
	1.0	23.0	6.7×10^{-4}	5.0×10^{-2}		1.9×10^{-3}	
	1.0	27.5	1.3×10^{-3}	9.5×10^{-2}		3.7×10^{-3}	
	1.0	32.0	2.6×10^{-3}	1.8×10^{-1}		6.9×10^{-3}	
	1.0	33.5	3.2×10^{-3}			8.6×10^{-3}	
	2.0	23.0	2.2×10^{-3}			7.1×10^{-3}	
	2.0	32.0	7.7×10^{-3}			2.1×10^{-2}	
5-CH_3	1.0	52.0	2.2×10^{-2}	1.4×10^{-2}		8.3×10^{-3}	
	1.0	64.0	9.3×10^{-2}	6.2×10^{-2}		3.6×10^{-2}	
6-OH	0.1	28.0	2.6×10^{-3}		2.2×10^{-3}		4.8×10^{-3}
	0.2	28.0	5.1×10^{-3}		4.3×10^{-3}		9.6×10^{-3}
	0.4	28.0	1.1×10^{-2}		9.1×10^{-3}		2.1×10^{-2}
	0.6	28.0	1.7×10^{-2}		1.4×10^{-2}		3.2×10^{-2}
	0.4	23.0	5.2×10^{-3}		4.1×10^{-3}		1.0×10^{-2}
H	1.0	55.0	3.7×10^{-2}	3.7×10^{-4}	1.1×10^{-2}	1.9×10^{-3}	1.5×10^{-3}
	1.0	65.0	1.2×10^{-1}	1.2×10^{-3}	3.3×10^{-2}	6.5×10^{-3}	4.7×10^{-3}

[a] k is given in units of min^{-1}.

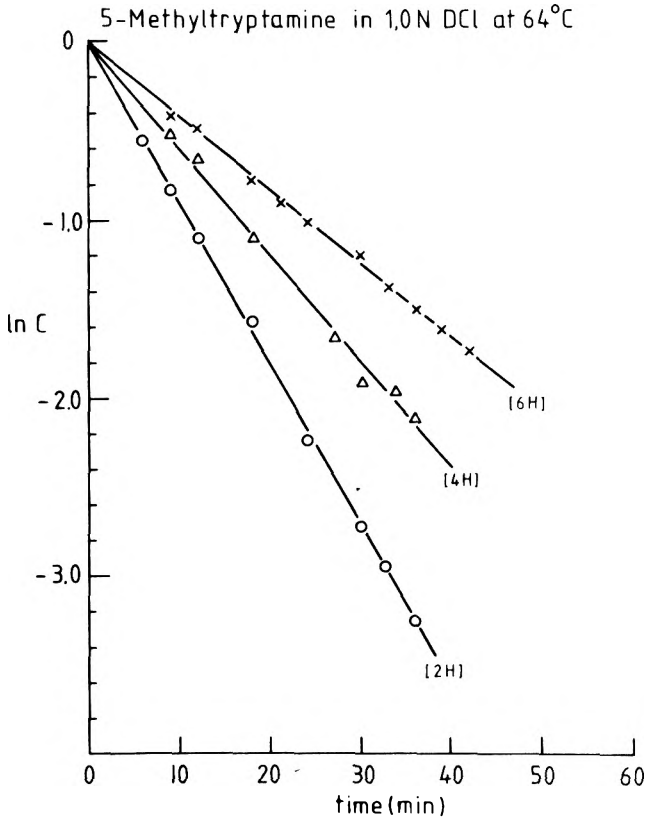

Figure 4. Exponential decay of the aromatic protons of 5-methyltryptamine as a function of time.

Table III. Arrhenius Activation Energy (kcal/mol) of Deuterium Exchange of Indole Ring Hydrogens of Tryptamine Derivatives

Ring substitution	H-2	H-4	H-5	H-6	H-7
5-OH	26.1	25.3		27.1	
5-CH_3	26.6	26.6		26.5	
6-OH	25.7		27.4		24.4
H	26.1	25.9	26.1	26.9	25.6

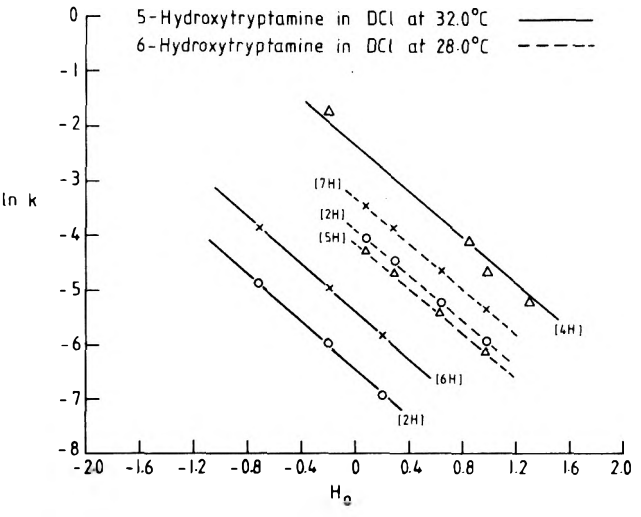

Figure 5. Exponential dependence of the first-order rate constants of deuterium exchange on the acidity function, H_0.

maining "triplet" is therefore H-6. These assignments for tryptamine are identical with those of tryptophan.[8]

It was observed that the aromatic proton resonances shift downfield upon protonation at the side chain alkylammonium group (Table I), but that the chemical shifts in an acidic medium were relatively independent of the acid concentration.

Deuterium Exchange of the Indole Ring Protons. The rate of disappearance of the ring protons of tryptamine derivatives in deuterium chloride (lower parts of Figures 1–3) is first order in the concentration of the ring proton, obeying the equation $A = A_0e^{-kt}$ (Figure 4). Because the deuterium exchange rate constants vary widely depending on the proton position, and because tryptamine derivatives show a wide range of solubilities, it is rather difficult to make a quantitative comparison under identical conditions. However, two parameters make such a comparison possible by extrapolation; one is the dependence of the rate constant on the DCl concentration, and the other is the temperature coefficient of the rate constant, i.e., the Arrhenius activation erergy, k =

Table IV. Calculated Deuterium Exchange Rate Constant (min^{-1}) of Indole Ring Hydrogens of Tryptamine Derivatives[a]

Ring substitution	H-2	H-4	H-5	H-6	H-7
5-OH	9.4×10^{-4}	6.5×10^{-2}		2.5×10^{-3}	
5-CH_3	5.4×10^{-4}	3.6×10^{-4}		2.0×10^{-4}	
6-OH	1.9×10^{-2}		1.5×10^{-2}		3.5×10^{-2}
H	6.4×10^{-4}	6.6×10^{-6}	1.8×10^{-4}	3.4×10^{-5}	2.6×10^{-5}

[a] In 1.0 N DCl at 25 °C.

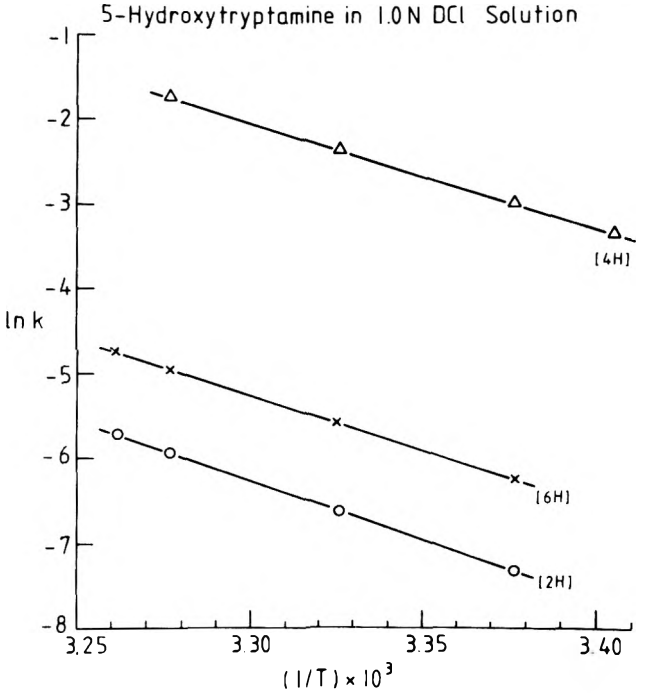

Figure 6. Arrhenius plot of the first-order rate constants of deuterium exchange of 5-hydroxytryptamine.

$Ae^{-\Delta E^{\ddagger}/RT}$ (Table II). It has been observed in these experiments that the first-order rate constants exponentially increase with increasing negative acidity function, $-H_0$,[9-12] of deuterium chloride, yielding the relationship, $k = k_0 e^{-H_0 \chi}$, where χ is a slope giving the value 2.45, and k_0 is the rate constant at the zero acidity function (Figure 5). It has been shown in these experiments that χ is independent of both ring proton species and temperature. The Arrhenius activation energy, $\Delta E^{\ddagger}$, for the deuterium exchange of the indole ring protons also shows a constant value of about 26 kcal/mol (Figure 6 and Table III). The constant values of these two parameters ($\chi = 2.45$ and $\Delta E^{\ddagger} = 26$ kcal/mol) for all species investigated ensure the validity of the temperature-independent Brønsted catalysis law ($\ln k = \alpha + \beta \ln K$),[13-15] where k and K represent the rate constant and equilibrium constant, respectively. Under these two conditions the logarithm of the rate constants then should be proportional to the stability of the ring-protonated aromatic conjugate acids.

Structural analysis shows that the deuterium exchange rate constants correlate with the stability of the resonance structure of the indole ring protonated conjugate acid (Table IV). These observations provide a basis for the validity of the Brønsted catalysis law in the protonation of the indole ring.

Experimental Section

5-Hydroxytryptamine creatine sulfate, 5-hydroxytryptamine bioxalate, 6-hydroxytryptamine creatine sulfate, 5-methyltryptamine, and tryptamine hydrochloride were purchased from Sigma Chemical Co., and used without further purification. Deuterium oxide and deuterium chloride were obtained from ICN Isotope and Nuclear Division. Throughout the experiments, 0.05 M solutions were prepared by dissolving the sample in DCl/D_2O solution of a known concentration, transferred quickly to the NMR tube, and equilibrated for few minutes in thermostated sample holder. When the temperature of measurement is significantly different from the room temperature, the samples were prepared in a water bath of desired temperature.

The 220-MHz NMR spectra were obtained in Fourier transform mode using a Varian HR 220 spectrometer equipped with a variable temperature unit and Nicolet Technology Corp. (NTC) pulse and Fourier transform accessories. A single 90° pulse was used to obtain each spectrum (2500 Hz sweep width and 8192 computer data points). There was sufficient time between successive spectral acquisitions to allow for proton relaxation. Chemical shifts are reported in parts per million (ppm) relative to internal TSP [3-(trimethylsilyl-2,2,3,3,-d_4)propionic acid sodium salt), and peak integrations were determined with the aid of the NTC NMR program. The collected data were analyzed using a simple regressional analysis method.

Acknowledgment. This research was supported by a Grant (MH-17489) from the National Institute of Mental Health. The 220-MHz NMR facilities at the Rockefeller University operated by a consortium are supported by a National Science Foundation Grant (BMS 74-12247).

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Pyridinium *p*-Toluenesulfonate. A Mild and Efficient Catalyst for the Tetrahydropyranylation of Alcohols

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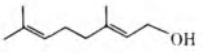
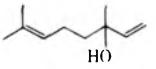
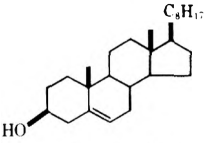
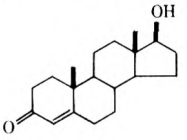
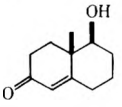
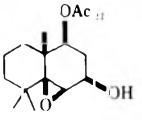
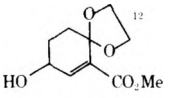
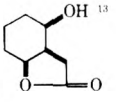
Tetrahydropyranylation of hydroxyl groups has been recognized as the useful and representative method for the protection of alcohols.[2] In addition, it has recently been shown that 2-tetrahydropyranyl (THP) ethers are important pre-

Table I. Tetrahydropyranylation of Alcohols and Hydrolysis of Tetrahydropyranyl Ethers with Pyridinium *p*-Toluenesulfonate

			Tetrahydropyranylation[a]			Hydrolysis of THP ethers[a]	
Registry no.	Entry	Alcohol	Reaction time, h	Isolated yield,[b] %	Registry no.	Reaction time, h	Isolated yield,[b] %
112-53-8	1	$CH_3(CH_2)_{11}OH$	3.5	96	63588-79-4	3	99
108-93-0	2		5.5	97	709-83-1	3.5	96
106-24-1	3		4	99[c]	59632-99-4	3	100
78-70-6	4		5	94	38844-76-7	1.5	99
57-88-5	5		5	97	6252-45-5	4	99
58-22-0	6		5.5	100[d]	516-63-2	3.5	98
878-47-7	7		4.5	99[d]	6252-45-5	3.5	95
52612-30-3	8		3	100[d]	516-63-2	3.5	98
63588-78-3	9		3	97	63588-80-7		
54911-63-6	10					3	100

[a] All of products showed satisfactory microanalytical values and spectral data. [b] Purified by silica gel chromatography unless otherwise stated. [c] Purifield by distillation. [d] Two equivalents of dihydropyran and 0.2 equiv of PPTS were used.

cursors for the synthesis of primary[3] and allylic alcohols,[4] and alkyl halides.[5]

For the tetrahydropyranylation of alcohols, *p*-toluenesulfonic acid is the most common catalyst and seems to be superior to other catalysts[6] such as hydrochloric acid,[2] phosphoryl chloride,[2] and boron trifluoride etherate.[7] Owing to its strong acidity, however, *p*-toluenesulfonic acid is still undesirable for highly acid-sensitive alcohols. We wish to report a much more efficient preparation of THP ethers from alcohols by the use of a new catalyst, pyridinium *p*-toluenesulfonate (PPTS).

Crystalline PPTS can easily be prepared from pyridine and *p*-toluenesulfonic acid monohydrate.[8] It is soluble in methylene chloride, chloroform, ethanol, and acetone, and slightly soluble in benzene but insoluble in ether. The procedure for the tetrahydropyranylation is remarkably simple and mild. The following is illustrative.

A solution of geraniol (154 mg, 1.0 mmol) and dihydropyran (126 mg, 1.5 mmol) in dry methylene chloride (7 mL) containing PPTS (25 mg, 0.1 mmol) is stirred for 4 h at room temperature. Then the solution is diluted with ether and washed once with half-saturated brine to remove the catalyst. After evaporation of the solvent, distillation [bp 140 °C (bath temperature)/10 mmHg] gives an essentially quantitative yield of geraniol THP ether (236 mg, 99%).

The results are summarized in Table I. The excellent yields realized in the present procedure demonstrate this catalyst to be superior to other catalysts. For example, testryl THP ether (entry 6) which was recently prepared in moderate yields using boron trifluoride etherate (67%)[7] or *p*-toluenesulfonic acid (71%)[6] is obtained quantitatively with our catalyst. Furthermore, THP ether of 4aβ-methyl-4,4a,5,6,7,8-hexahydronaphth-5β-ol-2(3*H*)-one (entry 7), which has frequently been used as the useful synthetic intermediate, was previously prepared in the reaction of long duration (2 days) in only 48% yield using hydrochloric acid as the catalyst,[9] while the present procedure affords it in 99% isolated yield after only 4.5 h.

It is noteworthy that PPTS is a weaker acid (pH 3.0 in 1.0 M aqueous solution) than acetic acid (pH 2.4 in 1.0 M aqueous solution). Consequently, our catalyst is mild enough to be used on complex systems containing sensitive polyfunctional groups. Thus, we have encountered no serious difficulty for

the tetrahydropyranylation of alcohols possessing acid-sensitive functional groups such as allylic hydroxyl, ketal, or epoxide (entry 3, 4, 8, and 9). PPTS would also be efficient for the methoxytetrahydropyranylation of alcohols.[6,10]

PPTS is efficient not only for the preparation of THP ethers but also for the deprotection of THP groups. The typical procedure is as follows.

A solution of geraniol THP ether (119 mg, 0.5 mmol) and PPTS (12.6 mg, 0.05 mmol) in ethanol (4 mL) was stirred at 55 °C (bath temperature) for 3 h. The solvent was evaporated in vacuo, and the residue was chromatographed on a silica gel column to afford pure geraniol (77 mg, 100%).

As shown by the results in Table I, the protecting group is quantitatively removed with this catalyst. Owing to its simplicity and mildness, the present procedure provides a highly efficient method for the preparation and deprotection of THP ethers.

Registry No.—PPTS, 24057-28-1; dihydropyran, 110-87-2; *p*-toluenesulfonic acid, 104-15-14; pyridine, 110-86-1.

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Reactivity of Photochemically Excited 3-Acylthiophenes, 3-Acylfurans, and the Formylthiophenes and Furans

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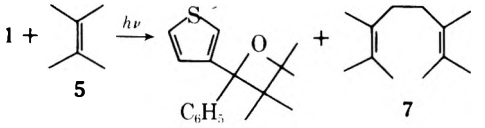
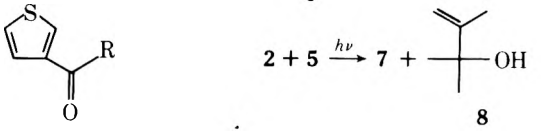
Recently I reported details of the photochemical reactions of 2-acetyl- and 2 benzoylthiophenes and furans with various alkenes.[1] The emission spectra of the four compounds indicated the lowest triplet to be of $\pi \rightarrow \pi^*$ character in each case. Consonant with this observation, the major photoprocess observed for the 2-acetyl derivatives was addition at ring positions, in a 4 + 2 fashion in the case of thiophene, and in the 2 + 2 manner for the furan. Surprisingly, the benzoyl compounds undergo oxetane formation to the complete exclusion of ring addition;[1,2] the reasons for this are not clear.

It has been observed by Arnold and Birtwell[3] that 3-benzoylthiophene and certain para-substituted derivatives thereof exhibit emission spectra indicative of $n \rightarrow \pi^*$ lowest triplet states, in contrast to the $\pi \rightarrow \pi^*$ assignment for the 2-benzoyl compounds. Consequently, a study of the photochemical reactions of 3-furyl and 3-thienyl ketones was deemed worthwhile. Although the behavior of the 3-substituted ketones proved to be relatively unexciting, we present our results here for comparison.

Irradiation of 3-benzoylthiophene (**1**) in the presence of excess 2,3-dimethyl-2-butene (**5**) gave, besides gum and recovered **1**, 28% of oxetane **6**. There was formed also 30% of a

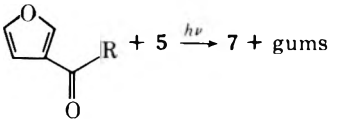




1, R = C_6H_5
2, R = CH_3

mixture of C_{12} hydrocarbons, mainly 2,3,6,7-tetramethylocta-2,6-diene (**7**), as was found in photochemical reactions of benzoic acid and its esters with the same alkene.[1,4,5]

Irradiation of 3-acetylthiophene (**2**) with alkene **5** afforded no oxetane or other cycloadducts, but instead afforded alcohol **8**, 2,3-dimethyl-1-buten-3-ol (17%), pinacol (12%), and 16% of the now familiar C_{12} hydrocarbon mixture. The pinacol most plausibly arises via 2 + 2 cycloreversion of the anticipated (but not observed) oxetane to acetone and an alkene analogous to **12** (vide infra). The acetone undergoes photoreduction of pinacol. The formation of **8** may be the result of either (a) dehydration of some of the pinacol produced, or (b) hydrogen abstraction of photoexcited **2**, followed by reaction of the dimethylbutenyl radical with traces of water in the solvent. Since the solvents employed were spectrograde, stored over molecular sieves, path (b) seems less likely. Since the publication of ref 4 and 5, alcohol **8** has been observed as a



3, R = C_6H_5
4, R = CH_3

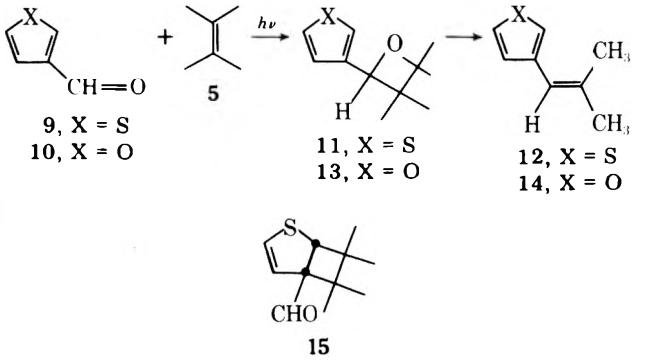
minor product sometimes present in the reaction mixtures from benzoic acid and methyl benzoate with **5**.[4,5]

Irradiation of 3-benzoylfuran (**3**), through uranium glass in the presence of an excess of alkene **5**, resulted only in slow decomposition to translucent gums; the only tractable product isolated was 14% of hydrocarbon **7**.

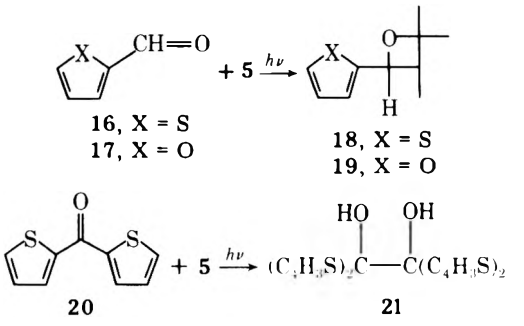
Irradiation through Pyrex of 3-acetylfuran (**4**) with either alkene **5** or furan for 18 h gave only 80% of recovered **4**, and in the experiments with **5**, 17% of hydrocarbon **7** and 11% of alcohol **9**.

The aldehydes 3-formylthiophene (**9**) and 3-formylfuran (**10**) proved to be considerably more reactive than the ketones **1**–**4**. Irradiation of **9** in the presence of excess 2,3-dimethyl-2-butene and separation of the products by GC afforded alkene **12** ($\Phi = 0.11$), the product of 2 + 2 cycloreversion of an initially formed oxetane, **11**, in the reverse sense to that via which it was formed, and also 2 + 2 ring adduct **15** (9%).

Irradiation of **10** under similar conditions, followed by GC purification, led to oxetane **13** as the sole product formed in 54% chemical yield (Φ = 0.12).



This facile addition across the carbonyl group of aldehydes **9** and **10** was in distinct contrast to the ketones **1–4**; consequently the 2-formyl compounds **16** (thiophene-2-aldehyde) and **17** (furfural) were examined. Both aldehydes underwent



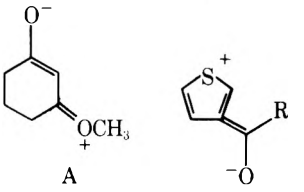
clean oxetane formation with alkene **5** (even to the extent of the products being pure after a simple distillation, obviating the need for GC purification) in high efficiency. Spectral details are given in Table I.

Finally, we include the results with di-2-thienyl ketone (**20**) and di-2-furyl ketone. The thienyl ketone **20** surprisingly gave neither oxetane nor cyclobutane, but instead the pinacol **21**, whereas **22** only decomposed to gums.

Thus the 3-acylthiophenes and 3-acylfurans examined (**1–4**) were found to be far more sluggish in their photochemical reactivity toward alkenes than the 2-acyl heterocycles which we had studied previously.[1] Furthermore, three of the four compounds yielded products derived only from radicals produced by hydrogen abstraction from the substrate alkene. This was surprising, especially for 3-benzoylthiophene, for that is the opposite of the behavior to be expected of an aryl ketone with the lowest lying n,π^* triplet excited state, to which category 1 had been assigned by Arnold and Birtwell.[3] One way of rationalizing the pronounced photochemical inertness of **1–4** may be in considering the similarity of their excited states to those of 2-cyclohexen-1-ones bearing in the 3 position groups capable of electron donation via resonance, such as methoxyl. These compounds, including 3-chloro- and 3-alkoxycyclohexenones, were previously found to be very slow in reacting with alkenes or with solvents containing abstractable hydrogen;[6] cycloadducts were minor products, when formed at all. This difference in behavior was attributed to the effect of the substituent on the electron distribution in the excited state. The nature of the ground state of such enones is perturbed as compared to that of simpler enones because of significant contribution from resonance structures of type A. It seems reasonable that the excited states of both the cyclohexenones and heterocycles **1–4** have considerably less 1,4-diradical character than those of the parent ketones. This effect should cause a reduced reactivity toward hydrogen abstraction or toward bonding to alkenes.

Table I

Oxetane	NMR signals		Mass spectra
13	2.6 (2 H, m) 3.7 (1 H, m, br) 4.7 (1 H, s)	8.56, 8.74, 8.83, 9.13 (3 H each, s)	*m/e* 181, 180 (CI) Base peak at 122 (EI)
18	2.6 (1 H, t, *J* = 2.4) 2.9 (1 H, t) 3.4 (1 H, m) 4.8 (1 H, s)	8.52, 8.71, 8.82, 9.10 (3 H each, s)	*m/e* 197, 196 (CI)
19	2.6 (2 H, t, *J* = 1.6 3.68 (1 H, d, *J* = 1.6) 4.86 (1 H, s)	8.57, 8.64, 8.85, 9.04 (3 H each, s)	*m/e* 181, 180 (CI)



This, however, fails to account for the difference in reactivity of the heterocyclic ketones **1–4** and aldehydes **9–10**. All four of the aldehydes examined underwent efficient oxetane formation with **5** (for **9**, Φ = 0.3 at infinite substrate concentration), whereas the only ketone studied, either in the present report or in ref 1, to react with **5** with $\Phi > 0.02$ is 2-benzoylthiophene. In the carbocyclic series, benzaldehyde, acetophenone, and benzophenone undergo 2 + 2 cycloaddition to alkenes to afford oxetanes, all doing so with fairly high efficiency.[8] The reasons for the differences in the carbocyclic series and the heterocycles are evidently a blend of subtle electronic factors whose nature remains to be determined.

Experimental Section

Irradiations were conducted in an annular apparatus using light from a Hanovia 450-W medium-pressure mercury arc lamp, filtered through Corex (transmits >260 nm), Pyrex (>290 nm), or uranium glass (>330 nm), and cooled by ice water in an immersion well. All photochemical reaction solutions were flushed with argon for 1 h prior to irradiation. NMR spectra were obtained on Varian A-60 and XL-100 instruments. Mass spectra were obtained on a Hitachi Perkin-Elmer Model RMU-6E. Gas chromatography was performed on the following columns: column A, 2 ft × 0.25 in., 10% SE-30 on Chromosorb W; column B, 2 ft × 0.25 in., 15% Carbowax 20M on Chromosorb W; column C, 6 ft × 0.25 in., 10% SE-30; column D, 6 ft × 0.25 in., 15% Carbowax 20M; and column E, 6 ft × 0.375 in., 25% SE-30. Ketones **1–4** were prepared by reaction of the appropriate heterocyclic carboxylic acid with phenyl- or methyllithium.[9]

Photochemical Reaction of 3-Benzoylthiophene with 2,3-Dimethyl-2-butene. A solution of 3-benzoylthiophene (1.5 g) and 2,3-dimethyl-2-butene (20 g) in spectrograde hexane (100 mL) was irradiated in a Rayonet chamber equipped with 3500-Å lamps for 1.5 h. Distillation of the solvent and excess alkene gave a semicrystalline residue which was triturated with pentane at 0–5 °C and filtered. Recrystallization of the solid from ethyl acetate–hexane gave oxetane **6** as off-white prisms, mp 92 °C dec (0.60 g, 27%). Spectral data: IR (KBr) 1080–1005 cm^{-1}; NMR ($CDCl_3$) τ 2.3–2.9 (8 H, m), 8.64, 8.72, 8.89, and 9.02 (all 3 H each, s); *m/e* (chemiionization) 273 (P + 1), 214 (20), 189 (45), 105 (25), 84 (100). Anal. $C_{17}H_{20}OS$: (C, H).

From the mother liquors and triturate there was recovered unchanged **1** (0.38 g) plus a tarry residue.

Photochemical Reaction of 3-Acetylthiophene (2) with 2,3-Dimethyl-2-butene. A solution of 3-acetylthiophene (**2**, 1.0 g) and 2,3-dimethyl-2-butene (20 g) in spectrograde hexane (100 mL) was

irradiated through uranium glass for 30 h. Fractional distillation of the reaction mixture gave, besides 0.33 g of recovered **2**, an oil, bp 36–54 °C (0.8 mm), from which was isolated by GC on column B the following products: 0.070 g of 2,3,6,7-tetramethylocta-2,6-diene (**7**), identical with material isolated in other studies;[1,4] and 0.086 g (17%) of alcohol **8**, 2,3-dimethyl-1-buten-3-ol [IR (film) 3580 cm^{-1}; NMR (CCl_4) τ 5.2 (2 H, s, br), 8.02 (1 H, s, br), 8.3 (3 H, s, br), 8.56 (6 H, s); Anal. $C_6H_{12}O$ (C, H)].

Irradiation of 3-Benzoylfuran and 3-Acetylfuran with Alkene 5. Irradiation of hexane solutions of 3-benzoylfuran (**3**)[9] with excess alkene **5** through uranium glass filters for up to 40 h gave yellow solutions from which 10–20% of diene **7** could be isolated by vacuum distillation. Chromatography of the residue on silica gel gave only ~30% of recovered 3 and high molecular weight material.

From similar experiments with **4**, using a Pyrex filter, there was isolated ~70% of recovered ketone, together with 17% of **7**, 11% of **8**, and small amounts of tarry residue.

Photolysis of 3-Formylthiophene (9) with 2,3-Dimethyl-2-Butene. Irradiation of **9** (1.4 g, 0.012 mol) with alkene **5** (20 g) in spectrograde hexane through Pyrex for 2.5 h led to complete consumption of aldehyde. Workup as described above for **2** led to the isolation of (a) alkene **12** (retention time on column B at 110°, 5.8 min.) in 46% yield [IR (film) 1080 cm^{-1}; NMR τ 2.7–3.1 (3 H, m), 3.7 (1 H, m, br), 8.0 (6 H, s, br); mass spectrum (CI) *m/e* 138 (P, 100), 133 (72), 121 (67); Anal. $C_8H_{10}S$ (C, H)], and (b) 2 + 2 ring adduct **15** (retention time 16 min) [IR (film) 1720 cm^{-1}; NMR τ 3.7 (1 H, m), 3.9 (2 H, m, br), 6.8 (1 H, s), 8.45, 8.69, 8.80, and 8.82 (3 H each, s); mass spectrum *m/e* 196 (P, 7), 181 (19), 112 (47), 84 (100); Anal. $C_{11}H_{16}OS$ (C, H)].

The photochemical reactions of aldehydes **10**, **16**, and **17** with **5** were conducted in the same manner. Spectral data on the products are given in Table I.

Photochemical Reaction of Di-2-thienyl Ketone with 2,3-Dimethyl-2-butene. A solution of ketone **20** (1.0 g) and alkene **5** (20 g) in spectrograde hexane was irradiated through a uranium glass filter for 6 h. Evaporation of solvent and excess alkene gave a yellow residue which, on trituration with 3:1 hexane–benzene, partially crystallized. Recrystallization of the solid from benzene–hexane gave 0.56 g of white prisms: mp 127–128 °C; IR (KBr) 3500 cm^{-1}; NMR ($CDCl_3$) τ 2.6–3.2 (12 H, m), 6.49 (2 H, s, br); mass spectrum *m/e* 310 (P, CI). Anal. $C_{18}H_{14}O_2S_4$ (C, H).

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Registry No.—**1**, 6453-99-2; **2**, 1468-83-3; **3**, 6453-98-1; **4**, 14313-09-8; **5**, 563-79-1; **6**, 63466-41-1; **7**, 18495-18-6; **8**, 10473-13-9; **9**, 498-62-4; **10**, 498-60-2; **12**, 63466-42-2; **13**, 63466-43-3; **15**, 63466-44-4; **16**, 98-03-3; **17**, 98-01-1; **18**, 63466-45-5; **19**, 63466-46-6; **20**, 704-38-1; **21**, 51248-22-7.

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Deuterium or Tritium Labeling by Ionic Hydrogenation. A Convenient Route to Specifically Labeled Dethiobiotin

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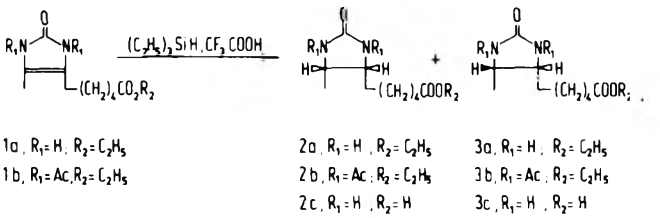
In connection with our investigation of the biosynthetic conversion of dethiobiotin to biotin, we had to synthesize specifically C-3 and/or C-4 deuterated and tritiated *cis*-dethiobiotin.[1] One convenient route was the reduction of the unsaturated precursor 4-methyl-5-(ω-carboethoxyamyl)-2-imidazolone (**1a**).[2] After a thorough investigation we found that ionic hydrogenation was the only efficient noncatalytic method to reduce the carbon–carbon double bond of the imidazolone ring.[3]

Scheme I



1a, R_1 = H, R_2 = C_2H_5
1b, R_1 = Ac, R_2 = C_2H_5
2a, R_1 = H, R_2 = C_2H_5
2b, R_1 = Ac, R_2 = C_2H_5
2c, R_1 = H, R_2 = H
3a, R_1 = H, R_2 = C_2H_5
3b, R_1 = Ac, R_2 = C_2H_5
3c, R_1 = H, R_2 = H

This paper reports our study of the scope of this reduction and observations regarding the stereoselectivity of the reaction and regioselectivity of the labeling with deuterated silanes.

We also explore the possibility of using the different combinations of hydrogenating pairs CF_3COOH, CF_3COOD, R_3SiH, and R_3SiD to invert the labeling regioselectivity or to prepare dideuterated compounds. The corresponding tritiated compound has been obtained with Et_3Si^3H. Reductions with Et_3Si^3H which have not yet been performed appear of general interest for specific tritiation of organic molecules.

Results and Discussion

Stereoselectivity. Since our goal was to obtain *cis*-dethiobiotin, we investigated the factors which might influence the course of hydrogenation and lead to the desired isomer (Table I).

1a treated with 1 equiv of Et_3SiH or Et_3SiD in CF_3COOH at 50 °C afforded in 70% yield a 1/1 mixture of *cis*- and *trans*-(*dl*) dethiobiotin ethyl ester (**2a** and **3a**) (run 1, see also Scheme I).

These isomers have been separated by TLC as *N*-diacetyl derivatives **2b** and **3b**. The cis isomer **2b** has been identified after treatment with sodium hydroxide by comparison with an authentic sample of dethiobiotin obtained by Raney nickel desulfuration of biotin.[4] The structure of the trans isomer **3b** was based on NMR and mass spectral data (see Experimental Section).[5] We also carried out, with the same hydrogenating pair, the reduction of the *N,N'*-diacetyl derivative **1b** (run 2), the double bond of which is more reactive because of the dearomatization of the imidazolone ring.[6] In this case, we observed an important variation of the stereoselectivity with a high predominance of the cis isomer (cis/trans: 95/5). The same variation in isomer ratio is observed for reductions of 3,4-dimethyl-2-imidazolone (**4a**) and its *N,N'*-diacetyl derivative **4b** (runs 6, 7).

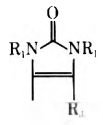
On the other hand, the variation of steric bulk of the different hydride donors tested, Et_3SiD, Ph_3SiD, Ph_2SiD_2, and Ph_3GeD, does not lead to significant variations (runs 2–5).

Since examination of molecular models shows that the acetyl groups in **1b** and **4b** do not increase significantly, with respect to **1a** and **4a**, the steric discrimination between the two faces of the imidazolone ring, our results clearly show that steric interaction between the intermediate carbenium ion and hydride donor is not the major factor governing the stereochemistry of ionic hydrogenation as previously claimed.[7a,8]

Regioselectivity. In order to select the best conditions for specific incorporation of deuterium at C-3 and/or C-4, we carried out reduction of **1a** and **1b** using hydride donors of different donating ability and steric bulk.[7a,9]

Some results are listed in Table II. In runs 1–4 the isolated dethiobiotin has incorporated, as expected, only one deuterium atom (mass spectrometry determination). There is al-

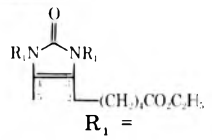
Table I. Stereoselectivity of the Reduction of the Double Bond of 2-Imidazolone Derivatives by Ionic Hydrogenation



Run no.	R_1	R_3	Registry no.	Hydride donor	Time, h	Temp, °C	% yield[c]	% cis[d]
1	H	$(CH_2)_5COOEt$	63466-47-7	Et_3SiH or Et_3SiD[a]	20	50	70	50
2	Ac	$(CH_2)_5COOEt$	27051-51-0	Et_3SiH or Et_3SiD[a]	60	25	70	95
3	Ac	$(CH_2)_5COOEt$		Ph_3SiD[b]	60	25	30	96
4	Ac	$(CH_2)_5COOEt$		Ph_2SiD_2[b]	60	25	23	94
5	Ac	$(CH_2)_5COOEt$		Ph_3GeD[b]	20	25	27	98
6	H	CH_3	1072-89-5	Et_3SiH[a]	20	50	65	50
7	Ac	CH_3	21265-71-4	Et_3SiH[a]	20	25	78	92

[a] Solvent CF_3COOH. [b] Solvent CF_3COOH + CH_2Cl_2, added for homogeneity. [c] Total yield cis + trans. [d] Accuracy on % cis isomer (determined by GLC, cf. Experimental Section) was evaluated to 1%. The reproducibility of these data, within these limits, was checked over several experiments.

Table II. Deuterium Incorporation in Dethiobiotin Obtained by Ionic Hydrogenation of 4-Methyl-5-(ω-carboethoxyamyl)-2-imidazolone



Run no.	R_1 =	Hydrogenating pair[a]	No. of D atoms on the indicated carbon[b] C-3	C-4	C-2	C-5
1	H	Et_3SiD/CF_3COOH	0.30	0.70	0	0
2	Ac	Et_3SiD/CF_3COOH	0.15	0.85	0	0
3	Ac	Ph_3SiD/CF_3COOH	0.24	0.76	0	0
4	Ac	Ph_2SiD_2/CF_3COOH	0.07	0.93	0	0
5	Ac	Ph_3GeD/CF_3COOD	0.96	0.96	0.6	1.2
8	Ac	Et_3SiH/CF_3COOD	0.79	0.10	1.2	2.1
9	H	Et_3SiD/CF_3COOD	0.96	0.96	0.8	1.9
10	Ac	Et_3SiD/CF_3COOD	0.96	0.96	0.9	1.8

[a] The experimental conditions are the same as those used for the corresponding runs listed Table I. [b] Using a strip chart recorder at low speed, we evaluated the accuracy of deuterium incorporation to 1% at C-3 and C-4 for runs 1—4. The reproducibility of these data, within these limits, was checked for runs 1 and 2 over several experiments.

ways a large predominance of the C-4 deuterated product. The regioselectivity is sensitive to the nature of the substrate (runs 1, 2) and also to the nature of silane (runs 2–4); it reaches 93% for the reduction of **1b** with Ph_2SiD_2.

It was attractive to prepare dideuterated compounds with R_3SiD in CF_3COOD or to invert the regioselectivity of the labeling with R_3SiH/CF_3COOD instead of R_3SiD/CF_3COOH. The use of deuterated solvent for this purpose has been suggested, but it has never been investigated.[7b] In CF_3COOD one cannot ignore the risk of further deuterium incorporation through olefin formation by loss of a proton α to the carbenium ion, the importance of such a competing process depending on its relative rate with respect to the trapping rate of carbenium ion by hydride donor. We carried out some experiments in CF_3COOD to ascertain this point.

Reduction of **1b** with Et_3SiH/CF_3COOD (run 8) inverts effectively the deuterium incorporation at C-3 and C-4, but unfortunately there is a fairly large deuterium incorporation at C-2 and C-5.[10]

However, this process is greatly minimized when a more reactive hydride donor like Ph_3GeD is used (run 5). This suggests that it should be possible to block this undesired reaction in some favorable cases.

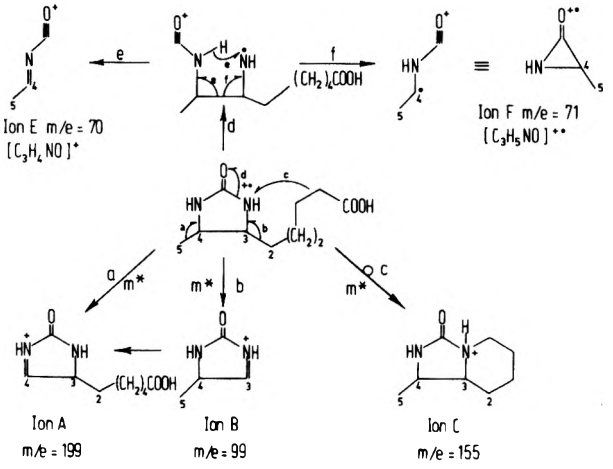
Synthesis of Tritiated Dethiobiotin. The experimental conditions described above (run 2, Tables I and II), which lead, in satisfactory yield and with excellent reproducibility, to a highly stereoselective and regioselective deuteration of **1b**, were selected to carry out the synthesis of (±)-dethiobiotin specifically tritiated at C-3 and C-4, using Et_3Si^3H prepared by LiB^3H_4 reduction of Et_3SiCl.

Since the primary kinetic isotope effect k_H/k_D measured for carbenium ion–silane hydride and deuteride transfer reaction are small,[11] we assume the same distribution of the label in deuterated and tritiated dethiobiotin prepared in the same conditions.

The use of tritiated organosilicon compounds has not yet been explored. Our finding that Et_3Si^3H of high specific activity can be readily prepared opens a valuable route for tritiation via ionic hydrogenation of olefins or more generally in carbenium ion hydride transfer reactions.

Deuterium Localization by Mass Spectrometry. Different fragmentations are found at high and low ionizing voltage. Relying on structural variation in the side chain and on deuterium labeling we could analyze the structure of the different ions and find out consistent fragmentation patterns which permit accurate localization of deuterium (Scheme II). The possibility of isotope scrambling was also ruled out by these experiments.[12] The most intense peaks in the mass spectrum of dethiobiotin at 70 eV are *m/e* 199, 155, 99. Fragmentation of the imidazolidone ring does not occur at 70 eV, but it becomes significant at low ionization potential and gives peaks at *m/e* 71 and 70 at 11 eV (ratio 9/1), the elemental composition of which was determined by high-resolution mass measurements. The molecular peak ($M^{+\cdot}$) at *m/e* 214 is not abundant and is always accompanied by peak (MH^+) at *m/e* 215 (due to chemical ionization in the source). Consequently this peak must be rejected for measuring the total deuterium content. But the ion C, in which hydrogen (or deuterium) atoms are kept intact at positions 2, 3, 4, and 5, can be used advantageously for this determination. For runs 1–4 deuterium content at C-3 and C-4 can be easily deduced from direct measurement of the peak intensities corresponding to ions C,

Scheme II



E, and F. When labeling occurs at C-2, C-3, C-4, and C-5 positions (runs 5–8), deuterium content at C-2 and C-5 is deduced from the relative heights of the peak due to ions A, B, C, E, and F.

Experimental Section

NMR spectra were recorded on a Varian HA 100 spectrometer in D_2O and chemical shifts are reported in parts per million (δ) from external HMDS. The gas chromatograph used was a GIRDEL 3000 unit. The mass spectra were obtained using a ATLAS CH_5 mass spectrometer (source at 210 °C). Scintillation counting was carried out with a Intertechnique SL_{30} spectrometer in Bray's liquor. All the results were corrected for quenching by external standard method.

Material. LiB^3H_4 (1 Ci/mmol) was obtained from C.E.A. Saclay France. All the deuterated silanes and germanes used in this study were prepared by $LiAlH_4$ reduction of the corresponding chloro compounds according to known methods.[13] No ≡SiH or ≡GeH could be detected by NMR.

The 4-methyl-5-(ω-carboethoxyamyl)-2-imidazolone (**1a**) and *N,N'*-diacetyl-4-methyl-5-(ω-carboethoxyamyl)-2-imidazolone (**1b**) were prepared in good yield according to Duschinky and Dolan.[2]

Preparation of Labeled Dethiobiotins. A typical reduction experiment was performed as follows.

Reduction of 4-Methyl-5-(ω-carboethoxyamyl)-2-imidazolone. To a mixture of 360 mg (1.5×10^{-3} mol) of **1a** in 1 mL of CF_3COOH, 180 mg (1.5×10^{-3} mol) of Et_3SiH is added gradually. The mixture is kept at 50 °C under shaking. The reduction progress is followed by NMR (disappearance of the $C(5)H_3$—C(4)= signal, singlet at δ 1.95/Me_4Si). The reduction is completed after 20 h. The excess of CF_3COOH and $Et_3SiOOCCF_3$ which has been produced is removed in vacuo. The crude material is then acetylated by two short refluxings with 5 mL of acetic anhydride, the excess of which is distilled off.

The cis/trans ratio **2b/3b** is determined on the crude acetylated mixture by GLC (SE 30 10% on Chromosorb G, WHMDS), **2b/3b** = 1/1. The preparative separation of **2b** and **3b** is performed by silica gel TLC (eluent: ethyl acetate–chloroform, 2/8).

After separation of **2b** and **3b**, saponification of each isomer with 1 N sodium hydroxide (20 °C, 2 h) afforded the corresponding dethiobiotins **2c** and **3c**.

Purification of **2c** and **3c** is carried out on a Dowex AG 50 WX_2 formate column. Dethiobiotin is eluted with 0.05 M formic acid. Total yield (**2c** + **3c**) = 70%: **2c**, mp 159 °C (lit. mp 159 °C);[4] **3c**, mp 156 °C.

The structures of **2c** and **3c** are determined by NMR and mass spectrometry. **2c:** NMR δ 1.44 (3 H, d, J = 6 Hz, CH_3CH), 4.11 (2 H, m, H_3, H_4), 2.45 (2 H, t, J = 7 Hz, $-CH_2COOH$); mass spectrum *m/e* 214 (M^+), 199, 155, 99. **3c:** NMR δ 1.54 (3 H, d, J = 5, 7 Hz, CH_3CH), 3.76 (2 H, m, H_3, H_4), 2.45 (3 H, t, J = 7 Hz, $-CH_2COOH$); mass spectrum *m/e* 214 (M^+), 199, 155, 99.

When the reduction is carried out with Et_3SiD in CF_3COOH, the deuterium distribution at C-4, and consequently at C-3, can be deduced from the integration of the signals: δ 1.43 (3 H, s, CH_3CD) and 1.44 (3 H, d, J = 6 Hz, CH_3CH). However, a better accuracy is obtained by mass spectroscopy.

[^{3}H]Triethylsilane. LiB^3H_4 (88 mg, 4×10^{-3} mol, 1 Ci/mmol) was allowed to react with Et_3SiCl (0.6 g, 4×10^{-3} mol) in 4 mL of dry triglyme under nitrogen at 50 °C. Et_3Si^3H was distilled and trapped at −70 °C in vacuo. Its chemical purity was controlled by GLC (SE 30 20% on Chromosorb Z): yield, 98%, 470 mg; 0.2 Ci/mmol.

Tritiated Dethiobiotin. Et_3Si^3H, prepared as described, was transferred into a flask containing 242 mg (0.75×10^{-3} mol) of *N,N'*-diacetyl-4-methyl-5-(ω-carboethoxyamyl)-2-imidazolone in 2 mL of CF_3COOH (freshly distilled on H_2SO_4). After 60 h at room temperature, excess Et_3Si^3H, CF_3COOH, and $Et_3SiOOCCF_3$ produced were removed in vacuo. Saponification and deacetylation of the crude residue with 1 N sodium hydroxide at 20 °C during 2 h afforded dethiobiotin. The pH of the solution was adjusted to 8 and then the solution was taken on to a Dowex AG 50 WX_2 formate column for purification. Dethiobiotin eluted with 0.05 M formic acid was obtained in 75% yield: 120 mg; mp 159 °C (198 mCi/mmol). The structure and purity were controlled by mass spectrometry and radiochromatography.

Acknowledgments. We are indebted to Dr. Pichat for helpful advice and for allowing one of us (G.G) to prepare (±)-[^{3}H]dethiobiotin in his laboratory (Service des Molecules Marquees, C.E.A. Saclay).

Registry No.—**2a**, 63526-69-2; **2a** C-3 deuterated derivative, 63466-48-8; **2a** C-4 deuterated derivative, 63466-49-9; **2a** deuterated derivative, 63466-50-2; **2b**, 63466-51-3; **2b** C-3 deuterated derivative, 63466-52-4; **2b** C-4 deuterated derivative, 63466-53-5; **2b** deuterated derivative, 63466-54-6; **2b** C-3 tritiated derivative, 63466-55-7; **2b** C-4 tritiated derivative, 63466-56-8; **2c**, 636-20-4; **3a**, 63526-70-5; **3a** C-3 deuterated derivative, 63466-57-9; **3a** C-4 deuterated derivative, 63466-58-0; **3a** deuterated derivative, 63466-59-1; **3b**, 63466-60-4; **3b** C-3 deuterated derivative, 63466-61-5; **3b** C-4 deuterated derivative, 63466-62-6; **3b** deuterated derivative, 63466-63-7; **3b** C-3 tritiated derivative, 63466-64-8; **3b** C-4 tritiated derivative, 63466-65-9; **3c**, 34879-36-2; Et_3SiT, 63466-66-0; LiB^3H_4, 23683-78-5; Et_3SiCl, 994-30-9; Et_3SiD, 1631-33-0; Ph_3SiD, 18536-60-2; Ph_2SiD_2, 17950-94-6; Ph_3GeD, 2816-42-4; Et_3SiH, 617-86-7; *cis*-3,4-dimethyl-2-imidazolinone, 63466-67-1; *trans*-3,4-dimethyl-2-imidazolinone, 63466-68-2; *cis*-3,4-dimethyl-*N,N'*-diacetylimidazolin-2-one, 63466-69-3; *trans*-3,4-dimethyl-*N,N'*-diacetylimidzolin-2-one, 63466-70-6.

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Nucleophilic Substitution with Inversion of Alcohol Configuration with the Reagent Complex Triphenylphosphine–Diethyl Azodicarboxylate–Carboxylic Acid. A Convenient Preparation of Epicholesterol

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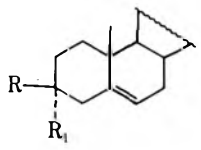
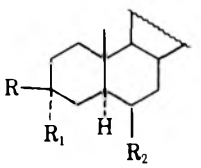
Several methods have been reported recently for preparing epicholesterol (**1**) from cholesterol (**2**) in fair to good yield.[1,2]

A procedure is described here which is amenable to large-scale synthesis of pure epicholesterol without contamination by cholesterol and it is of good yield.

The reagent complex triphenylphosphine–diethyl azodicarboxylate–carboxylic acid (Bose reagent)[3] is an excellent system for inverting the alcohol configuration in unhindered molecules.[3-5] However, although the initial report by Bose et al.[3] stated that cholesterol (2) was readily converted to its epimeric benzoate (3), product mixtures were obtained on





	R	R_1		R	R_1	R_2
(1)	H	OH	(4)	OH	H	OH
(2)	OH	H	(5)	H	$PhCO_2$	OH
(3)	H	$PhCO_2$	(6)	H	$PhCO_2$	CH_3SO_3
(7)	$PhCO_2$	H				

repeating the reaction and these contained only a small amount of the required epimer **3**.[6] Since homoallylic participation of the double bond of the reacting substrate **2** interfered with the required reaction pathway, a different preparative route for **3** was successfully attempted. The starting material was 5α-cholestane-3β,6β-diol (**4**), available in 72% yield from cholesteryl acetate via a facile three-step synthesis involving hydroboration, Jones oxidation of the resulting mixture of 6α- and 6β-alcohols to the 3,6-dione and its $NaBH_4$ reduction.[7] The Bose reagent using benzoic acid as the carboxylic acid reacted selectively with the equatorial 3β-hydroxyl group of **4** resulting in an 88% conversion to 3α-benzoyloxy-5α-cholestan-6β-ol (**5**). Mesylation of the 6β-hydroxyl group of **5** gave **6** accompanied by some of the required elimination product **3**. The pure 6β-mesylate **6** on treatment with Li_2CO_3 in DMF gave epicholesteryl benzoate (**3**) in 84% yield. Finally, alkaline hydrolysis of **3** generated a 90% yield of epicholesterol (**1**). The overall yield from the diol **4** was 67% when all intermediates were isolated and purified. Since impure fractions and mother liquors were not worked up for further material, the yield could be made substantially higher if this was pursued, especially since all the steps were fairly clean, and crude material could be taken right through the sequence, thus requiring only a final purification.

The melting points and optical rotations of the two cholesterol epimers **1** and **2** are very similar (mp 142–143 and 148–149 °C, respectively; $[\alpha]_D$ −42° and −39°, respectively) so that these two criteria of identity and purity cannot be used in this instance. However, the corresponding benzoates **3** and **7** are readily distinguished (mp 99–100 and 143–150 °C, respectively; $[\alpha]_D$ −29° and −15°, respectively). Furthermore, differentiation by the NMR spectrum of the benzoates is the method of choice, since the H-3α signal of **7** follows the pattern of axial proton signals by appearing upfield of the H-3β signal of **3** by 0.42 ppm, and the olefinic proton at C-6 becomes shielded by 0.15 ppm when the benzoate group is in the 3α orientation (see Experimental Section for values) so that any impurity of one isomer in the other can be detected readily on a semiquantitative basis. The free alcohols **1** and **2** can also be distinguished by their NMR spectra as the H-3 resonances are separated by 0.49 ppm, although the olefinic proton at C-6 absorbs in practically the same region for both compounds.

The above inversion reaction was carried out successfully on cholesteryl α-epoxide, but failed with 5α,6β-dibromo-5α-cholestane, since the triphenylphosphine reacted with the halogen substituents giving complex mixtures of products.

Experimental Section

General. All melting points were determined on a Kofler hot stage and are uncorrected. NMR spectra were recorded in $CDCl_3$ solution with Me_4Si as an internal standard on a Varian T60 and Varian HA100 spectrometer. Silica gel for column chromatography was Merck grade 7734. All crystalline compounds gave satisfactory analytical data.

3α-Benzoyloxy-5α-cholestan-6β-ol (5). To a stirred solution of the diol **4**[7] (2.00 g, 4.95 mmol), PPh_3 (2.59 g, 9.90 mmol), and benzoic acid (1.21 g, 9.90 mmol) in dry THF (30 mL) under argon at room temperature (rt) was added dropwise a solution of diethyl azodicarboxylate in dry THF (1.72 g, 9.90 mmol in 10 mL) over a 5-min period. TLC (15% ethyl acetate in benzene) indicated almost complete reaction of the diol **4** after 10 min. After 15 h, the solvent was removed under vacuum, and the residue was partially dissolved in a mixture of ethyl acetate and benzene (15:85, respectively), when the insoluble, crystalline material $C_2H_5O_2CNHNHCO_2C_2H_5$, mp 132–134 °C (lit.[8] 135 °C), was filtered off and the filtrate chromatographed on silica gel using the same solvent mixture as above. Compound **5** was eluted (pure by TLC) as an oil, 2.23 g, which could not be induced to crystallize.

6β-Mesylate (6). To a solution of the above product **5** (2.22 g) in dry pyridine (15 mL) was added CH_3SO_2Cl (4 g) at −5 °C. The mixture was left at 5 °C overnight before it was worked up with water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed once with dilute HCl followed by twice with water, then dried, and evaporated leaving a gum consisting of a mixture of two compounds. Chromatography on silica gel with benzene followed by 5% ethyl acetate in benzene gave pure epicholesteryl benzoate (**3**), mp 100–102 °C (yield 0.862 g), followed by a combined fraction containing both **3** and **6** as 1.255 g of oil.

Epicholesteryl Benzoate (3). The oil containing both **3** and **6** (1.255 g) was dissolved in dry DMF (15 mL) and heated under argon with Li_2CO_3 (2.0 g) at 110 °C for 1.5 h. The cooled reaction mixture was poured into a slurry of ice in dilute HCl and extracted twice with ethyl acetate. The combined organic phases were washed once with water, once with saturated $NaHCO_3$ solution, and finally four times with water before drying. The oil obtained on evaporation was essentially **3** but contained small quantities of polar material (TLC). This oil was chromatographed with hexane–benzene (1:1 mixture) giving first a compound (0.008 g) which was tentatively identified as 5α-cholest-6-enyl 3α-benzoate (M^+ 490), followed by epicholesteryl benzoate (**3**) (0.933 g) which was crystallized from THF–methanol: mp 101–103 °C (lit.[9] 99.5 °C); NMR δ 5.26 (2 H, m, $W_{1/2}$ = 16 Hz, H-3β and H-6), *compare* cholesteryl benzoate (**7**) δ 4.84 (1 H, m, $W_{1/2}$ = 20 Hz, H-3α), 5.41 (1 H, *m*, $W_{1/2}$ = 9 Hz, H-6).

Epicholesterol (1). A solution of the benzoate (**3**) (0.955 g) and KOH (1.0 g) in methanol (50 mL) and THF (2 mL) was refluxed for 3 h when TLC indicated complete hydrolysis of the ester. The reaction mixture was cooled, poured into dilute HCl and twice extracted with ethyl acetate, and the extract was washed with water. Drying and evaporation of the organic phase left a solid which was crystallized from acetone as leaflets (0.672 g): mp 140–142 °C (lit.[10] 142–143 °C); NMR δ 4.02 (1 H, m, $W_{1/2}$ = 8 Hz, H-3β), 5.43 (1 H, m, $W_{1/2}$ = 9 Hz, H-6).

Registry No.—**1**, 474-77-1; **3**, 42921-42-6; **4**, 570-85-4; **5**, 63528-70-1; **6**, 63528-71-2; **7**, 604-32-0; triphenylphosphine, 603-35-0; diethyl azodicarboxylate, 4114-28-7; benzoic acid, 65-85-0; 5α-cholest-6-enyl 3α-benzoate, 63528-72-3.

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An Efficient Synthetic Route to a Lactone Model for the Gibberellin A Ring[1]

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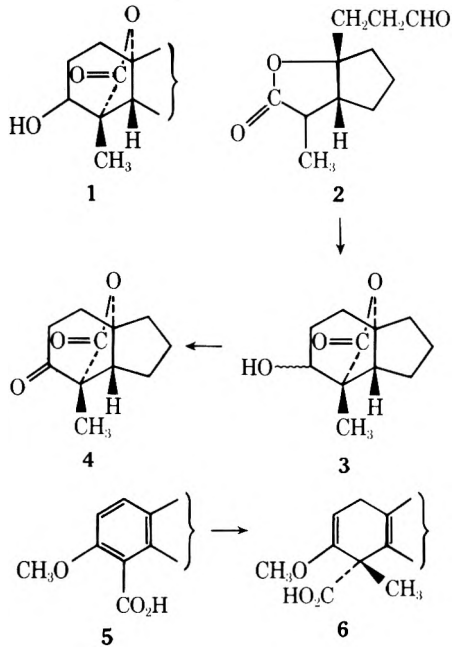
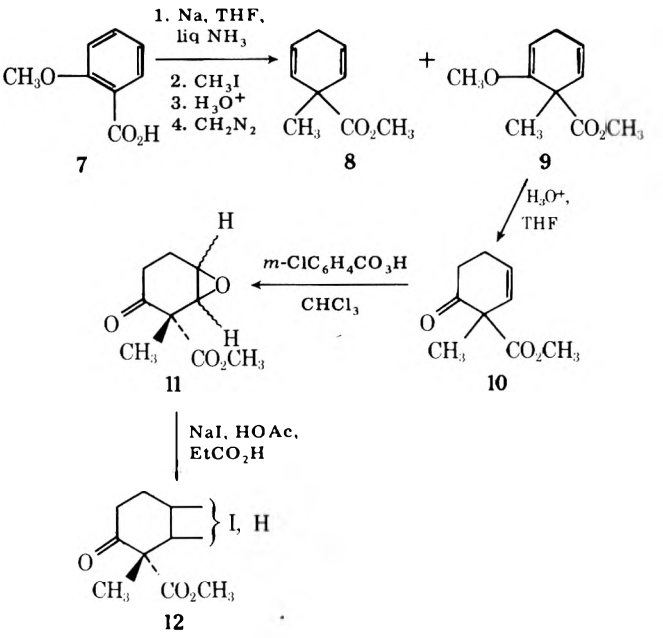
Several reaction sequences have been explored[2] as synthetic routes to the lactone system 1 (Scheme I) present in the A ring of the natural gibberellins. Certain of the synthetic routes were directed toward gibberellins (e.g., gibberellins A_1, A_2, A_4, and A_9) with a saturated A ring (cf. structure 1), while other syntheses offered the possibility of producing gibberellins (e.g., gibberellic acid and gibberellin A_7) in which the A ring contained an additional carbon–carbon double bond. These routes include the acid-catalyzed cyclization of appropriate cyclohexenecarboxylic acid derivatives,[2a–d] the reaction of the unsaturated acids with a peracid,[2e,f] the iodolactonization of the unsaturated acids,[2c,f] and an aldol condensation of the aldehyde lactone 2 to the hydroxy lactones 3, followed by oxidation to the keto lactone 4.[2g] We were particularly interested in developing a route to the lactone system 1 from the cyclohexadiene intermediate 6 because of our finding[3] that this cyclohexadiene system 6 with the correct stereochemistry could be formed by application of the Lowenthal reduction–methylation procedure[2c] to an aromatic acid 5 with an appropriately located carboxyl function in ring B.

We initially examined the possible formation of a lactone from the keto ester 10, derived from the aromatic acid 7 via the cyclohexadiene derivative 9 (Scheme II). Treatment of the keto ester 10 with aqueous mineral acid resulted either in no reaction or in hydrolysis of the ester and subsequent decarboxylation with no evidence for lactone formation. Reaction with *m*-chloroperbenzoic acid converted the keto ester 10 to a separable mixture of comparable amounts of the two stereoisomeric epoxides 11. Each of the epoxides 11 reacted with iodide ion in acidic solution to form a single iodohydrin 12 of uncertain structure. However, we were unsuccessful in finding conditions that would convert either epoxide 11 or iodohydrin 12 to a lactone. Consequently, we turned our attention to halolactonization reactions with unsaturated acids.

Scheme I



Scheme II

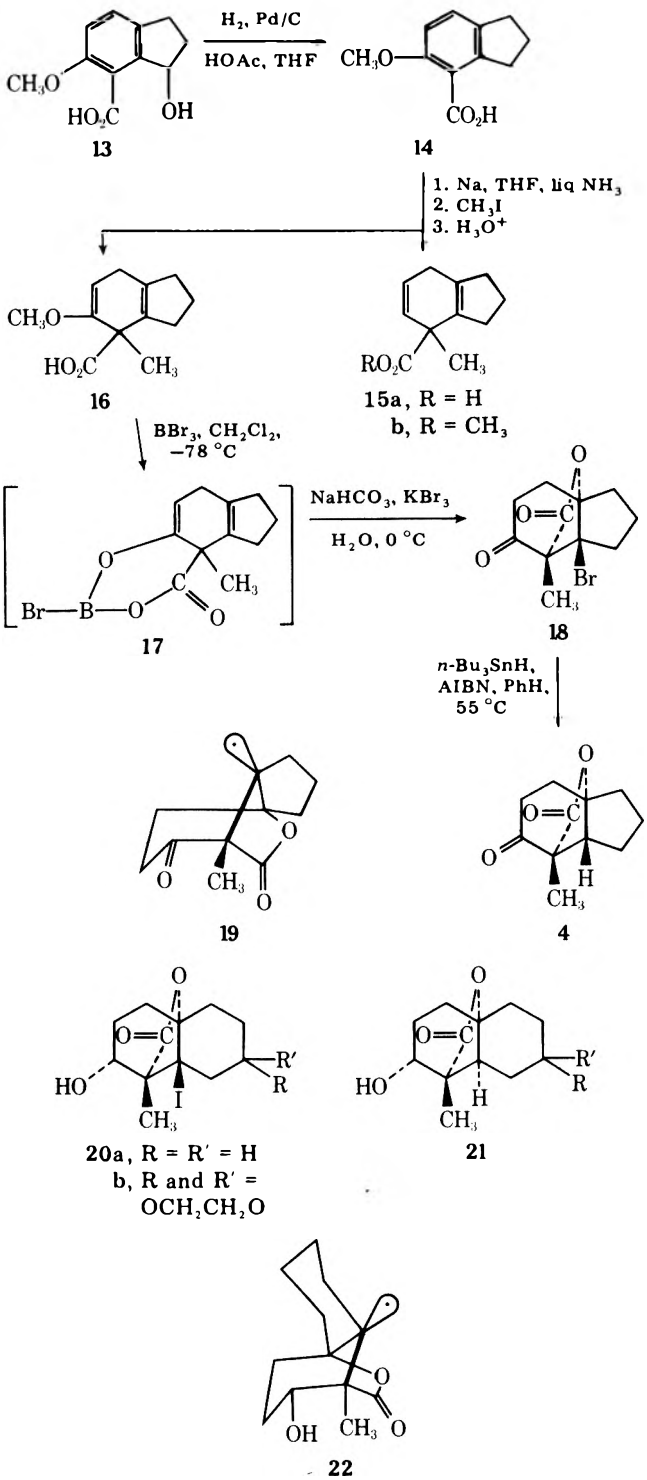


For this study, we employed the unsaturated acid 16 that was prepared from the aromatic acid 14, as indicated in Scheme III. As noted previously,[3] the yield of the demethoxylated by-product 15 was increased when the reduction–methylation sequence was performed with Li rather than Na as the reducing agent. Our attempts to hydrolyze the enol ether acid 16 to the corresponding β-keto acid with aqueous acid were complicated by the fact that the temperature required to hydrolyze the enol ether function in 16 was sufficient to cause decarboxylation of the β-keto acid product. This problem was overcome by reaction of the enol ether 16 with 2–3 molar equiv of BBr_3 in CH_2Cl_2 at −78 °C. The initial product (presumably an enol borate such as 17) was stable under these conditions and could be dissolved in cold aqueous $NaHCO_3$ and KBr_3 to form the salt of the β-keto acid and effect its bromolactonization to the keto lactone 18. Reduction of this bromo keto lactone 18 with *n*-Bu_3SnH yielded the same keto lactone 4 that had been prepared previously.[2g,4]

The reduction of the bromide 18 to form a single stereoisomer of the lactone 4 would at first appear surprising, since a free-radical intermediate (e.g., 19) is involved in this reduction.[5] However, examination of molecular models revealed that the indicated conformation 19 of the free-radical intermediate (the precursor for lactone 4) with the two five-membered rings cis fused is clearly more stable than the alternative conformation with the five-membered rings trans fused. By contrast, in an earlier study[2c] of reduction of the iodolactones 20 by methods [Cr(II) + EtSH, *n*-Bu_3SnH] involving a free-radical intermediate (e.g., 22) either a mixture of stereoisomeric lactones (21 and its epimer) or the lactone 21 with the undesired cis fusion of the two carbocyclic rings was obtained. Examination of molecular models of the radical intermediate in this case (which does not involve two fused five-membered rings) revealed little difference between conformer 22 (the precursor of lactone 21) and the related conformer that would yield a trans-fused decalin system.

As a result of these studies and the related study of the reduction–methylation stereochemistry,[3] we believe that sequence reduction–methylation (e.g., 14 → 16), cleavage and bromolactonization (16 → 17 → 18), and *n*-Bu_3SnH reduction (18 → 4) offers a viable synthetic pathway from a precursor with an aromatic A ring to a product with the functionality and stereochemistry present in the A ring of certain of the natural gibberellins.

Scheme III



Experimental Section[6]

Preparation of the Keto Ester 10. Following a previously described[3] procedure, a solution of 30.9 g (0.204 mol) of acid **7** in 125 mL of THF was added to 900 mL of cold (ca. −78 °C) liquid NH_3. The resulting suspension was allowed to warm to −33 °C and 14.7 g (0.64 g-atom) of Na was added, portionwise and with stirring. While the resulting blue solution was maintained at −33 °C, 92 g (0.64 mol) of MeI was added, dropwise with stirring and cooling, causing the reaction solution to change from blue to red to colorless. After the NH_3 had been allowed to evaporate, the residue was diluted with 200 mL of H_2O, concentrated under reduced pressure, treated with 250 mL of CH_2Cl_2, and acidified by addition, with cooling and stirring, of cold aqueous 1 M HCl. The combined CH_2Cl_2 layer and the CH_2Cl_2 extract of the aqueous phase were washed with aqueous NaCl, dried, concentrated, and esterified with excess ethereal diazomethane. After the resulting product had been partitioned between Et_2O and aqueous $NaHCO_3$, the organic layer was dried, concentrated, and distilled through a 25-cm Vigreux column. After separation of the lowest boiling fraction containing (GLC, LAC-728 on Chromosorb P) 7.14 g (23%) of the crude ester **8** (retention time 5.8 min), bp 80–86 °C (13 mm), n^{25}_D 1.4715 [lit.[3] bp 85–86 °C (18 mm), n^{25}_D 1.4732], the next fraction, 4.17 g of colorless liquid, bp 86–110 °C (13 mm), n^{25}_D 1.4750, contained (GLC) a mixture of esters **8** (5.8 min) and **9** (16.2 min). Subsequent fractions contained (GLC) 15.1 g (41%) of practically pure ester **9**, bp 95–113 °C (5–13 mm), n^{25}_D 1.4833–1.4852 [lit.[3] bp 113–116 °C (16 mm), n^{25}_D 1.4829].

A cold (0 °C) solution of 5.29 g (29.0 mmol) of the ester **9** in 30 mL of THF was treated with 4 mL (48 mmol) of aqueous 12 M HCl, and the mixture was stirred for 1 h while it was allowed to warm to 25 °C. After the mixture had been diluted with H_2O and concentrated under reduced pressure, it was partitioned between H_2O and CH_2Cl_2. The organic layer was washed with aqueous NaCl, dried, and concentrated to leave 4.95 g of the crude keto ester **10** as a pale yellow liquid. Chromatography on silica gel with an Et_2O–hexane eluent (1:9 v/v) afforded 3.89 g (80%) of the keto ester **10** as a colorless liquid, n^{25}_D 1.4707, that exhibited a single peak (retention time 15.5 min) on GLC analysis (LAC-728 on Chromosorb P). A collected (GLC) sample of the keto ester **10**, n^{25}_D 1.4724, was used for characterization: IR (CCl_4), 1745 (ester C=O), 1720 (C=O), 1655 cm^{-1} (weak, C=C); UV (95% EtOH), end absorption (ϵ 1100 at 210 nm) with a maximum at 287 nm (ϵ 34); NMR (CCl_4), δ 5.5–6.1 (2 H, m, vinyl CH), 3.67 (3 H, s, OCH_3), 2.2–2.9 (4 H, m, allylic CH_2 and CH_2CO), 1.32 (3 H, s, CH_3); mass spectrum, *m/e* (rel intensity), 168 (M^+ 39), 140 (36), 126 (100), 125 (40), 112 (34), 111 (60), 109 (71), 108 (27), 96 (44), 95 (53), 81 (65), 79 (33), 67 (56), 53 (39), 43 (23), 41 (61), 39 (54).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.30; H, 7.20.

Preparation of the Epoxides 11 and the Iodohydrins 12. A solution of 2.84 g (16.9 mmol) of the keto ester **10** and 3.70 g of a reagent containing 18.2 mmol of *m*-chloroperbenzoic acid in 50 mL of $CHCl_3$ (EtOH free) was refluxed for 5 h and then allowed to stand for 9 h at 25 °C. After the mixture had been partitioned between CH_2Cl_2 and aqueous Na_2SO_3, the organic layer was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl, and then dried and concentrated. The residual yellow liquid (4.0 g) was chromatographed on silica gel with an EtOAc–hexane eluent (1:3 v/v). The early chromatography fractions contained 1.708 g (55%) of the epoxide **11** (isomer A) as a colorless liquid, n^{25}_D 1.4710. Short-path distillation (0.3 mm with an 85 °C bath) afforded the pure epoxide **11** (isomer A): n^{25}_D 1.4703; IR (CCl_4), 1760 (ester C=O), 1720 cm^{-1} (C=O); UV λ_{max} (95% EtOH), 283 nm (ϵ 36); NMR (CCl_4), δ 3.73 (3 H, s, OCH_3), 3.1–3.5 (2 H, m, epoxide CHO), 2.0–2.6 (4 H, m, CH_2), 1.42 (3 H, s, CH_3); mass spectrum, *m/e* (rel intensity), 184 (m^+, 1), 128 (32), 125 (32), 124 (28), 97 (84), 84 (30), 82 (30), 69 (71), 68 (30), 59 (46), 56 (50), 55 (65), 43 (33), 41 (100), 39 (79).

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.70; H, 6.59.

The later chromatography fractions contained 930 mg (30%) of the epoxide **11** (isomer B) as a colorless liquid, n^{25}_D 1.4751. Short-path distillation (0.3 mm with an 85 °C bath) afforded the pure epoxide **11** (isomer B): n^{25}_D 1.4752; IR (CCl_4), 1745 (ester C=O), 1720 cm^{-1} (C=O); UV λ_{max} (95% EtOH), 285 nm (ϵ 25); NMR (CCl_4), δ 3.75 (3 H, s, OCH_3), 3.0–3.5 (2 H, m, epoxide CHO), 1.9–2.8 (4 H, m, CH_2), 1.38 (3 H, s, CH_3); mass spectrum, *m/e* (rel intensity), 184 (M^+, 1), 128 (25), 125 (28), 124 (23), 110 (28), 101 (29), 97 (78), 85 (32), 69 (55), 68 (25), 59 (41), 58 (24), 56 (43), 55 (54), 43 (32), 41 (100), 39 (61).

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.84; H, 6.61.

Following a general procedure described previously,[7] a solution of 216 mg (1.17 mmol) of the epoxide **11** (isomer A), 445 mg (2.97 mmol) of NaI, 123 mg (1.5 mmol) of NaOAc, and 1.0 mL of HOAc in 2.0 mL of propionic acid was stirred at 25 °C for 2.5 h. After the mixture had been partitioned between Et_2O and an aqueous solution of $NaCHO_3$ and $NaHSO_3$, the organic layer was washed with aqueous NaCl, dried, and concentrated. The residual liquid (331 mg) crystallized from a CCl_4–hexane mixture as 279 mg of colorless solid, mp 93–94 °C. Recrystallization separated 233 mg (65%) of the iodohydrin **12** (isomer A) as colorless prisms, mp 96–97 °C. Further recrystallization gave the iodohydrin **12** (isomer A): mp 97–99 °C; IR ($CHCl_3$), 3570, 3410 (OH), 1740 (ester C=O), 1712 cm^{-1} (C=O); UV λ_{max} (95% EtOH), 260 nm (ϵ 620); NMR ($CDCl_3$), δ 4.2–4.7 (2 H, m, CHO, CHI), 3.78 (3 H, s, OCH_3), 2.9–3.1 (1 H, m, OH, exchanged with D_2O), 1.9–2.9 (4 H, m, CH_2), 1.43 (3 H, s, CH_3); mass spectrum, *m/e* (rel intensity), 312 (M^+, <1), 185 (41), 153 (36), 125 (30), 107 (45), 97 (32), 83 (55), 79 (40), 71 (32), 69 (32), 59 (45), 56 (28), 55 (99), 54 (25), 42 (30), 41 (100), 39 (64).

Anal. Calcd for $C_9H_{13}IO_4$: C, 34.64; H, 4.20; I, 40.66. Found: C, 34.58; H, 4.26; I, 40.71.

The same procedure was employed with 142 mg (0.77 mmol) of the epoxide **11** (isomer B), 239 mg (1.59 mmol) of NaI, 48 mg (0.59 mmol) of NaOAc, 0.6 mL of HOAc, and 1.0 mL of propionic acid with a reaction time of 3 h at 25 °C. The crude neutral product (199 mg of colorless solid, mp 79–95 °C) was triturated with pentane and recrystallized from a PhH–hexane mixture to separate 121 mg (50%) of the iodohydrin **12** (isomer B) as colorless prisms: mp 106–107 °C; IR ($CHCl_3$), 3500 (br, OH), 1735 (sh, ester C=O), 1718 (shoulder), 1708 cm^{-1} (C=O); UV λ_{max} (95% EtOH), 261 nm (ϵ 640); NMR ($CDCl_3$), δ 4.4–4.9 (1 H, m, CHO or CHI), 3.75 (3 H, s, OCH_3), 3.59 (1 H, OH, exchanged with D_2O), 3.47 (1 H, d, J = 11 Hz, CHO or CH-I), 2.1–2.9 (4 H, m, CH_2), 1.53 (3 H, s, CH_3); mass spectrum, *m/e* (rel intensity), 294 (4), 185 (44), 153 (31), 147 (28), 127 (28), 125 (30), 97 (29), 85 (62), 83 (60), 71 (30), 69 (30), 59 (45), 56 (29), 55 (94), 43 (68), 41 (100), 39 (60).

Anal. Calcd for $C_9H_{13}IO_4$: C, 34.64; H, 4.20; I, 40.66. Found: C, 34.69; H, 4.24; I, 40.69.

Preparation of the Acid 14. Several modifications in the previously described[8] procedure for the hydroxy acid **13** were found desirable. Thus, reduction of 6-methoxyindan-1-one (23.7 g or 146 mmol) with $LiAlH_4$ (2.6 g or 68 mmol) in 250 mL of THF gave 22.8 g (95%) of 6-methoxyindan-1-ol, mp 45.5–46 °C (lit.[8] mp 46–47.5 °C). Reaction of a suspension of 12.3 g (75 mmol) of this alcohol with 194 mmol of *n*-BuLi in 460 mL of hexane at 25 °C for 12 h yielded a red solution of the lithium reagent. This solution was cooled to −78 °C and stirred under an atmosphere of CO_2 for 45 min. The usual isolation procedure[8] yielded 14.7 g (94%) of the hydroxy acid **13,** mp 155–157 °C dec (lit.[8] mp 150–151 to 160–161 °C dec).

A suspension of 3.82 g (18.4 mmol) of the acid **13** in 40 mL of THF and 10 mL of HOAc containing 0.4 mL of aqueous 70% $HClO_4$ was hydrogenated at 25 °C and 1 atm over 300 mg of 5% Pd/C catalyst. After 2 h the H_2 uptake (21.4 mmol) was complete and the reaction mixture was filtered and concentrated. A solution of the residual material in CH_2Cl_2 was washed with H_2O, dried, and concentrated to leave 3.40 g of the solid acid **14,** mp 135–138 °C. Recrystallization from a hexane–CH_2Cl_2 mixture afforded 3.14 g (89%) of crops of the acid **14** as colorless prisms, melting within the range 135–139 °C. Another recrystallization gave the pure acid **14**: mp 138–139 °C; IR ($CHCl_3$), 3250 (carboxyl OH), 1735 (shoulder), and 1725 cm^{-1} (carboxyl C=O); UV λ_{max} (95% EtOH), 294 nm (ϵ 2700) with intense end absorption (ϵ 18 000 at 210 nm); NMR ($CDCl_3$), δ 7.31 (1 H, d, J = 8.5 Hz, aryl CH), 6.82 (1 H, d, J = 8.5 Hz, aryl CH), 3.96 (3 H, s, OCH_3), 3.31 (2 H, t, J = 7.5 Hz, benzylic CH_2), 2.86 (2 H, t, J = 7.5 Hz, benzylic CH_2), 1.7–2.4 (2 H, m, CH_2); mass spectrum, *m/e* (rel intensity), 192 (M^+, 62), 174 (100), 159 (25), 117 (30), 116 (73), 115 (53), 103 (30), 77 (35), 51 (25).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.87; H, 6.30.

Preparation of the Acid 16. A solution of 1.51 g (7.87 mmol) of the acid **14** in 10 mL of THF was added, dropwise and with stirring, to a refluxing solution of 530 mg (23 mg-atom) of Na in 250 mL of liquid NH_3. After the resulting blue solution had been stirred at −33 °C for 15 min, it was cooled in a dry ice–acetone bath and treated with 4.5 g (32 mmol) of CH_3I. The NH_3 was allowed to evaporate from the resulting colorless solution and the residue was acidified with dilute aqueous HCl, the aqueous phase was saturated with NaCl, and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried and concentrated to leave 1.54 g of pale yellow solid that contained (NMR analysis) ca. 75% of the acid **16** and ca. 25% of the acid **15a.** Recrystallization from an EtOAc–hexane mixture separated 748 mg (46%) of the acid **16,** mp 125–128 °C dec. An additional recrystallization gave the pure acid **16** as colorless plates: mp 126–129 °C dec; IR ($CHCl_3$), 2800–3200 (associated OH), 1708, 1695 (carboxyl C=O), 1658 cm^{-1} (C=C); UV (95% EtOH), end absorption with ϵ 3700 at 210 nm; NMR ($CDCl_3$), δ 11.5 (1 H, s, OH), 4.83 (1 H, t, J = 3.5 Hz, vinyl CH), 3.57 (3 H, s, OCH_3), 1.6–2.9 (8 H, m, CH_2), 1.41 (3 H, s, CH_3); mass spectrum, *m/e* (rel intensity), 164 (48), 149 (21), 91 (22), 44 (100).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.24; H, 7.76.

In a similar experiment a solution of 841 mg (4.38 mmol) of the acid **14** in 20 mL of THF was added to a cold (−33 °C) solution of 113 mg (19 mg-atom) of Li in 100 mL of NH_3. After the resulting mixture had been stirred at −33 °C for 15 min, it was cooled in a dry ice bath and 9.1 g (64 mmol) of MeI was added. The mixture was allowed to warm to −33 °C with stirring, the NH_3 was allowed to evaporate, and the previously described isolation procedure was followed to separate 800 mg of crude acidic product containing (NMR analysis) ca. 45% of the acid **16** and ca. 55% of the acid **15a.** A solution of this mixture in 10 mL of THF and 2 mL of aqueous 6 M HCl was stirred at 25 °C for 30 min to hydrolyze the enol ether **16** and decarboxylate the corresponding keto acid. The resulting mixture was partitioned between aqueous $NaHCO_3$ and Et_2O, and the resulting aqueous phase was acidified (HCl) and extracted with Et_2O. After this extract had been dried and concentrated, the crude residual acid **15a** (418 mg) was esterified with excess ethereal CH_2N_2. The resulting Et_2O solution was washed with aqueous $NaHCO_3$, dried, and concentrated to leave 398 mg of a pale yellow liquid containing (GLC, silicone DC-710 on Chromosorb P) the ester **15b** (retention time 7.0 min) and several minor unidentified impurities (3.0, 8.4 min). A collected (GLC) sample of the ester **15b** was obtained as a colorless liquid: $n^{25}D$ 1.5000; IR (CCl_4), 1735 (C=O), 1645 cm^{-1} (C=C); UV (95% EtOH), end absorption (ϵ 2400 at 210 nm) with inflections at 235 (ϵ 1100) and 270 nm (ϵ 295); NMR (CCl_4), δ 5.4–5.9 (2 H, m, vinyl CH), 3.61 (3 H, s, OCH_3), 1.7–2.9 (8 H, m, aliphatic CH), 1.28 (3 H, s, CH_3); mass spectrum, *m/e* (rel intensity), 192 (M^+, 10), 134 (23), 133 (100), 117 (34), 115 (19), 105 (70), 91 (21).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.00; H, 8.40.

Preparation of the Lactone 4. To a cold (−78 °C) suspension of 528 mg (2.54 mmol) of the acid **16** in 6 mL of CH_2Cl_2 was added, dropwise and with stirring, 1.4 mL of a CH_2Cl_2 solution containing 2.8 mmol of BBr_3. The resulting mixture, which rapidly changed to a clear yellow solution, was stirred at −78 °C for about 1 min and then added to a cold (0 °C) mixture of 7 mL of saturated aqueous $NaCHO_3$ and 7 mL of aqueous 0.8 M KBr_3 (KBr + Br_2). After the resulting two-phase mixture had been stirred at 0 °C for 10 min, sufficient $Na_2S_2O_3$ was added to consume the excess Br_2, and the mixture was partitioned between Et_2O and aqueous $NaHCO_3$. After the ethereal solution had been dried and concentrated, the crude bromo lactone **18** remained as 675 mg of colorless liquid which contained (TLC, silica gel coating with an EtOAc–hexane eluent, 1:4 v/v) the bromo lactone **18** (R_f 0.38) and a minor unidentified impurity (R_f 0.30). The crude bromo lactone **18** from a comparable experiment was partially purified by preparative TLC to obtain the bromo lactone as a colorless semisolid: IR ($CHCl_3$), 1785 (γ-lactone C=O), 1725 cm^{-1} (C=O); NMR ($CDCl_3$), δ 1.8–3.0 (10 H, m, aliphatic CH), 1.35 (3H, s, CH_3). Since samples of the crude bromo lactone **18** rapidly turned blue on standing, our efforts to effect further purification were unsuccessful.

A solution of the crude bromo lactone **18** (675 mg), 1.33 g (4.5 mmol) of *n*-Bu_3SnH, and 5 mg of azobis(isobutyronitrile) in 2 mL of PhH was heated to 55 °C with stirring under an N_2 atmosphere for 1 h and then stirred for an additional 1 h at 25 °C. The crude product contained (TLC) the lactone **4** (R_f 0.19) and several minor components with higher R_f values, but none of the starting bromo lactone **18** was detected. The reaction mixture was concentrated and then chromatographed on silica gel with an EtOAc–hexane eluent (1:4 v/v). The crude lactone **4** obtained (364 mg, contaminated with tin compounds) was chromatographed a second time to separate 322 mg (65% based on the acid **16**) of the lactone **4** as a colorless liquid that solidified on standing, mp 48–50 °C. Recrystallization from Et_2O–pentane afforded 282 mg (57% based on acid **16**) of the pure lactone **4** as colorless prisms: mp 51–52 °C (lit.[2g] mp 45–47 °C); IR (CCl_4), 1786 (γ-lactone C=O), 1725 cm^{-1} (C=O); UV λ_{max} (95% EtOH), 299 nm (ϵ 53); NMR ($CDCl_3$), δ 1.6–3.0 (11 H, m, aliphatic CH), 1.25 (3 H, s, CH_3); mass spectrum, *m/e* (rel intensity), 194 (M^+, 26), 151 (23), 111 (100), 108 (20), 95 (20), 55 (22), 41 (20). Our sample was identified with the previously described product[4] by comparison of IR and NMR spectra.

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.09; H, 7.30.

Registry No.—**4,** 10258-34-1; **8,** 59034-54-7; **9,** 21173-69-3; **10,** 63548-79-8; **11,** 63548-80-1; **12,** 63548-85-6; **13,** 33521-61-8; **14,** 60346-39-6; **15a,** 63548-81-2; **15b,** 63548-82-3; **16,** 63548-83-4; **18,** 63548-84-5; 6-methoxyindan-1-one, 13623-25-1; 6-methoxyindan-1-ol, 3469-09-8.

References and Notes

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Photocyclization of 2-Methoxy-4,5-dimethylstilbene

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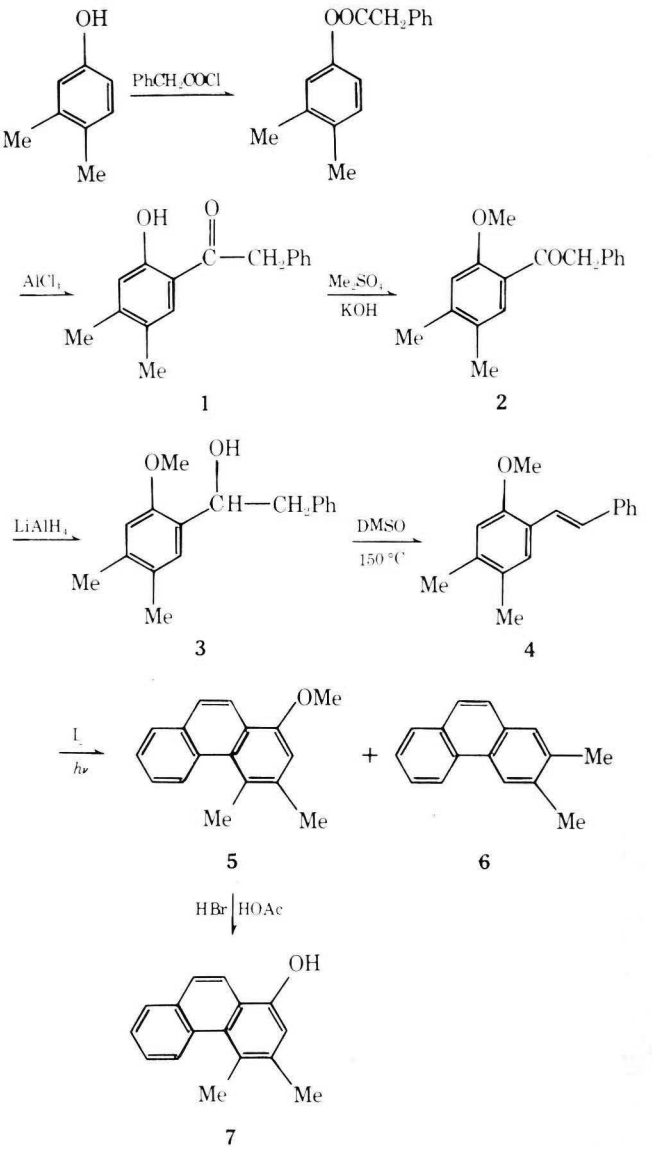
Synthesis of small quantities of substituted phenanthrenes by photocyclization of stilbenes in the presence of an oxidant is the method of choice.[1] Since the procedure does not lead to rearrangement of the substituents, this route is also recommended for the preparation of authentic samples of known structure. Having a need for a comparison sample of 1-hydroxy-3,4-dimethylphenanthrene some years ago we turned to this approach. The results were unsatisfactory in that the sole phenanthrene ring containing compound obtained was 2,3-dimethylphenanthrene. This was one of the earliest reports of the loss of an ortho substituent in this photocyclization.[2] More recently we returned to this reaction and can now report that 1-methoxy-3,4-dimethylphenanthrene can indeed be obtained from the reaction, albeit in low yield. The problems associated with separation of pure products from the reaction mixture and the low yields obtained limit the value of this approach for synthesis of 1-hydroxy-3,4-dimethylphenanthrene in sizable amounts.

Preparation of 2-methoxy-4,5-dimethylstilbene was carried out from 3,4-dimethylphenol in about 40% overall yield in five steps as illustrated in Scheme I. Each step proceeds in good yield and the procedure is nicely adapted to the preparation of large amounts. The stilbene was irradiated with a medium-pressure ultraviolet lamp in cyclohexane solution in the presence of iodine. The photo reaction was not clean; some amorphous yellow powder was always produced along with considerable material which would not migrate on thin-layer chromatograms. The brown oil obtained from the irradiation was readily separated by preparative layer chromatography into two fractions, that with the higher R_f value being 2,3-dimethylphenanthrene. The slower moving band had the same R_f value as the stilbene, and it was a mixture (two OMe bands in the NMR). Repeated development of this band eventually permitted isolation of the desired 1-methoxy-3,4-dimethylphenanthrene. Though it appeared that at least part of the separation problem arose because stilbene remained in the irradiation product, longer irradiation gave intractable black oils. In one case a high melting product (mp 205–207 °C) was isolated in low yield. This was assumed to be a dimer but was not investigated further.

Scheme I



Perhaps the most interesting point, i.e., the relative amounts of 2,3-dimethylphenanthrene and 1-methoxy-3,4-dimethylphenanthrene formed in the photolysis, was not possible to determine with any degree of certainty because of the difficulty of separating the ether from the reaction mixture. However, since the crude separation on thin-layer plates gave about a 2.5 to 1 ratio of the bands from which the ether and the hydrocarbon respectively were isolated, and since the pure compounds were obtained in ca. 1.5 to 1.0 ratio, an estimate of 2 to 1 is probably quite reasonable. In this case then reaction at the substituted ortho position and loss of methanol occurs about half as often as reaction at the unsubstituted position followed by loss of hydrogen. This ratio might be expected to be dependent on the iodine concentration, but though no careful test of this point was made, no dramatic effect was observed by altering the ratio of stilbene to iodine by a factor of fivefold.

Loss of methanol has been observed in a number of examples,[3] and when the irradiation was carried out under conditions similar to those used in our work, the ratio of loss of hydrogen to loss of methanol varied from about two to three. When nonoxidative conditions were employed only methanol loss was observed.[4] It is also interesting that the ratio of loss

of hydrogen to loss of methane during irradiation of 2,2′,-3,3′-tetramethylstilbene was found to be about two.[5] However, Servis and Fang[6] reported a smaller amount of methane loss with 2,2′-dimethyl-5,5′-difluorostilbene.

Our result and those of Sargent[3,4] along with the finding by several groups[5-7] that an *o*-methyl group can be lost during irradiation clearly add one additional limitation to the photocyclization route to substituted phenanthrenes. Mallory[1b] has already called attention to the formation of mixtures with meta-substituted stilbenes. The limitation applies principally to preparative use of the reaction where the need to separate similar compounds reduces yields severely but does not prevent the use for generation of authentic samples.

Experimental Section

3,4-Dimethylphenyl Phenylacetate. To a solution of 83.1 g (0.68 mol) of 3,4-dimethylphenol in 100 mL of anhydrous pyridine was added 105 g (0.68 mol) of phenylacetyl chloride. The reaction mixture was stirred for 1 h after the addition was complete and was allowed to stand overnight. About 200 mL of water was added to the semisolid mixture, the organic materials were taken up in ether, and the ether solution was washed with water, dilute hydrochloric acid, and 5% sodium bicarbonate. The crude product, 137 g (84%), was recrystallized from ethanol giving white crystals: mp 53–54 °C; IR (CCl_4) 1760 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.76; H, 6.55.

2-Phenacetyl-4,5-dimethylphenol (1). A mixture of 46.2 g (0.19 mol) of the above ester and 38 g (0.28 mol) of anhydrous aluminum chloride was heated at 130 °C for 25 min. The cool mixture was treated with 270 mL of 10% hydrochloric acid, and the mixture was extracted with benzene. The solution was dried ($MgSO_4$) and the benzene was removed. Recrystallization from 80% ethanol gave 33.5 g (72%) of crystals: mp 69–70 °C; IR (CCl_4) 1680, 1495, 1255 cm^{-1}; NMR (CCl_4) δ 2.12, 2.16 (6 H, 2ArMe), 4.10 (s, 2 H, CH_2CO), 6.65 (s, 1 H, ArH ortho to OH), 7.2 (s, 5 H, Ph), 7.43 (s, 1 H, ArH). Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.12; H, 6.65.

2-Methoxy-4,5-dimethylphenyl Benzyl Ketone (2). A solution containing 30.5 g (0.13 mol) of the above phenol and 30.6 g (0.24 mol) of dimethyl sulfate in 120 mL of acetone was stirred vigorously while 26 mL of a solution of potassium hydroxide (25 g of KOH in 15 mL of water) was added dropwise. After the addition had been completed the solution was heated to reflux for 15 min. The cool solution was poured into water and the organic products were extracted with petroleum ether. The extracts were washed with Claisen's alkali and then with water, and the solution was dried (Na_2SO_4). The petroleum ether was evaporated and the residue was recrystallized from methanol/petroleum ether: yield 13.2 g (41%) of fine white crystals; mp 51–52 °C; IR (CCl_4) 1660, 1600, 1500, 1380, 1260 cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.12; H, 6.98.

2-Methoxy-4,5-dimethylphenylbenzylcarbinol (3). A solution containing 25.4 g (0.1 mol) of the above ketone in 125 mL of anhydrous ether was added to 1.15 g (0.028 mol) of lithium aluminum hydride in 50 mL of ether. The rate of addition was sufficient to maintain a gentle reflux, and the solution was stirred 1 h at reflux after addition had been completed. The mixture was treated carefully with dilute sulfuric acid, and the ether layer was separated and washed with water. The ether solution was dried ($MgSO_4$), the solvent was removed by distillation, and the product was recrystallized from 60–80 °C petroleum ether. The product was obtained in 90% yield: mp 86–88 °C; IR (CCl_4) 3600, 1500, 1380, 1090 cm^{-1}; NMR (CCl_4) δ 7.07 (s, 5 H, phenyl), 6.94 and 6.45 (two s, 2 H on substituted phenyl), 4.9 (X part of ABX, C(OH)**H**), 3.79 (s, 3 H, OCH_3), 2.6–3.0 (AB part of ABX, CH_2), 2.18, 2.12 (two s, 3 H and 3 H, CH_3's on phenyl). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.61; H, 7.75.

2-Methoxy-4,5-dimethylstilbene (4). Two methods were employed. **Method A.** The carbinol, 12.4 g (0.048 mol), was added slowly to a mixture of 3 mL of phosphorus oxychloride and 3 mL of anhydrous pyridine. When addition had been completed an additional 2 mL of phosphorus oxychloride and 2 mL of pyridine were added, and the solution was heated at reflux for 12 h. The solution was poured onto cracked ice, and the organic products were taken up in pentane. The pentane solution was washed with water and dried ($MgSO_4$) and the pentane was evaporated. The crude product, 10.8 g (93%), was recrystallized from ethanol, mp 55–56 °C.

Method B.[8] A solution of 18.7 g of the carbinol in 55 mL of DMSO was heated 9.5 h at 140 °C. The mixture was poured into water and the product was extracted into 40–60 °C petroleum ether. The solution was dried ($MgSO_4$) and the solvent was evaporated giving 16.7 g (96%) of an oil. Recrystallization from ehtanol gave white crystals: yield 14.0 g (80%); mp 54–55 °C; IR (CCl_4) 3030, 1500, 1380, 965 cm^{-1}; max UV (cyclohexane) 233 (14 900), 290 (18 900), 301 sh (16 800), 323 (19 900), 333 nm (19 600); NMR (CCl_4) δ 7.5-7.1 (m, 2 H, CH=CH), 7.2 (s, 5 H, phenyl), 6.98 and 6.48 (two s, 2 H, substituted phenyl), 3.81 (s, 3 H, OCH_3), 2.18, 2.19 (two s, 6 H, CH_3). Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.85; H, 7.33.

Irradiation of 2-methoxy-4,5-dimethylstilbene. A sample, usually 1.0–2.0 g, of 2-methoxy-4,5-dimethylstilbene in 1 L of cyclohexane containing 40–50 mg of iodine was irradiated in an immersion reactor using a 450-W medium-pressure Hanovia ultraviolet lamp cooled by a quartz condenser. The reaction was monitored by withdrawing aliquots and determining the UV spectrum of each after appropriate dilution. The stilbene spectrum degrades and a rather monotonically increasing broad band from ca. 400 results with weak shoulders near 315, 292, and 276 nm. The usual irradiation time was about 6 h, and further exposure leads to decreasing intensity of the spectrum and loss of product. Careful control of the irradiation time appears essential to ease of isolation of the products. During the irradiation a light yellow amorphous solid comes out of solution but does not appear to interfere with the reaction. The solid was not identified.

After completion of the irradiation the solution was filtered and then washed with sodium bisulfite solution and dried ($MgSO_4$) and the solvent was evaporated. A light-brown oil remained which was chromatographed on preparative layer plates (alumina) using hexane–2% benzene as eluant. Three separate developments were used to give reasonable separation. Three bands were observed: (1) R_f 0.73 ca. 12%; (2) R_f 0.55 ca. 30%, and (3) R_f 0.00 ca. 50%.

Band 1 (6). Elution of the high R_f band gave a white solid which was recrystallized from 95% ethanol: 10% yield; mp 79–80 °C (lit.[9] mp 79–81 °C); UV_{max} 297 (16 500), 286 (16 300), 278 nm (21 400); IR (CS_2) 880, 872, 805, 742 cm^{-1}; NMR (CCl_4) δ 2.29 and 2.34 (two s, 6 H, CH_3), 7.2–8.3 (two m, 8 H).

Band 2 (5). Elution of the lower R_f band gave a clear oil which was dissolved in a minimum of 95% ethanol. About one-third of the oil eventually was induced to crystallize: yield 10%; mp 50–51 °C; UV_{max} (EtOH) 231 (26 700), 247 (42 000), 276 sh (15 200), 309 nm (11 000); IR (CCl_4) 1500, 1380, 1260, 1225, 1120, 1100, 820, 755 cm^{-1}; NMR (CCl_4) δ 2.38 (s, 3 H, CH_3), 2.72 (s, 3 H, CH_3), 3.82 (s, 3 H, OCH_3), 6.57 (s, 1 H, H_2), 7.41 and 8.0 (AB, 2 H, J_{AB} = 9 Hz, H_9 and H_{10}), 7.2–7.75 (m, 3 H, ArH), 8.4–8.6 (m, 1 H, ArH). Anal. Calcd for $C_{17}H_{16}O$: C, 86.41; H, 6.82. Found: C, 86.28; H, 6.67.

3,4-Dimethyl-1-phenanthrol (7). A mixture of the methyl ether obtained from band 2 (80 mg) and 3 mL of 48% hydrobromic acid and 3 mL of glacial acetic acid was heated at reflux under nitrogen for 2.5 h. About 10 mL of water was added and the mixture was allowed to stand several hours. The crystalline product was isolated by filtration and recrystallized from hexane/benzene: 55 mg (73%); mp 113–116 °C dec; IR (KBr) 1600, 1380, 1060, 910, 820, and 752 cm^{-1}; UV_{max} 344 (1430), 303 (4900), 240 nm (22 200).

An acetate was preapred by treating 24 mg of the above phenanthrol with 1 mL of acetic anhydride and 5 mL of anhydrous pyridine at 55 °C for 10 h. The mixture was poured into ice water and the precipitated product was recrystallized from ethanol/water: mp 121.5–122 °C; IR 1755, 1205, 810, 760 cm^{-1}. Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.52; H, 6.34.

Registry No.—**1**, 18439-99-1; **2**, 54468-76-7; **3**, 63609-31-4; **4**, 63609-32-5; **5**, 63609-33-6; **6**, 3674-65-5; **7**, 63609-34-7; **7** acetate, 63609-35-8; 3,4-dimethylphenyl phenylacetate, 63609-36-9; 3,4-dimethylphenol, 95-65-8; phenylacetyl chloride, 103-80-0.

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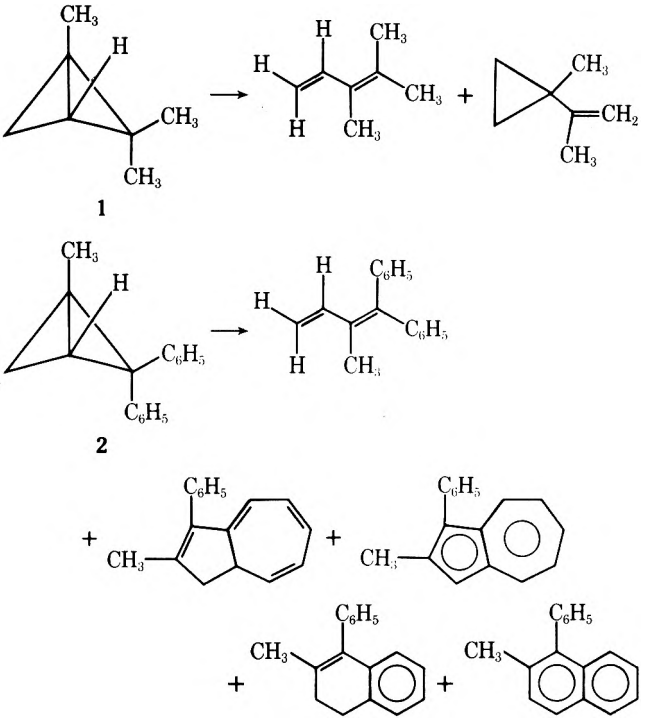
Kinetic Resolution via the Transition Metal Complex Promoted Rearrangement of Strained Hydrocarbons

Summary: Chiral rhodium (DIOP) chloride complexes have been shown to selectively promote the rearrangement of one enantiomer of racemic bicyclo[1.1.0]butane derivatives. This kinetic resolution has been shown to give greater than 30% enantiomeric excess. A chiral shift reagent was used to determine the amount of resolution.

Sir: The use of optically active transition metal complexes to promote reactions in which achiral or racemic starting materials are converted into optically active hydrocarbons has recently received considerable attention.[1] This is particularly true in the area of catalytic reductions with homogeneous, optically active, Wilkinson[2] type catalysts.[1,3,4] In addition, a few isolated examples exist in which optically inactive olefins or acetylenes have been isomerized over chiral catalysts to yield optically active products.[5] We now wish to report what we believe to be the first examples of transition metal complex promoted kinetic resolution of highly strained hydrocarbons.

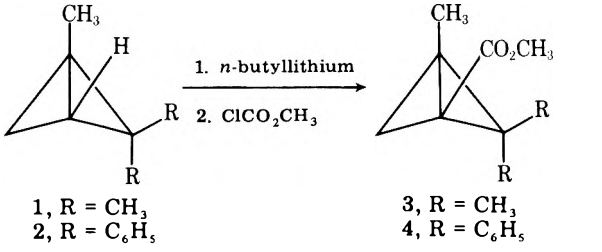
We had previously demonstrated that certain rhodium(I) complexes promoted the rapid rearrangement of 1,2,2-trimethylbicyclo[1.1.0]butane (**1**)[6] and 1-methyl-2,2-diphenylbicyclo[1.1.0]butane (**2**)[7] into the products shown. Our desire for optically active variants of **1** and **2** prompted us to explore the possibility of a kinetic resolution based on the selective isomerization of one member of each of the enantiomeric pairs **1** and **2**. In order to accomplish our objectives, we prepared the diphosphinerhodium(I) complexes from both (+)- and (−)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (hereafter referred to as DIOP) according to literature procedures.[8] It was found that Rh(DIOP)Cl promoted the rapid isomerization of both **1** and **2**.

In order to determine the degree of kinetic resolution obtained when chiral DIOP complexes were used, it was necessary to develop a method for establishment of the enantiomeric excess (ee) which existed after partial rearrangement of **1** and **2**. The method of analysis, which we developed, involved treatment of the residual bicyclo[1.1.0]butane, **1** or **2**, with *n*-butyllithium in ether followed by addition of methyl chloroformate to yield **3** or **4**, respectively.[9] Nuclear magnetic resonance spectral analysis of **3** and **4** in the presence of the chiral shift reagent, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) resulted in the clean separation of both of the enantiomeric *exo*-methyl resonances and of the corresponding methoxyl group resonances of **3**, and of both of the enantiomeric bridgehead methyl resonances and of the corresponding methoxyl group resonances of **4**. This provided a double check on the enantiomeric excesses which we hoped to generate.



1

2



1, R = CH_3
2, R = C_6H_5

3, R = CH_3
4, R = C_6H_5

Table I lists the degree of kinetic resolution observed for

Table I. Kinetic Resolution of Racemic Bicyclo[1.1.0]butanes Using Rh(DIOP)Cl Complexes

Compd	DIOP	Time	Temp, ±2 °C	% conv[a]	% enantiomeric excess (±5)	$[\alpha]^{25}_{D}$[b]
1	(−)[c]	9 h	0	61	2	+0.48
1	(+)[d]	9 h	0	40[e]	4[f]	−0.84
2	(−)[g]	30 d	4	56	18	−23.2
2	(+)[g]	18 d	4	53	17	+25.3
2	(−)[g]	22 h	24	62	33	−43.6
2	(+)[g]	17 h	24	73	35	+45.5

[a] % conversion was determined by NMR analysis vs. an internal standard. [b] Rotations were measured in carbon tetrachloride (c 0.5–5.0) using a Perkin-Elmer recording polarimeter model 241. [c] Reaction run in 3:4 v/v veratrole/diethyl ether. [d] Reaction run in 3:2 v/v veratrole/diethyl ether. [e] The percent conversion varied considerably from run to run due to the sensitivity of the reaction to the presence of oxygen. [f] The percent enantiomeric excess for **3** is less than the error factor in determining these values by NMR analysis. Thus, the agreement of the rotation of **3** with the determined percent enantiomeric excess may be fortuitous. [g] Chloroform as solvent.

both 1 and 2 with both (+)- and (−)-DIOP complexes. As noted in the table, the degree of kinetic resolution in the rearrangement of 1 was very small, but it did exist. In contrast, the diphenyl-substituted bicyclo[1.1.0]butane (2) showed excellent sensitivity to the chirality of the transition metal complex. The development of greater than 30% enantiomeric excess in this kinetic resolution indicates to us that the transition metal complex promoted rearrangement of strained hydrocarbons may be extremely sensitive to steric factors.[10,11]

In summary, we have provided the first example of a kinetic resolution of a strained polycyclic compound. Our procedure makes optically active derivatives of bicyclo[1.1.0]butane readily available for the first time. We hope that this process can be extended to the kinetic resolution of other highly strained polycyclic hydrocarbons.

Acknowledgment. We are indebted to the National Science Foundation for a grant which supported this investigation.

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(9) Satisfactory spectral data, elemental analysis, and exact mass molecular weight were obtained for both **3** and **4**. Racemic **4** has mp 57–58 °C.
(10) We were somewhat surprised that the selectivity appeared to be less at 4 °C than it was at 24 °C. We can only theorize that during the extremely long time required for rearrangement at the lower temperature, some of the starting material may have been consumed in nonmetal promoted rearrangements.
(11) While the exact absolute rotation of **4** cannot be determined due to the error limits in determining the enantiomeric excess by NMR, it can be assumed that the value will be in the 130–140° range.
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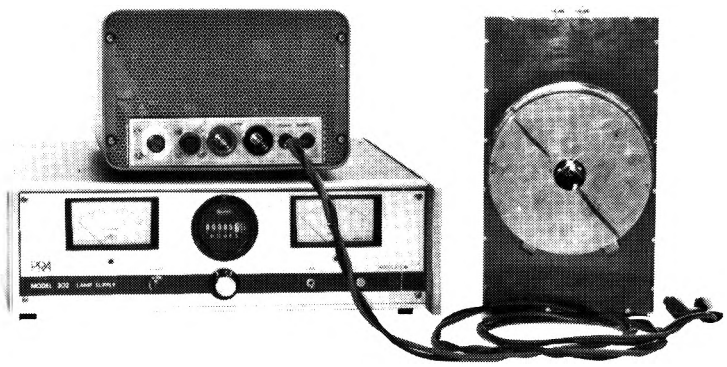

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