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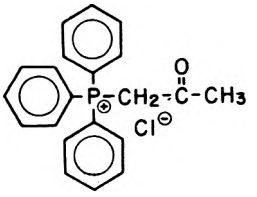

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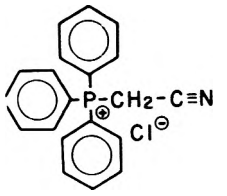

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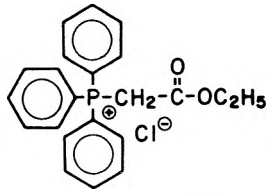

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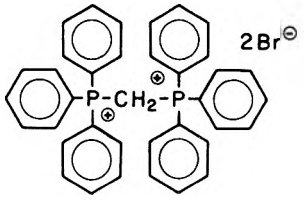

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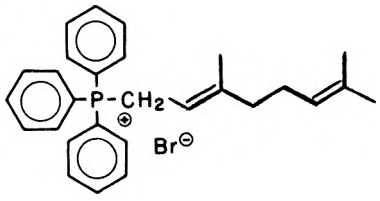

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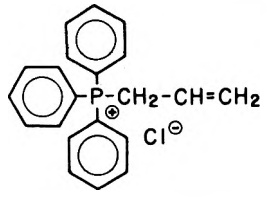

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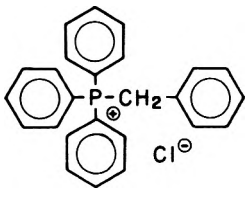

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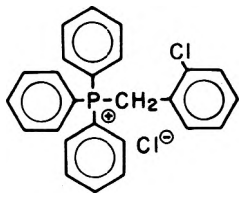

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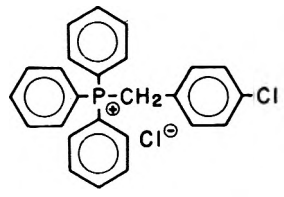

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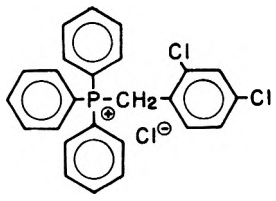

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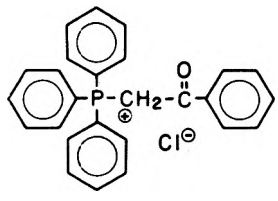

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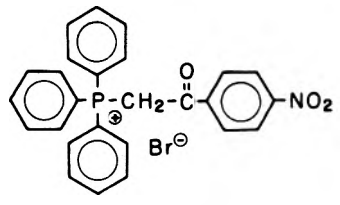

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Studies on the Solid-Phase Synthesis of Bovine Pancreatic Trypsin Inhibitor (Kunitz) and the Characterization of the Synthetic Material

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A resin-bound protected linear polypeptide of 58 residues with the sequence of the bovine pancreatic trypsin inhibitor (Kunitz) was synthesized by the solid-phase method. The polypeptide was removed from the solid support by cleavage with HF and purified, and the three disulfide bonds were formed by air oxidation of the reduced form. The synthetic inhibitor was purified by gel filtration, trypsin–Sepharose affinity chromatography, and finally by ion-exchange chromatography. A highly purified inhibitor which inhibited trypsin stoichiometrically was isolated. The synthetic trypsin inhibitor was indistinguishable from natural trypsin inhibitor by chromatography on CM-Sephadex, polyacrylamide gel electrophoresis, amino acid analysis, peptide maps of tryptic digests, and circular dichroism spectra. The dissociation constant for the trypsin–synthetic trypsin inhibitor complex also agreed well with that for the trypsin–native trypsin inhibitor complex.

The methodology of Merrifield solid-phase synthesis[1-3] has gained considerable acceptance, particularly in the preparation of peptides of moderate molecular weight. This has encouraged a number of investigators to attempt the synthesis of large biologically active polypeptides by the solid-phase approach. However, the difficulties associated with a stepwise solid-phase strategy are expected to increase in magnitude with increases in the length of the polypeptide chain.

We have undertaken studies on solid-phase peptide synthesis with a view toward eventually using this method in the design of polypeptide model enzymatic catalysts. In this paper, we present the results of our solid-phase synthesis of a polypeptide with the amino acid sequence of bovine pancreatic trypsin inhibitor (Kunitz) and of our characterization of the synthetic species. We selected this inhibitor (BPTI) for synthesis because its amino acid chain length (58) is in the same range as the model enzymes we plan to prepare and because it is a very stable, well-characterized protein which has been studied in great detail in many laboratories.[4-6] Both its amino acid sequence[7-10] and crystallographic structure[11-13] have been determined. Also, it has been established with the native inhibitor that the denatured, reduced peptide chain can be reoxidized and refolded into a structure possessing full inhibitory activity.[14-16] Furthermore, the extraordinarily low dissociation constant (6×10^{-14} M t pH 8, 25 °C) which has been measured for the trypsin inhibitor–trypsin complex[17] provides a stringent criterion by which the purity of synthetic material can be assessed. Finally, if success in the solid-phase synthesis of a peptide possessing the amino acid sequence of native BPTI and meeting high standards of purity can be achieved, this could open the way to the preparation of analogues with variations in the amino acid composition in the vicinity of the "reactive site" which would be useful in mechanistic studies of the inhibition process.

Results

Solid-Phase Synthesis. The yield of crude uncleaved peptide we obtained (77%, Table I) suggests that the average yields of the individual steps in our synthesis were very high and that little peptide must have been lost from the resin during the course of synthesis. The conventional protecting groups for the hydroxyl function of tyrosine (Bzl) and for the ϵ-amino function of lysine (Z) are not very satisfactory for the stepwise synthesis of long peptide chains and their loss during synthesis can easily lead to extensive chain branching.[18-20] To reduce this problem the Bzl (2,6-Cl_2) and ϵ-Z (2-Cl) protecting groups were used for tyrosine and lysine, respectively.

In our synthetic work the individual coupling steps and deprotecting steps were monitored by the ninhydrin test.[21] Repeated coupling was used to ensure complete reaction when the ninhydrin test was positive after the initial coupling had occurred. This was found to be a necessary procedure only in the cases of three residues. Thus, it appears that the long, growing peptide chain was able to react rapidly and in high yield with added Boc-amino acids.

Purification of the Synthetic Peptide. The most powerful purification step employed in this synthesis is that involving trypsin–Sepharose affinity chromatography. Gel filtration on Sephadex G-50 of an acetic acid extract of the resin–peptide mixture obtained after the HF cleavage step gave a solution containing a polypeptide of approximately the correct molecular weight. After treatment with β-mercaptoethanol and passage again through a Sephadex G-50 column, the solution was diluted to a concentration of 0.01 mg of the polypeptide per ml. The latter solution was air oxidized for

Table I. Summary of Yields and Inhibitory Activities Obtained for Synthetic Material [a,b]

Stage of synthesis or purification	Yield, %	Inhibitory activity against trypsin, %
1. Protected BPTI-resin	77	
2. Crude, cleaved peptide	75	
3. BPTI monomer isolated by gel filtration through Sephadex G-50	58	10
4. BPTI isolated by affinity chromatography	9.5	80–90
5. BPTI isolated after ion-exchange chromatography	90	100

[a] The overall yield at the end of the fifth stage was 2.9% of material which was 100% active as a β-trypsin inhibitor. [b] When HF treated sulfonated native BPTI was purified by the procedure outlined in the table a final yield of 50% of material which was 100% active as a β-trypsin inhibitor was obtained.

Table II. Amino Acid Composition of Purified Synthetic Trypsin Inhibitor

Amino acid	Number of residues found: Expected[4]	Native inhibitor	Synthetic inhibitor
Arg	6	5.89	5.97
Lys	4	4.12	4.25
Asx	5	5.10	4.98
Thr	3	3.11	2.95
Ser	1	0.97	0.89
Glx	3	3.11	2.95
Pro	4	4.15	3.96
Gly	6	6.11	6.25
Ala	6	6.21	6.30
Val	1	0.75	0.79
Met	1	0.78	0.85
Ile	2	0.98	0.98
Leu	2	2.00	2.00
Tyr	4	3.69	3.57
Phe	4	4.15	4.05
Cys	6	Not determined	Not determined

4 days and applied to a trypsin–Sepharose column, yielding an inhibitor after lyophilization which was 80–90% active. The inactive fractions obtained from the affinity column presumably consisted of peptides with failure sequences and of peptides with the correct amino acid sequence but incorrectly paired disulfide bonds. No attempt was made to recycle the inactive material.

The overall yield of active inhibitor in our synthesis (see Table I) might have been higher if the proper pairing of the sulfhydryl groups (Cys 5–55, 14–38, 30–51) could have been ensured. We tried to avoid intermolecular side reactions by using an anaerobic system during the handling of the synthetic inhibitor in the reduced form and by employing high dilution during the air oxidation. However, even though our observation that the synthetic inhibitor was 100% active and exhibited essentially the correct dissociation constant in its complex formation with β-trypsin provides extremely strong support for the tenet that the tertiary structure of a protein is determined by its primary sequence,[22] in the absence of an efficient disulfide reshuffling process the incorrect pairing of disulfide bonds must have certainly played a significant role in lowering the final yield. To assist the disulfide reshuffling process we tried to use the oxidized glutathione-reduced glutathione system,[23] but the yield was even lower here. Application of the disulfide reshuffling enzyme[24] would probably be very helpful.

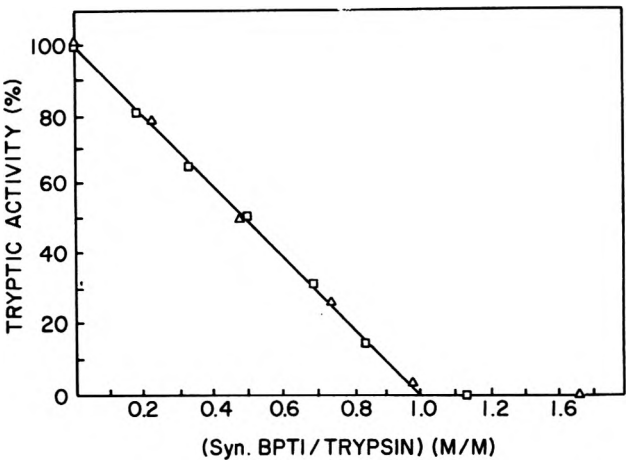

Figure 1. Assay of highly purified synthetic BPTI. The titration of synthetic BPTI was carried out employing increasing inhibitor to β-trypsin radios. The titrations were monitored by assaying the remaining β-trypsin activity. BPTI was incubated with β-trypsin for 3 min, followed by addition of the appropriate substrate. The remaining trypsin activity was measured by (a) rate assay (△); (b) NPGB active site titration (□).

Characterization of the Synthetic Peptide. Amino Acid Analysis of the Synthetic Inhibitor. The highly purified synthetic BPTI had the overall amino acid composition (Table II) expected of BPTI except for Ile, which gave only 1 (theory 2) molar equiv after 24 h acid hydrolysis, as already discussed by Dlouha et al.[25]

Inhibitory Activity of Synthetic BPTI. The trypsin concentration employed was 4.00×10^{-7} M when *N*-α-benzoyl-DL-arginine *p*-nitroanilide (BAPNA) was used as the substrate and 5.33×10^{-6} M when *p*-nitrophenyl *p'*-guanidinobenzoate (NPGB) was used as an active site titrant. The stoichiometry of inhibition was followed by adding increasing quantities of synthetic BPTI and by measuring the residual activity after 3 min of incubation (Figure 1 and Table III). For our highly purified synthetic BPTI, both methods gave excellent 1:1 stoichiometry with pure β-trypsin. Thus, the highly purified synthetic BPTI is 100% active.

Circular Dichroism Spectra of the Natural and the Synthetic Inhibitor. The CD spectra of synthetic and natural BPTI are shown in Figure 2. The solvent was a pH 5.0 acetate buffer (0.01 M sodium acetate, 0.14 M NaCl). The molecular ellipticity is given by eq 1 where M is the gram-molecular weight of the sample, c is the concentration of the peptide in g cm^{-3}, and l is the pathlength of sample solution in cm.[26] The sample solution contained ca. 0.2 mg/ml.

$$[\theta] = \frac{\theta}{10}\frac{M}{lc} \text{ (deg cm}^2\text{/dmol)} \quad (1)$$

The fact that the CD spectra of synthetic and native BPTI are virtually identical indicates that they must have very similar, if not the same, conformation and that a substantial degree of racemization of the various amino acids present in the synthetic peptide had not occurred.

Polyacrylamide Gel Electrophoresis. The synthetic BPTI was indistinguishable from native BPTI on disk polyacrylamide gel electrophoresis (7.5% gel, stacked at pH 4.0, run at pH 2.3). When a mixture of the synthetic and native inhibitors was developed on a disk gel the combined protein moved as a single band and behaved identically with pure native BPTI. This indicated a high degree of homogeneity for the highly purified synthetic inhibitor.

Table III. Stoichiometric Titration of Trypsin by Highly Purified Synthetic Inhibitor

A. Using BAPNA Rate Assay to Monitor Residual Tryptic Activity

Trypsin concn 4.00×10^{-7} M

Inhibitor concn $\times 10^6$, M	Inhibitor to trypsin ratio	Residual activity, %
0.000	0.00	100
0.099	0.24	77
0.199	0.50	51
0.248	0.74	26
0.397	0.98	3
0.595	1.47	0

B. Using Active Site Titrant NPGB to Monitor Residual Tryptic Activity

Trypsin concn 5.33×10^{-6} M

Inhibitor concn $\times 10^6$, M	Inhibitor to trypsin ratio	Residual activity, %
0.00	0.00	100
0.88	0.17	78
1.76	0.34	65
2.65	0.51	52
3.53	0.67	33
4.45	0.85	15
5.95	1.13	0

Peptide Maps of Native and Synthetic BPTI. Samples of native and synthetic BPTI were oxidized with performic acid.[27] The oxidized derivatives were then subjected to trypsin digestion, and the peptide maps obtained for natural and synthetic material were identical.[28]

Determination of the Dissociation Constant of the Trypsin–Synthetic Inhibitor Complex.[29] One of the most notable features of the trypsin–BPTI complex is the unusually tight binding of the two proteins to each other. The dissociation constant is 6.0×10^{-14} M at pH 8.0, 25 °C.[6,17] The magnitude of the dissociation constant (K_I) is very sensitive to alterations in the structure of the inhibitor. It was found that selective reduction of the Cys 14–38 bridge in the inhibitor raised the value of K_I to 1.8×10^{-9} M,[17] 3×10^4 times higher than the dissociation constant of the trypsin–native inhibitor complex. Modification of the selectively reduced inhibitor by iodoacetamide lowered the K_I value to 1.7×10^{-10} M. Thus, measurement of the K_I value for the complex of synthetic BPTI with trypsin should provide strong evidence with regard to the identity of the structure of the synthetic inhibitor with that of the native inhibitor, at least in the region of the reactive site.

Owing to the unusually strong binding of BPTI to trypsin, the dissociation constant cannot be evaluated by conventional methods.[5] In analogy to the work of Vincent and Lazdunski, competition for trypsin between the synthetic BPTI and reduced, ^{14}C-carboxyamidomethylated BPTI (abbreviated RCAM*BPTI) was used to obtain the ratio $K_I/K_{I'}$, where K_I represents the dissociation constant of the trypsin–synthetic inhibitor and $K_{I'}$, the dissociation constant for the trypsin–RCAM*BPTI complex.[6,17] Equations 2–4 below define K_I, $K_{I'}$, and their ratio. From this ratio and the known value of $K_{I'}$, it is possible to calculate K_I for the synthetic inhibitor.

$$\text{trypsin} + \text{syn-BPTI} \underset{K_I}{\rightleftharpoons} \text{trypsin-syn-BPTI} \quad (2)$$

$$\text{trypsin} + \text{RCAM*BPTI} \underset{K_{I'}}{\rightleftharpoons} \text{trypsin–RCAM*BPTI} \quad (3)$$

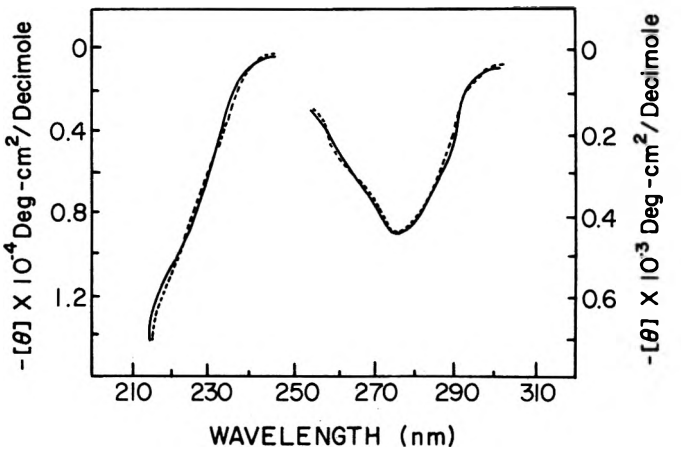

Figure 2. Circular dichroism spectra of natural (solid line) and synthetic (broken line) BPTI. The solvent was a pH 5 buffer containing 0.01 M sodium acetate and 0.14 M NaCl. The left-hand scale is for the far uv region, and the right-hand scale is for the near-uv region.

$$\frac{K_I}{K_{I'}} = \frac{(\text{syn-BPTI})(\text{trypsin-RCAM*BPTI})}{(\text{RCAM*BPTI})(\text{trypsin-syn-BPTI})} \quad (4)$$

Since we could not be sure at the outset whether our synthetic material would bind to trypsin as well as native BPTI does, to avoid wasting ^{14}C-RCAM*BPTI we carried out the following preliminary experiment first. At 25 °C in 0.05 M Tris (pH 8.0, 0.1 M NaCl, 0.05 M $CaCl_2$), 0.15 μmol of β-trypsin was incubated with 0.15 μmol of labeled RCAM*BPTI (0.98 mg). After an incubation period of 15 min, 0.15 μmol of synthetic BPTI was added. The total volume was 15 ml with a 10 μM concentration of each of the partners in complex formation. At times 0, 10 days, and 17 days, aliquots of 4 ml each were passed through a Sephadex G-75 column (2.5 × 72 cm). Since almost all of the labeled RCAM*BPTI was displaced from its complex with β-trypsin, this indicated that the synthetic inhibitor formed a very strong complex indeed with the enzyme.

To determine the dissociation constant for the β-trypsin–synthetic BPTI complex accurately, 0.15 μmol of purified β-trypsin (3.6 mg) was incubated with 15 μmol of ^{14}C-RCAM*BPTI (97.5 mg). After 15 min, 0.15 μmol (0.98 mg) of synthetic BPTI was added. An aliquot of 4 ml of the mixture (containing 0.04 μmol each of β-trypsin and synthetic BPTI and 4.0 μmol of ^{14}C-RCAM*BPTI) was taken and passed through a Sephadex G-75 column, as mentioned above. From the elution profile of Figure 3 it was possible to determine the concentration of trypsin–synthetic BPTI and trypsin–RCAM*BPTI after 10 and 17 days. Equilibrium was attained after 10 days. The concentrations of RCAM*BPTI and of synthetic BPTI were also easily determined.

Unfortunately, in the radioactivity elution pattern shown in Figure 3 the peaks of the complex and the free inhibitor were not completely separated. The total counts of radioactivity in the complex were estimated by assuming a Gaussian distribution for both peaks. The value thus obtained for zero time was checked by applying 0.04 μmol of trypsin–RCAM*BPTI complex to the same column and by determining that the measurement made in the latter experiment was within 5% of that in the former.

From Figure 3 we calculate that $K_I/K_{I'}$ is 4.9×10^{-4}. Since $K_{I'} = 1.7 \times 10^{-10}$ M,[17] we find that $K_I = 8.4 \times 10^{-14}$ M for the complex of β-trypsin with the synthetic inhibitor, a value in very good correspondence with the value of 6×10^{-14} M found in the case of the native inhibitor.[17]

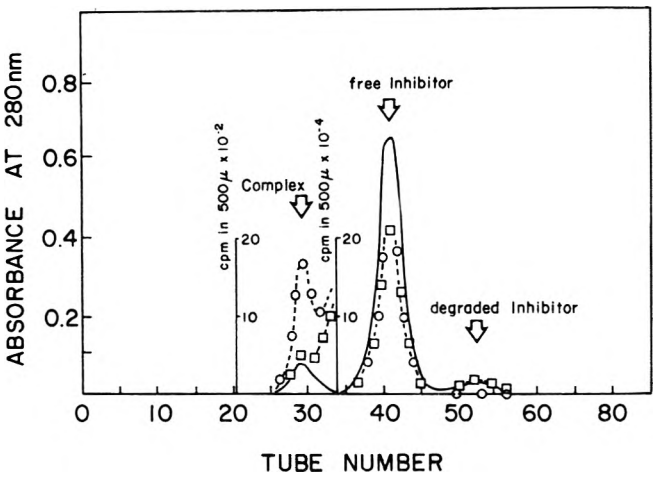

Figure 3. A competition experiment for the evaluation of the dissociation constant of the trypsin–synthetic BPTI complex. First, β-trypsin (0.15 μmol) was incubated with a 100-fold molar excess of ^{14}C-RCAM*BPTI at 25 °C. The association process was completed after 15 min had elapsed.[6,17] At that time, the dissociation of ^{14}C-RCAM*BPTI from the trypsin–^{14}C-RCAM*BPTI complex was initiated by adding synthetic BPTI to give a final concentration of 10.0 μM. Aliquots were taken at different times and gel filtration was performed on a 2.5 × 72 cm Sephadex G-75 column. Solid line: optical density profile at 280 nm. Broken line: radioactivity elution profile patterns at different times in the competition reaction; -O-O-O- time zero; □-□-□- 10 days and 17 days. As shown in this figure, equilibrium was attained after 10 days.

Discussion

Chemical and Physical Evidence for the Purity of the Synthetic Inhibitor and Its Similarity to the Native Inhibitor. The various data recorded and discussed here strongly support the view that our synthetic inhibitor is highly homogeneous and shows virtual identity with the native inhibitor with respect to all chemical and physical properties examined. The evidence for this identity can be summarized as follows. The purified synthetic inhibitor had the overall amino acid composition expected for BPTI. The circular dichroism spectra of the synthetic inhibitor and the native inhibitor were identical within experimental error, indicating that the conformation of the synthetic inhibitor was indistinguishable from that of the native inhibitor. Although, predictably, the synthetic trypsin inhibitor was very resistant to trypsin, it was readily digested after performic acid oxidation. Peptide maps of the digests showed, as expected, ten spots that corresponded very well with the positions of the peptides derived from the native inhibitor. However, the possibility exists that peptides arising from very small amounts of chains with different sequences would have gone undetected. The chromatographic behavior on CM-Sephadex of the highly purified synthetic inhibitor corresponded exactly with that of native BPTI. Furthermore, the synthetic inhibitor was indistinguishable from the native inhibitor on polyacrylamide gel electrophoresis, providing evidence for the similarity of the net charge, size, and shape of the two species. The most important criterion for the identity of the synthetic inhibitor with the native inhibitor, particularly in the region of the crucial reactive site, is the good agreement of the dissociation constant of the β-trypsin–synthetic inhibitor complex with that of the β-trypsin–native inhibitor complex. Our value (8×10^{-14} M) is practically the same as the literature [6,17] value (6×10^{-14}M). The small difference between the values is within the experimental error of our determination and is probably due to the incomplete separation of the peaks in the radioactivity elution pattern of the complex and free inhibitor species.

Conclusions

In 1971, Noda et al.[30] reported the synthesis using the Merrifield solid-phase method[1-3] of a polypeptide with 35–39% of the inhibitory activity of BPTI against trypsin, as determined by a rate assay method. Later, Yajima et al.[31,32] used fragment condensation on a solid support to synthesize a polypeptide which had 82% of the inhibitor activity of BPTI against trypsin, using the same rate assay technique. On this basis the latter workers argued that fragment condensation is a better procedure for the preparation of peptides than the simple stepwise solid-phase synthesis. However, a major problem with this argument is that the inhibitory activity of the synthetic inhibitor measured by a rate assay technique with a good substrate like α-*N*-tosyl-L-arginine methyl ester (see Noda et al.[30] and Yajima et al.[31,32]) provides very weak evidence indeed for the identity of the reactive site region of the synthetic and native inhibitor or for the homogeneity of the synthetic material. This statement is made because the binding of the native inhibitor to trypsin is very tight (dissociation constant = 6×10^{-14} M at pH 8, 25 °C). Since even the most sensitive rate assays for trypsin require trypsin concentrations of at least 10^{-9} M, this means that any synthetic trypsin inhibitor which has a dissociation constant appreciably below 10^{-10} M could appear to be 100% pure using an assay substrate like α-*N*-tosyl-L-arginine methyl ester. Hence, if the synthetic inhibitor were heterogeneous or had an incorrect sequence around the reactive site, as long as the average dissociation constant was significantly less than 10^{-10} M, the synthetic inhibitor would appear to be 100% active, using the rate asaay criterion. On the basis of the published information it is not possible to tell whether Noda et al.[30] obtained an inhibitor in their synthesis which was 35–39% pure BPTI or whether they synthesized another inhibitor with a much higher dissociation constant than BPTI. A similar question arises with regard to the work of Yajima et al.[31,32]

In our synthesis we have been able to determine the dissociation constant of the synthetic BPTI–trypsin complex which is 8×10^{-14} M under conditions where a value of 6×10^{-14} M has been reported in the literature[6,17] for the native inhibitor trypsin complex. This observation, in addition to the peptide mapping, polyacrylamide gel electrophoresis, circular dichroism, and amino acid analysis data, indicates that we do have a synthetic inhibitor which has properties identical with those of the native inhibitor within experimental error. In conclusion, we feel that the present status of work on the synthesis of BPTI does not provide support for the contention of Yajima et al.[31] that "fragment condensation in peptide synthesis is better than simple stepwise solid phase synthesis".

Experimental Section

Materials and Methods. Glass-distilled dichloromethane and chloroform from Burdick and Jackson Laboratories were distilled before use. Trifluoroacetic acid (Aldrich) was distilled and stored in amber bottles with polyethylene-lined screw caps. Analytical grade dimethylformamide from J. T. Baker Chemical Co. was purified and tested according to the procedure of Stewart and Young[3] and was stored under a nitrogen atmosphere at 4 °C in brown bottles over molecular sieves (Linde Type 4A). Triethylamine (Eastman Kodak) was distilled from calcium hydride. Dicyclohexylcarbodiimide from Aldrich Chemical Co. was distilled under reduced pressure.

Chloromethylated styrene–divinylbenzene (DVB) copolymer (1% cross-linked) was purchased from Schwarz/Mann. The *tert*-butyloxycarbonyl amino acid derivatives used were the following: Ala, Asp(β-benzyl), Asn-*p*-nitrophenyl ester, Glu(γ-benzyl), Gln-*p*-nitrophenyl ester, Gly, Lys(ε-2-chlorobenzyloxycarbonyl), Phe, Thr(benzyl), Ser(benzyl), Tyr(2,6-dichlorobenzyl), Cys(*p*-methoxybenzyl), Met, Val, Leu, Ile, and Pro. These were all purchased from Bachem Inc., Calif. The purity of each amino acid derivative was checked by thin layer chromatography on silica gel chromatogram sheets (Eastman) before use.[3]

Sodium acetate, sodium sulfite, sodium carbonate, sodium bicar-

bonate (Baker Analyzed grade), β-mercaptoethanol (Eastman Kodak), Tris (Tris base, Schwarz/Mann), *N*-benzoyl-DL-arginine *p*-nitroanilide (Sigma), *p*-nitrophenyl *p*-guanidinobenzoate HCl (Schwarz/Mann), calcium chloride (Baker), benzamidine HCl, cyanogen bromide, and ninhydrin (Aldrich) were used without further purification. Reagent grade urea (Fisher Scientific Co.) was recrystallized from 95% ethanol prior to use.[33] Sephadex G-50, CM Sephadex C-25, Sephadex SEC-50, and Sepharose 4B were obtained from Pharmacia Fine Chemicals.

Trypsin was purchased from Sigma and purified by Sephadex SEC-50 ion exchange chromatography.[34] β-Trypsin was used throughout the whole experiment. A trypsin–Sepharose column was prepared according to Chauvet and Acher.[35] The native BPTI was a gift from Bayer Co., with part of it isolated from bovine lung.[4] The protein was pure[36] as judged by polyacrylamide gel electrophoresis and stoichiometry of the inhibition with trypsin. ^{14}C-Carboxamidomethylated BPTI selectively reduced at S–S bond 14–38 was a gift from Professor M. Lazdunski and Dr. J. P. Vincent. (Radioactivity was 4.4×10^6 dpm/μmol.)

The optical densities of column effluents were measured with a Gilford spectrophotometer. Circular dichroism spectra were measured on a Cary 60 spectropolarimeter. Trypsin assays and active site titration were carried out on a Cary 15 spectrophotometer. A Packard Tri-Carb liquid scintillation spectrometer was used for counting of radioactive samples. Amino acid analyses were performed using the 0.2 and 2.0 scales on a Beckman Spinco Model 121 automatic amino acid analyzer. The Beckman Model 990 peptide synthesizer was used for the synthetic work.

All pH measurements were carried out on a Beckman Research pH meter with combined glass–calomel electrodes (Thomas no. 4094 L60). The meter was standardized against Fisher Certified standard buffers prior to use. Deionized water was obtained by passing distilled water through a Continental demineralizer.

BPTI and trypsin concentrations were estimated on the basis of the absorbance of their solutions at 280 nm with a conversion factor to mg/ml of 1.206 and 0.67, respectively.[37]

Assay of Trypsin Inhibitor. The inhibitory activity of trypsin inhibitor was measured as a function of the inhibitor to proteinase ratio.[7] As described below, two methods were employed to monitor the titration of trypsin's active site with the inhibitor.

A. Rate Assay Employing *N*-α-Benzoyl-DL-arginine *p*-Nitroanilide (BAPNA)[4] to Measure the Remaining Tryptic Activity. To 3 ml of 0.1 M Tris buffer (pH 7.8, 0.02 M $CaCl_2$) 100 μl of β-trypsin solution (ca. 10^{-5} M) was added. An appropriate amount of inhibitor was added and the resultant solution was incubated for 3 min at 25 °C. Then 100 μl of BAPNA solution (10 mg/ml of DMF) was added. The Δ OD_{405} per min was measured with a Cary 15 spectrophotometer. The final concentrations of the enzyme and inhibitor were ca 10^{-7} M.

B. Active Site Titration to Measure the Remaining Tryptic Activity.[38,39] An aliquot of trypsin solution (in 10^{-3} M HCl, 0.02 M $CaCl_2$) was diluted with 0.1 M veronal buffer (pH 8.3, 0.02 M $CaCl_2$) to give 1.0 ml of 5×10^{-6} M trypsin solution. An appropriate amount of trypsin inhibitor was added. The resultant solution in a 1 ml capacity cuvette was placed in the sample cell position of the spectrophotometer and the instrument balanced against a reference cell containing the same buffer. Then a solution of 10 μl of 0.01 M NPGB (*p*-nitrophenyl *p'*-guanidinobenzoate) in DMF was added to the reference cuvette, the contents mixed, and the cell replaced in the instrument; the same procedure was followed with the sample cuvette and the instrument turned on. The "burst" was measured and the concentration of active trypsin calculated by assuming ϵ_{410} = 16 595.

Anaerobic Column Chromatography.[40] In order to minimize the undesirable intermolecular cross-linking of free thiol groups during the column chromatography of the concentrated reduced inhibitor, an anaerobic system was used. It consisted of a column and an elution buffer vessel, both modified to facilitate anaerobic assembly and operation. Oxygen-free nitrogen gas was used for flushing and bubbling throughout the experiment.

Synthesis of the Protected Linear 58 Amino Acid Residue Polypeptide Chain of Bovine Pancreatic Trypsin Inhibitor. Boc-Ala-resin ester was prepared essentially as described in the literature.[41] The hydrolysis of 20 mg of the sample with 6 M HCl in dioxane yielded 0.28 mmol of Ala per gram of resin.

Synthesis of the Protected Peptide. Boc-Ala-resin ester (1.2 mequiv, 4.28 g) was placed in the small vessel (5 g capacity) of the automated Beckman Model 990 peptide synthesizer. The instrument was programmed to perform the remainder of the synthesis automatically.

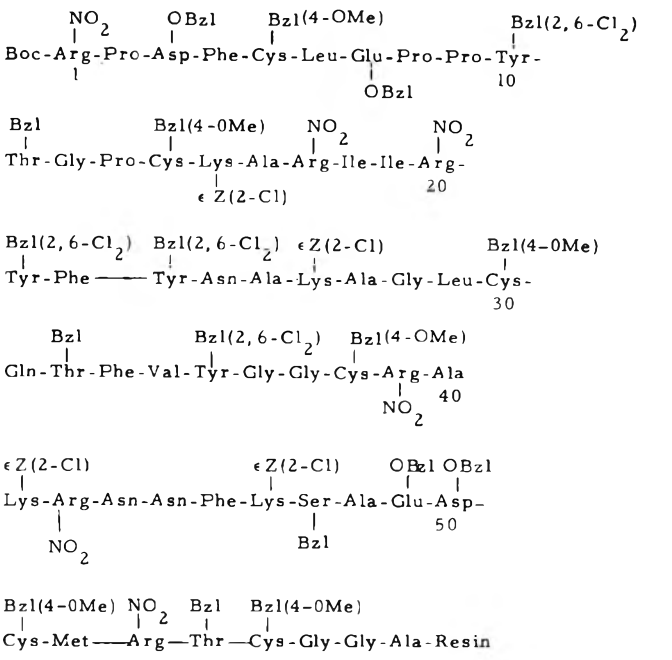

Figure 4. Structure of fully protected BPTI resin.

One cycle of the synthesis (DCC-mediated coupling) consisted of (1) CH_2Cl_2 wash (2 × 40 ml); (2) TFA–CH_2Cl_2 (1:1) prewash (20 ml); (3) TFA–CH_2Cl_2 (1:1, 40 ml) for 30 min; (4) CH_2Cl_2 wash (3 × 40 ml); (5) methanol wash (25 ml); (6) CH_2Cl_2 wash (3 × 40 ml); (7) 10% triethylamine in chloroform (40 ml); (8) CH_2Cl_2 wash (4 × 25 ml); (9) Boc-amino acid (2.5-fold excess in CH_2Cl_2, the Boc derivatives of ε-2-chloro-Z-lysine and nitroarginine were dissolved in a minimum amount of DMF before dilution to 10 ml with CH_2Cl_2); (10) dicyclohexylcarbodiimide (5 ml, threefold excess), 4–6 h; (11) CH_2Cl_2 wash (3 × 25 ml); (12) DMF wash (2 × 25 ml); (13) CH_2Cl_2 wash (3 × 25 ml). The time for all washing steps was set at 1 min.

For an active ester coupling cycle (Asn or Gln), the Boc-amino acid *p*-nitrophenyl ester (ca. fourfold excess) was dissolved in DMF, and addition of the ester was preceded by washing twice with 25-ml portions of DMF. Of course, addition of DCC was omitted. The coupling time was usually 18 h.

The program was interrupted after steps 8 and 13, and a small sample of the resin (ca. 5–10 mg) was removed in order to carry out the ninhydrin color test.[21] When the ninhydrin test for step 13 was negative, the same cycle of reactions was repeated for the next amino acid residue. When a positive result was obtained, the resin was washed with absolute ethanol (2 × 40 ml) and the test repeated. If a positive result was still observed, the coupling reaction (steps 9–15) was repeated. Recoupling was found necessary for the following amino acid residues: Asn 44 (recoupled twice), Asn 43 (recoupled twice), and Asn 24. Following the second recoupling of Asn 43, the ninhydrin test was still slightly positive, and the peptide resin was then acetylated with a mixture of 2 ml of acetic anhydride (J. T. Baker Chemical Co.) and 1 ml of *N*-methylmorpholine (Aldrich) in 25 ml of DMF (30 min shaking), followed by through washing with DMF and CH_2Cl_2.

In addition to the small analytical samples a large sample (6.7 g) was removed after the peptide chain reached 42 residues for the synthesis of inhibitor analogues.

Upon completion of the synthesis, the resin was washed with ethanol (3 × 25 ml) and dried under vacuum. The final weight was 4.45 g. Taking into account the amounts removed in the synthesis the crude yield was 77%. The structure of the fully protected BPTI resin is illustrated in Figure 4.

HF Cleavage.[42] The apparatus was similar to that described by Sakakibara.[43] It consisted of three vessels (a reservoir, a reactor, and a trap) molded from Kel-F rods. All valves were made of Teflon. Liquid HF in stainless steel cylinders were obtained from Matheson Co. A typical HF cleavage procedure for a 1-g resin peptide sample is described below.

The reservoir was charged with 10 ml of HF and 50 mg each of tyrosine and tryptophan. The dried resin peptide sample was placed in the reactor, and 1 ml of anisole (Aldrich, 99%) and 200 mg of methionine were added. The reactor was kept at ice bath temperature (0–4 °C) and 5 ml of HF was distilled from the reservoir into the reactor over a period of a few minutes. The reaction mixture usually

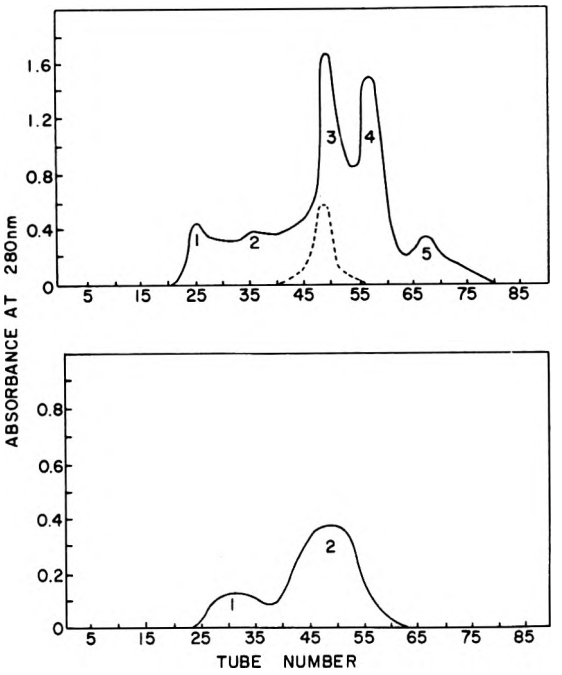

Figure 5. Gel filtration on Sephadex G-50 of the cleaved peptide. The column (4 × 50 cm) was eluted with 0.1 M acetic acid. Top—solid line: crude extract from 450 mg of resin peptide in ca. 25 ml of 10% acetic acid. Peaks 1 and 2, 51 mg; peak 3, 65 mg; peaks 4 and 5, 55 mg. Fraction size: 4.3 ml. Broken line: native BPTI applied to the same column. Bottom—the peptides present in the fractions under peaks 1 and 2 of the top chromatogram were reduced and then gel filtered on the same column. Peak 1, 16 mg; peak 2, 34 mg.

became orange-brown. After 40 min, HF was removed by distillation at room temperature over a period of about 15 min. The resin was broken up in ethyl acetate (250 ml) to wash out HF and anisole. The ethyl acetate filtrate was usually slightly hazy.

Purification of Synthetic BPTI. Sephadex G-50 Gel Filtration. Deaerated 10% HOAc (25 ml) was used to extract peptide from a 450-mg resin–peptide mixture. The solution was then fractionated on a Sephadex G-50 column (4 × 50 cm) by elution with deaerated 0.1 M acetic acid under anaerobic conditions. The synthetic product was separated into five peaks with the following yields: peak 1 and 2 combined, 51 mg; peak 3, 65 mg; peaks 4 and 5 combined, 55 mg.

Peak 3, emerging from the column between tube number 44 and 54, behaved similarly to native BPTI with respect to elution volume (Figure 5, top). Peaks 1 and 2 probably consisted of interchain disulfide aggregates of BPTI. Peaks 4 and 5 comprised a mixture of peptides with lower molecular weights. They presumably resulted from incomplete reaction during the synthesis. There was also some Met in peak 5.

The protein aggregates present under peaks 1 and 2 were lyophilized. They were reduced by dissolving in 10 ml of 1.4 M Tris buffer (pH 8.7, 8 M urea)[16] and incubated with about 1 ml of β-mercaptoethanol for 4 h under an atmosphere of nitrogen at room temperature. The solution was then applied to the 4 × 50 cm Sephadex G-50 column and was separated into two peaks (Figure 5, bottom). Peak 2 (34 mg) came out at the same elution volume as native BPTI. It was treated in the same way as peak 3 in the first fractionation.

Reduction and Reoxidation of the Synthetic Material.[16] The fractions under peak 3 obtained from the first Sephadex G-50 fractionation were combined. In the presence of 8 M urea, the pH of the solution was raised to 8.7 by adding Tris. β-Mercaptoethanol (5 ml) was then added and the solution incubated for 4 h at room temperature under a nitrogen atmosphere.

The protein was separated from the reagents with the 4 × 50 cm Sephadex G-50 column, using 0.1 M acetic acid as the eluent under anaerobic conditions. The solution containing the reduced peptide (100 mg) was then diluted to about 4 l., and the pH was raised to 4.5 by adding ammonium bicarbonate. The dilute peptide solution was then air oxidized for 4 days at room temperature.

Purification of the Synthetic Peptide by Affinity Chromatography. The solution containing the air-oxidized peptide (ca. 10% active as a trypsin inhibitor) was applied to the trypsin–Sepharose column. The column was then eluted with 0.1 M acetate buffer (pH 4.0, 0.3 M NaCl, 0.01 M $CaCl_2$) followed by 0.1 M HCl (pH 1.2, 0.5 M NaCl, 0.01 M $CaCl_2$). After lyophilization of the peptide fractions eluted with HCl, 9.5 mg of white powder which was about 80–90% active as a trypsin inhibitor was obtained.

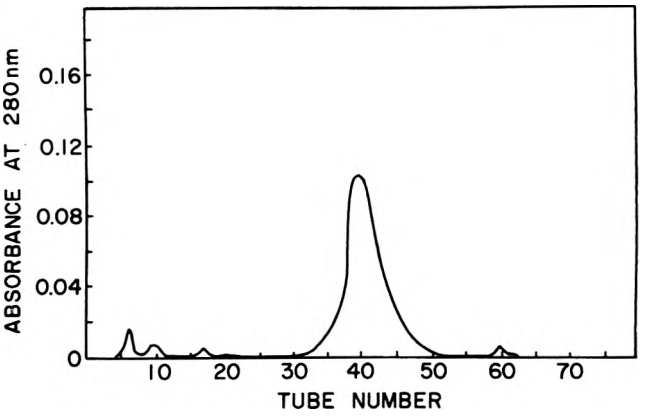

Figure 6. Chromatography of the synthetic BPTI on CM Sephadex C-25. Column, 1 × 15 cm; inhibitor load 4.3 mg; fractions, 4.3 ml each; flow rate about 15 ml/h. The mixing chamber consisted of a 500-ml flask containing 250 ml of 0.01 M phosphate buffer at pH 6.2. The influent to the mixing chamber was the same buffer solution which was also 1 M in NaCl. Yield: 3.9 mg of purified protein which inhibited trypsin stoichiometrically.

Further Purification of Synthetic Material by CM Sephadex C-25 Chromatography. CM Sephadex C-25 was equilibrated with 0.01 M phosphate buffer, pH 6.2. The synthetic inhibitor to be loaded on the column (4.3 mg) was dissolved in 1.5 ml of the same buffer. A 1 × 15 cm column was used. The protein was eluted with a NaCl linear gradient (0–0.25 M NaCl). The chromatogram obtained is shown in Figure 6. The only major peak constituted about 90% of the total protein, and its position agreed well with native BPTI with respect to elution volume. As described below, the highly purified synthetic BPTI showed 1:1 stoichiometry in its complex formation with trypsin.

Effect of HF treatment of Native BPTI. The native inhibitor (39.5 mg) was sulfonated,[44] subjected to HF treatment (in the presence of 2 mg of methionine, 0.4 ml of anisole, yield of recovered crude material 27.3 mg), and reduced.[44] The reduced native inhibitor was then air oxidized for 4 days (pH 4.5, concentration 0.01 mg/ml). After affinity chromatography and CM-Sephadex C-25 ion-exchange chromatography, fully active BPTI was obtained. A recovery of 50% (19.8 mg) of pure BPTI was achieved.

Acknowledgments. We wish to thank Professor M. Lazdunski and Dr. J. P. Vincent for a generous gift of ^{14}C-carboxamidomethylated BPTI and for their advice on the measurement of the dissociation constant of the β-trypsin–BPTI complex. We appreciate very much the numerous HF cleavages performed for us by Mr. J. Geever of the Armour Pharmaceutical Co. and the amino acid analyses carried out by Dr. Y. Nakagawa. This investigation was supported by Grant Number CA-17150, awarded by the National Cancer Institute, DHEW.

Registry No.—Boc-Ala, 15761-38-3; Boc-Asp(β-benzyl), 7536-58-5; Boc-Asn-*p*-nitrophenyl ester, 4587-33-1; Boc-Glu(γ-benzyl), 13574-13-5; Boc-Gln-*p*-nitrophenyl ester, 15387-45-8; Boc-Gly, 4530-20-5; Boc-Lys(ε-2-chlorobenzyloxycarbonyl), 54613-99-9; Boc-Phe, 13734-34-4; Boc-Thr(benzyl), 54784-63-3; Boc-Ser(benzyl), 23680-31-1; Boc-Tyr(2,6-dichlorobenzyl), 40298-71-3; Boc-Cys(*p*-methoxybenzyl), 18942-46-6; Boc-Met, 2488-15-5; Boc-Val, 13734-41-3; Boc-Leu, 13139-15-6; Boc-Ile, 13139-16-7; Boc-Pro, 15761-39-4; BPTI, 12407-79-3.

References and Notes

(1) R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149 (1963).
(2) R. B. Merrifield, *Biochemistry*, **3**, 1385 (1964).
(3) J. M. Stewart and J. D. Young, "Solid Phase Peptide Synthesis", W. H. Freeman, San Francisco, Calif., 1969.
(4) B. Kassell, *Methods Enzymol.*, **19**, 844–852 (1970).
(5) M. Laskowski, Jr., and R. W. Sealock in "The Enzymes", Vol. III. P. D. Boyer,

Ed., Academic Press, New York, N.Y., 1971, pp 375–473.
(6) M. Lazdunski, J. P. Vincent, H. Schweitz, M. Peron-Renner, and J. Pudles in "Proteinase Inhibitors", H. Fritz, H. Tschesche, L. J. Greene, and E. Truscheit, Ed., Springer-Verlag New York, New York, N.Y., 1974, pp 420–431.
(7) B. Kassel and M. Laskowski, Sr., *Biochem. Biophys. Res. Commun.*, **17**, 792 (1964).
(8) B. Kassell, M. Radicevic, M. J. Ansfield, and M. Laskowski, Sr., *Biochem. Biophys. Res. Commun.*, **18**, 255 (1965).
(9) B. Kassell and M. Laskowski, Sr., *Biochem. Biophys. Res. Commun.*, **20**, 463 (1965).
(10) B. Kassell and M. Laskowski, Sr., *Acta Biochim. Pol.*, **13**, 287 (1966).
(11) R. Huber, D. Kukla, A. Rühlmann, O. Epp, and H. Formanek, *Naturwissenschaften*, **57**, 389 (1970).
(12) R. Huber, D. Kukla, A. Rühlmann, and W. Steigemann, *Cold Spring Harbor Symp. Quant. Biol.*, **36**, 141 (1971).
(13) J. Deisenhofer and W. Steigemann in ref 6, pp 484–496.
(14) F. A. Anderer and S. Hörnle, *J. Biol. Chem.*, **241**, 1568 (1966).
(15) J. Chauvet and R. Acher, *Bull. Soc. Chim. Biol.*, **48**, 1248 (1966).
(16) D. Pospisilova, B. Meloun, I. Fric, and F. Sorm, *Collect. Czech. Chem. Commun.*, **32**, 4108 (1967).
(17) J. P. Vincent and M. Lazdunski, *Biochemistry*, **11**, 2967 (1972).
(18) B. W. Erickson and R. B. Merrifield, *J. Am. Chem. Soc.*, **95**, 3750 (1973).
(19) B. W. Erickson and R. B. Merrifield, *J. Am. Chem. Soc.*, **95**, 3757 (1973).
(20) D. Yamashiro and C. H. Li, *J. Am. Chem. Soc.*, **95**, 1310 (1973).
(21) E. Kaiser, R. L. Colescott, C. D. Bossinger, and P. I. Cook, *Anal. Biochem.*, **34**, 595 (1970).
(22) C. B. Anfinsen, *Biochem. J.*, **128**, 737 (1972).
(23) R. R. Hantgan, G. G. Hammes, and H. A. Scheraga, *Biochemistry*, **13**, 3421 (1974).
(24) R. F. Steiner, F. D. Lorenzo, and C. B. Anfinsen, *J. Biol. Chem.*, **240**, 4648 (1965).
(25) V. Dlouha, D. Pospisilova, B. Meloun, and F. Sorm, *Collect. czech. Chem. Commun.*, **30**, 1311 (1965).
(26) B. Jirgensons, M. Kawabata, and S. Capetillo, *Makromol. Chem.*, **125**, 126 (1969).
(27) C. H. Hirs, *J. Biol. Chem.*, **219**, 611 (1956).
(28) B. Meloun, I. Fric, and F. Sorm, *Eur. J. Biochem.*, **4**, 112 (1968).
(29) Professor M. Lazdunski and Dr. J. P. Vincent provided us with ^{14}C-RCAM*BPTI for this experiment.
(30) K. Noda, S. Terada, N. Mitsuyasu, M. Waki, T. Kato, and N. Izumiya, *Naturwissenschaften*, **58**, 147 (1971).
(31) H. Yajima, Y. Kiso, Y. Okada, and H. Watanabe, *J. Chem., Soc., Chem. Commun.*, 106 (1974).
(32) Y. Kiso and H. Yajima, *Chem. Pharm Bull.*, **22**, 1087 (1974).
(33) G. R. Stark, W. H. Stein, and S. Moore, *J. Biol. Chem.*, **235**, 3177 (1960).
(34) D. D. Schroeder and E. Shaw, *J. Biol. Chem.*, **243**, 2943 (1968).
(35) J. Chauvet and R. Acher, *FEBS Lett.*, **23**, 317 (1972).
(36) E. Sach, M. Thely, and J. Choay, *C. R. Acad. Sci.*, **260**, 3491 (1965).
(37) R. Avineri-Goldman, I. Snir, G. Blauer, and M. Rigbi, *Arch. Biochem. Biophys.*, **121**, 107 (1967).
(38) T. Chase and E. Shaw, *Biochem. Biophys. Res. Commun.*, **29**, 508 (1967).
(39) J. C. Zahnley and J. G. Davis, *Biochemistry*, **6**, 1428 (1970).
(40) R. Repaske, *Methods Enzymol.*, **22**, 322–325 (1971).
(41) A. Marglin, *Tetrahedron Lett.*, **33**, 3145 (1971).
(42) These cleavages were performed by Mr. Jim Geever of the Armour Pharmaceutical Co.
(43) S. Sakakibara, Y. Shimonishi, Y. Kishida, M. Okada, and H. Sugihara, *Bull. Chem. Soc. Jpn.*, **40**, 2164 (1967).
(44) W. C. Chan, *Biochemistry*, **7**, 4247 (1968).

Nucleosides. 100. General Synthesis of Pyrimidine C-5 Nucleosides Related to Pseudouridine. Synthesis of 5-(β-D-Ribofuranosyl)isocytosine (Pseudoisocytidine), 5-(β-D-Ribofuranosyl)-2-thiouracil (2-Thiopseudouridine) and 5-(β-D-Ribofuranosyl)uracil (Pseudouridine)[1]

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A general procedure for the synthesis of pyrimidine C-5 nucleosides related to pseudouridine was developed. 5-(β-D-Ribofuranosyl)isocytosine (**7**, pseudoisocytidine), the first chemotherapeutically active synthetic C nucleoside, was prepared from readily available ethyl 2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acetate (**3**). Compound **3** was formylated with ethyl formate and sodium hydride to the corresponding formylacetate sodium enolate **4** and methylated with methyl iodide in DMF to give 3-methoxy-2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acrylate (**5**). Cyclization of **5** with guanidine afforded the protected isocytosine C-5 nucleoside **6**. Treatment of **6** with methanolic hydrogen chloride gave the desired crystalline β nucleoside, pseudoisocytidine (**7**). From the mother liquor, the α isomer **8** was obtained. Compound **8** can be epimerized effectively to **7** in methanolic hydrogen chloride so that a very high yield of the desired isomer **7** from **6** is readily achieved. The general applicability of this method to the syntheses of other C nucleosides was demonstrated by the synthesis of 2-thiopseudouridine (**10**) and pseudouridine (**13**). Condensation of the acrylate derivative **5** with thiourea followed by deblocking of the product afforded **10**. When **5** was treated with urea, the protected pseudouridine derivatives (**11** and **12**) were obtained. After deprotection of **11**, pseudouridine (**13**) was obtained.

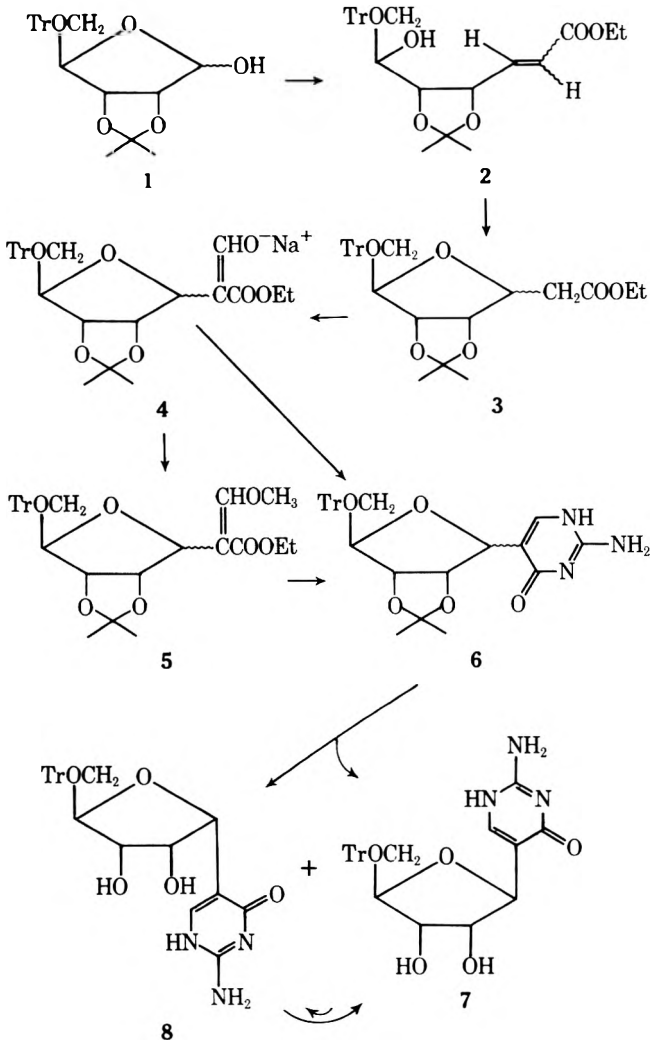
Pseudouridine, the first C nucleoside found in nature, has attracted the interest of organic chemists and biochemists since its discovery in 1957.[2] Recently, other C nucleosides have also been isolated as nucleoside antibiotics from the culture filtrates of various *Streptomycetes*.[3] The unique structural characteristic of C nucleosides which distinguishes them from the ordinary nucleosides is the presence of a carbon to carbon linkage instead of a carbon to nitrogen bond between the aglycon and sugar moieties. This structural feature renders traditional approaches[4] for nucleoside synthesis of limited value.

Although several reports have appeared on the synthesis of pseudouridine[5] and pseudocytidine,[6] these methods involve the condensation of a suitably protected sugar with a preformed pyrimidine-5-yllithium derivative. These procedures are difficult to perform and are not suitable for large-scale preparations. More importantly these methods are specific for each C nucleoside, i.e., for the synthesis of a modified base analogue preparation of a particular pyrimidine 5-lithio derivative is required individually.

As a part of our efforts to develop a *general* method for the synthesis of pseudouridine and analogues thereof we reported in a recent communication[7] a synthesis of 5-(β-D-ribofuranosyl)isocytosine (**7**, pseudoisocytidine) in four steps from 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose (**1**) via intermediates **3** → **4** → **6** (see Chart I).

Owing to the potential clinical importance[8] of pseudoisocytidine as an antileukemic agent, we now report our synthetic

Chart I



procedures including modifications which result in improved yield of pseudoisocytidine. Further, the general applicability of our methods for the synthesis of pyrimidine C nucleosides is exemplified by the synthesis of 2-thio-pseudouridine (**10**) and pseudouridine (**13**).

Treatment of **1** with (ethoxycarbonylmethylene)triphenylphosphorane according to Ohrui et al.[9] afforded ethyl 2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acetate (**3**). This reaction is often accompanied by the formation of significant amounts of a more polar by-product as observed by thin layer chromatography (TLC) in addition to the desired product **3**. The by-product was isolated by silica gel column chromatography and was shown by ^{1}H NMR to be a mixture of cis and trans olefins **2** (see Experimental Section). Buchanan et al.[10] had reported the isolation of an olefin analogous to **2** after treatment of tri-*O*-benzyl-D-ribofuranose with the same Wittig reagent and showed that their olefin could be converted into a cyclic derivative analogous to **3** by base catalysis. Thus, after the reaction of **1** with the Wittig reagent, the product which contained the open-chain intermediate **2** was treated with alkoxide and the desired intermediate **3** was obtained in high yield. The epimeric configuration at C-1 of the "ribosyl" derivative **3** was not determined, and indeed is not crucial because epimerization occurs in subsequent steps (vide infra).

The key step in the synthesis of pseudoisocytidine and related C nucleosides is the formylation of **3**. Compound **3** was treated with ethyl formate and sodium hydride in a mixture of anhydrous ether and absolute ethanol. Without purification, the product sodium enolate **4** was treated with guanidine in ethanol in the presence of sodium ethoxide. Protected pseudoisocytidine (**6**) was obtained in 5% yield as colorless crystals after silica gel column chromatography. The reproducibility of the yield of **6**, however, was inconsistent. Owing to the low acidity of the α hydrogens of the ester **3**, formylation did not go to completion resulting in an intractable mixture.

Base-catalyzed cyclization of crude **4** with guanidine to the protected nucleoside **6** proceeded poorly owing to the preponderance of the enolate form **4** in base. The attack by the nitrogen nucleophile on the aldehydic (enolic) carbon atom would be electrostatically hindered by the adjacent negatively charged oxygen. Removal of the negative charge from the enolic oxygen by alkylation should therefore favor the cyclization reaction. Thus, the crude sodium enolate **4** was methylated with methyl iodide in DMF and the desired β-methoxyacrylate derivative [ethyl 3-methoxy-2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acrylate] (**5**) was isolated in crystalline form after column chromatography in ~25% yield from **1**.

Attempts to separate **5** on a large scale were found not practical owing to appreciable decomposition of this product on the silica gel column. Although the protected C nucleoside **6** could be obtained in ~90% yield from crystalline β-methoxyacrylate **5**, it was found more practical to use crude **5** directly for cyclization with guanidine. Under these conditions, pure compound **6** was isolated in crystalline form in ~15% overall yield from **1**.

The α configuration is assigned to crystalline **6** on the basis of Imbach's rule[11] and deblocking experiments. The difference in chemical shifts of the methyl signals of the isopropylidene group (11 Hz) falls into the α-nucleoside range (<15 Hz). Brief treatment of crystalline **6** with 10% methanolic hydrogen chloride gave predominantly the α isomer **8**, whereas prolonged treatment afforded predominantly the desired β isomer **7**. Compound **7** crystallized from the reaction mixture as its hydrochloride salt while the α isomer **8** remained in solution. Thus, the yield of the desired pseudoisocytidine **7** was readily raised to ~80%.

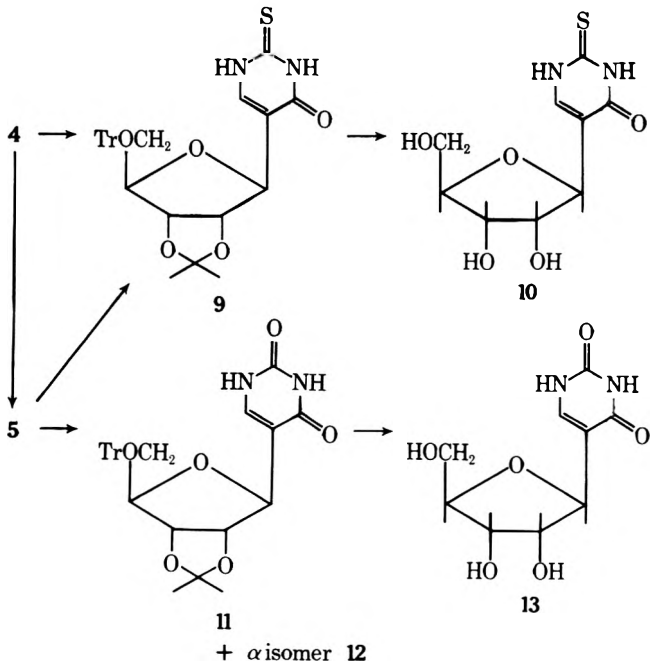
The assignment of configuration at C-1′ of pseudoisocytidine (**7**) and the α isomer **8** is based on ^{1}H NMR studies. The ^{1}H NMR spectrum of **7** is almost identical with that of pseudouridine[12] and quite different from the α-pseudouridine spectrum,[12] the latter of which is almost identical with the ^{1}H NMR spectrum of **8**. The chemical shift of H-1′ of **7** (δ 4.72) is higher than that of **8** (δ 5.04) and the chemical shift of H-6 of **7** (δ 7.75) is lower than that of **8** (δ 7.65). Furthermore, the allylic coupling between H-1′ and H-6 in **7** (0.78 Hz) is smaller than that of **8** (1.27 Hz). All of these NMR characteristics are also observed for the "anomeric" pseudouridines.[13] Moreover, the difference in chemical shifts for H-1′ (0.32) and H-6 (0.10) for the pseudoisocytidine isomers **7** and **8** are identical with the corresponding values for the isomeric pseudouridines.[12] The pK_a value for the β isomer **7** (8.97) is smaller than that of the α isomer **8** (9.12). Chambers[14] also observed that the pK_a value of pseudouridine (9.1) is smaller than that of α-pseudouridine (9.5) and suggested that the reason for this difference is that the monoanion of the β isomer is stabilized by a hydrogen bond between the 2-carbonyl and 5′-hydroxyl groups.

The pure α isomer **8** slowly underwent epimerization at C-1′ in dilute deuterium chloride to pseudoisocytidine **7** as indicated by ^{1}H NMR. The H-6 signal of **8** decreased slowly with concomitant increase of a new signal corresponding to the H-6 signal of **7**. Also, pure **7** epimerized to **8** under the same conditions, but the rate of epimerization was significantly lower than that of **8** to **7**. At the equilibrium point the α:β ratio was approximately 1:4. The formation of pyranosyl isomers, as

found in the case of pseudouridine,[14] was not observed. Pseudoisocytidine 7 was stable at pH 7.2 at 38 °C for at least 7 days. The mechanism for the interconversion (7 ⇌ 8) is probably akin to that proposed[15] for the isomerization of pseudouridines involving protonation of the sugar ring oxygen followed by opening of the furanoid ring. To our knowledge the synthesis of pseudoisocytidine is the first example of exploitation of epimerization at C-1′ to obtain the desired nucleoside isomer.

The versatility of intermediates 4 and 5 was further demonstrated (Chart II) by the synthesis of 5-(β-D-ribofurano-

Chart II



syl)-2-thiouracil (10). Treatment of 4 with 1.5 equiv each of thiourea and sodium ethoxide afforded the protected 2-thiopseudouridine 9 which was isolated in crystalline form after column chromatography. When the acrylate 5 was cyclized with thiourea, the same product 9 was obtained in higher yield. The large difference in chemical shifts of the two isopropylidene methyl signals in the ^{1}H NMR ($\Delta\delta$ 22.8) suggests that the crystalline product 9 is the β isomer. Brief treatment of 9 with methanolic hydrogen chloride afforded the pure β isomer 10, the ^{1}H NMR spectrum of which was almost identical with that of pseudouridine, whereas longer treatment gave an α,β mixture of isomers. The epimerization occurred much more rapidly than that noted above for pseudoisocytidines. At equilibrium, the α/β ratio was almost 1. Prolonged treatment of 10 with methanolic hydrogen chloride produced a complicated mixture, as indicated by the ^{1}H NMR spectrum, owing probably to the formation of pyranosyl isomers as well.

A total synthesis of pseudouridine (13) was also achieved from the common β-methoxyacrylate intermediate 5. Treatment of pure 5 with urea and sodium ethoxide in ethanol afforded an isomeric mixture of the protected C nucleosides (11 and 12, β:α ≃ 3:1) in 57% yield after chromatographic purification. A partial separation of the mixture of 11 and 12 was achieved on a thick layer plate using a multidevelopment technique. The β isomer 11 was isolated in pure form, but the minor nucleoside 12 was not obtained in pure state. When compound 11 was treated with methanolic hydrogen chloride, crystalline unprotected nucleoside 13 precipitated from the reaction mixture. Compound 13 was identical with natural pseudouridine.

Extensions of these syntheses to other pyrimidine C nucleosides with modifications in the aglycon and in the sugar moiety are underway in our laboratory.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are corrected. ^{1}H NMR spectra were obtained on a JEOL J1M-PET-100 spectrometer, and Me_4Si was the internal standard for organic solvents and $Me_3Si(CH_2)_3SO_3Na$ for D_2O; chemical shifts are reported in parts per million (δ) and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet); δ and J values are first order. TLC was performed on microscope slides coated with silica gel GF_{254} (Merck), and column chromatography on silica gel G or silica gel G60 (70–230 mesh, ASTM, Merck). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Spang Microanalytical Laboratory, Ann Arbor, Mich. Optical rotations were measured on a Rudolf polarimeter with a photomultiplier attachment.

Ethyl 2-(2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranosyl)acetate (3). 2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranose[16] (43.2 g, 0.1 mol) and (ethoxycarbonylmethylene)triphenylphosphorane (37.3 g, 0.11 mol) were dissolved in dry acetonitrile (500 ml, dried over 4-Å molecular sieves) and the solution was heated under reflux for 6 h. The mixture was allowed to cool to room temperature. If two sugar spots (R_f 0.45 for 2 and R_f 0.5 for 3) were found in the mixture on TLC (petroleum ether–ethyl acetate, 5:1), solid potassium *tert*-butoxide (~0.5 g) was added and the mixture was stirred at room temperature until the lower spot on TLC disappeared. The solvent was removed in vacuo and the residue was dissolved in ether (~500 ml). On cooling the solution in an ice bath, triphenylphosphine oxide precipitated which was removed by filtration and the filtrate was evaporated to dryness. This procedure was repeated three times to remove most of triphenylphosphine oxide. The yield of crude product 3 was 45 g (90%) which was sufficiently pure to be used in the formylation reaction to obtain the sodium enolate 4.

Separation of Ethyl 2,3-Dideoxy-4,5-*O*-isopropylidene-7-*O*-trityl-D-*ribo*-sept-2-enonates (2) and Their Conversion into 3. Occasionally in the reaction of 1 with the Wittig reagent, two product spots were observed by TLC. In one experiment a crude syrup (10 g), after removal of triphenylphosphine oxide, was chromatographed on a column of 250 g of silica gel G60 in nylon tube (2.25-cm diameter) using petroleum ether–ethyl acetate (5:1) as the eluent and *p*-dimethylaminoazobenzene (butter yellow) as the marker. After the yellow band of the marker came off, the column was cut up into 14 fractions. Each fraction was extracted with ethyl acetate and checked by TLC. From the 6th fraction from bottom, 490 mg of a colorless syrup was obtained after evaporation of the ethyl acetate extracts. ^{1}H NMR spectrum of the syrup showed complex olefinic signals that integrated for two protons at δ 5.51–6.18 in $CDCl_3$ (indicating a mixture of olefins 2).

To a solution of 2 (~100 mg) in acetonitrile (10 ml) was added potassium *tert*-butoxide (~5 mg) and the mixture was stirred for 1 h at room temperature. TLC showed a single spot corresponding to 3 in the mixture and complete disappearance of the spot for 2. After evaporation of the solvent, the residual syrup showed no olefinic signals at δ 5.51–6.18 in NMR spectrum which, in turn, showed the syrup to be an isomeric mixture of the acetates 3.

Ethyl 2-Formyl-2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acetate Sodium Enolate (4). To a suspension of sodium hydride (18 g, 50% in mineral oil) in absolute ether (300 ml, distilled over $LiAlH_4$) was added 2 ml of absolute ethanol followed immediately by dropwise addition of a mixture of compound 3 (155 g, 0.31 mol), ethyl formate (100 ml, distilled over K_2CO_3) and anhydrous ether (200 ml). The mixture was stirred overnight at room temperature, and then the solvent was removed by evaporation in vacuo at room temperature. The residue, 155 g of crude 4, was not purified but directly used in the next step.

Ethyl 3-Methoxy-2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acrylate (5). The crude sodium enolate 4 (155 g) was dissolved in DMF (745 ml, dried over 4-Å molecular sieves). Methyl iodide (75 ml) was added dropwise to the solution over a period of 1 h. The mixture was stirred for 4 h at room temperature and then poured into a mixture of ice and water (3 l.). The supernatant was removed by decantation and the residual syrup was dissolved in CH_2Cl_2 (1 l.), washed with water, dried over sodium sulfate, and evaporated to a brown syrup comprising crude 5 (149 g) which was

used directly in the cyclization reaction with guanidine to **6**.

TLC (benzene–ethyl acetate, 9:1) of crude product showed that it contained at least four components [R_f 0.3, 0.35, 0.4 (major), 0.5]. About 1.2 g of the crude material was chromatographed over a silica gel G column (20 g) using benzene as the eluent. The first compound eluted (203 mg, corresponding to R_f 0.5 on TLC) was compound **3**. The second fraction (402 mg, corresponding to R_f 0.4) was obtained after evaporation of the solvent. The residue, which solidified on standing, was recrystallized twice from ethanol; 135 mg of **5** (mp 161.5–162 °C) was obtained. ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 3 H, CH_3CH_2), 1.32 (s, 3 H, isopropylidene CH_3), 1.56 (s, 3 H, isopropylidene CH_3), 3.23 (m, 2 H, H-5′), 3.81 (s, 3 H, OCH_3), 3.96–4.20 (m, 3 H, CH_3CH_2 and H-4′), 4.90 (t, 1 H, H-3′, $J_{2',3'} \simeq J_{3',4'}$ 6.0 Hz), 4.92 (q, 1 H, H-2′, $J_{1',2'} \simeq 3.6$, $J_{2',3'} \simeq 6.0$ Hz), 5.10 (d, 1 H, H-1′, $J_{1',2'} \simeq 3.6$ Hz).

Anal. Calcd for $C_{33}H_{36}O_7$: C, 72.79; H, 6.62. Found: C, 72.92; H, 6.68.

5-(2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranosyl)isocytosine (6). Method A. From the Sodium Enolate 4. Guanidine hydrochloride (15.0 g) was added to ethanolic sodium ethoxide (prepared by dissolving 4.6 g of sodium in 200 ml of absolute ethanol) and the mixture was stirred for 10 min at room temperature, then the mixture was filtered through Celite and the filtrate was added to a solution of 55.2 g of the crude enolate **4** in absolute ethanol (100 ml). The reaction mixture was heated under reflux for 24 h and cooled in an ice bath, the insolubles were removed by filtration, and the filtrate was carefully neutralized with 1 N hydrochloric acid (to pH 6.8–7). During the addition of 1 N hydrochloric acid, a small amount of product precipitated. Water was added to complete precipitation. The supernatant was decanted and the residual brown syrup was dissolved in benzene (100 ml), dried over sodium sulfate, and chromatographed on a column of silica gel G (700 g) using benzene–ether (30:1) as the eluent to remove all the unknown by-products. One-liter fractions were collected and each fraction was checked by TLC. Finally, the column was washed with benzene–methanol (10:1). The crude syrup (~7 g), which was obtained after evaporation of the solvent, solidified when refluxed in methanol for ~10 min. Colorless crystals of **6** after cooling, were collected by filtration, 2.7 g, mp 251–253 °C.

Anal. Calcd for $C_{31}H_{31}N_3O_5$: C, 70.86; H, 5.90; N, 8.00. Found: C, 70.85; H, 5.81; N, 7.78.

Method B. From Crude 5. Cyclization of crude **5** (55 g) instead of **4** with guanidine under the same condition and procedure as method A afforded 6.6 g (13%) of **6**, mp 251–253 °C.

Method C. From Pure 5. Guanidine hydrochloride (950 mg, 0.01 mol) was added to ethanolic sodium ethoxide solution (prepared by dissolving 230 mg of metallic sodium in 30 ml of ethanol) and the mixture was stirred for 10 min at room temperature. Crystalline **5** (2.72 g, 0.005 mol) was added and the mixture was refluxed for 24 h, concentrated to ~15 ml, then neutralized with 1 N HCl. Compound **6** precipitated as colorless crystals which were collected by decantation of the supernatant and washed with methanol, mp 251.5–253 °C (2.32 g, 88%).

5-(β-D-Ribofuranosyl)isocytosine (7, Pseudoisocytidine). Method A. Compound **6** (525 mg) was dissolved in 10% methanolic hydrogen chloride (20 ml) and the solution was stirred for 6 h at room temperature. Compound **7** precipitated as colorless crystals which were filtered and washed with ethanol: 53 mg, mp 215–216 °C dec; $[\alpha]^{25}D$ +120° (c 0.1, water); uv[17] λ_{max} (pH 13) 277 nm (ϵ 7340), 232 (9700), λ_{min} (pH 13) 249 (2710); λ_{max} (pH 7.2) (5700), λ_{min} (pH 7.2) 248 (2750); λ_{max} (pH 1) 262 (7820), 221 (10 520), λ_{min} (pH 1) 241 (4920); pK_a 3.72 ± 0.05 and 8.97 ± 0.05.

Anal. Calcd for $C_9H_{13}N_3O_5$·HCl: C, 38.64; H, 5.02; N, 15.02; Cl, 12.70. Found: C, 38.74; H, 5.10; N, 14.91; Cl, 12.82.

The filtrate was evaporated in vacuo at room temperature and the residue was triturated with 5 ml of a mixture of ether and ethanol (1:1). Compound **8** precipitated as colorless crystals: 182 mg, mp 182–183°C dec; $[\alpha]^{25}D$ −164 (c 0.1, water); uv[17] λ_{max} (pH 13) 277 nm (ϵ 7170), 232 (9300), λ_{min} (pH 13) 253 (2640); λ_{max} (pH 7.2) 290 (3980), 270 (3890), λ_{min} (pH 7.2) 288 (3810), 249 (2900); λ_{max} (pH 1) 262 (7470), 222 (10 106), λ_{min} (pH 1) 242 (4800); pK_a 3.92 ± 0.05 and 9.12 ± 0.05.

Anal. Calcd for $C_9N_{13}N_3O_5$·HCl: C, 38.64; H, 5.02; N, 15.02; Cl, 12.70. Found: C, 38.81; H, 5.12; N, 14.88; Cl, 12.91.

Method B. A mixture of **6** (1.5 g) and 10% methanolic hydrogen chloride (50 ml) was stirred for 2 weeks at room temperature. Compound **7** (651 mg, 81%) precipitated and was collected by filtration, mp 215–216 °C dec.

Method C. For a large-scale preparation this method was found to be convenient. Crude syrup of **5** (149 g, 0.27 mol) was dissolved in 300 ml of absolute ethanol and the solution was added to ethanolic guanidine [prepared from guanidine hydrochloride (49 g, 0.47 mol), ethanol (300 ml), and metallic sodium (12 g, 0.52 mol)]; the mixture was heated under reflux for 24 h and cooled in an ice bath, and the insoluble materials were removed by filtration. The filtrate was carefully neutralized with 1 N hydrochloric acid (to pH 6.8–7), then the mixture was diluted with water (600 ml) and extracted with methylene chloride (500 ml × 3). The combined extracts were dried over sodium sulfate and evaporated to dryness to a dark syrup which was dissolved in 10% methanolic hydrogen chloride (300 ml) and the solution was stirred for 1 week at room temperature. Crude **7** (14.0 g) precipitated, and was collected by filtration and recrystallized from water–ethanol to give pale yellow microcrystals, 12.6 g, mp 215–216 °C dec.

5-(2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranosyl)-2-thiouracil (9). Method A. From the Sodium Enolate 4. A mixture of **4** (55.2 g of crude syrup, 0.1 mol) and thiourea (11.4 g, 0.15 mol) in ethanolic sodium ethoxide (prepared from 4.6 g of metallic sodium and 200 ml of absolute ethanol) was refluxed for 15 h. The reaction mixture was allowed to cool to room temperature and neutralized with 1 N hydrochloric acid, and the brown syrup which precipitated was collected by decantation of the supernatant. The syrup was dissolved in ether (~200 ml), washed with water, and dried over sodium sulfate. The ether was evaporated to a syrup which was purified by alumina column chromatography (400 g, Bio-Rad neutral alumina AG-7 100–200 mesh) using chloroform–methanol (4:1) as the eluent. Fractions with a uv absorbing spot and a positive sulfuric acid spray test were collected and evaporated to dryness to give a foam (2.5 g) which was crystallized from ethanol. Compound **9** was obtained as colorless needles: mp 82–83 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3 H, isopropylidene CH_3), 1.55 (s, 3 H, isopropylidene CH_3), 3.24 (q, 1 H, H-5′, $J_{5',5''} \simeq 10.3$, $J_{4',5'} \simeq 10.3$, $J_{4',5''} \simeq 6.6$ Hz), 3.41 (q, 1 H, H-5″, $J_{5',5''} \simeq 3.1$), 4.24 (m, 1 H, H-4′), 4.65 (m, 2 H, H-2′, 3′), 4.89 (q, 1 H, H-1′, $J_{1',2'} \simeq 2.8$, $J_{1',6} \simeq 0.9$), 7.24–7.48 (m, 16 H, trityl H and H-6), 9.79 (d, 1 H, N1-H, exchangeable), 9.94 (s, 1 H, N3-H, exchangeable).

Anal. Calcd for $C_{31}H_{30}N_2O_5S$: C, 68.63; H, 5.54; N, 5.17; S, 5.90. Found: C, 68.69; H, 5.65; N, 5.05; S, 5.77.

Method B. From Compound 5. A mixture of crude **5** (54.4 g, 0.1 mol) and thiourea (11.4 g, 0.15 mol) was treated with methanolic sodium ethoxide as described above. Compound **9** (3.5 g) was obtained as colorless needles, mp 83–84 °C.

5-(β-D-Ribofuranosyl)-2-thiouracil (10, 2-Thiopseudouridine). A mixture of **9** (542 mg, 0.001 mol) and 10% methanolic hydrogen chloride (25 ml) was stirred for 10 min at room temperature. The solvent was evaporated in vacuo (below 25 °C) to give a syrup which was triturated with 10 ml of water and filtered. The filtrate was decolorized with charcoal and evaporated to dryness in vacuo. The residue was triturated with cold ethanol and the white precipitate was collected by filtration. The ^{1}H NMR spectrum (D_2O) of this sample was very similar to that of pseudouridine.[12] The signals for H-6 and H-1′ occurred at δ 7.65 and 4.69 with $J_{1',6} \simeq 0.91$ Hz. Uv λ_{max} (pH 1–7) 276 nm, 290 (shoulder), λ_{min} (pH 1–7) 242, λ_{max} (pH 12) 313, 263, 235 (shoulder), λ_{min} (pH 12) 298. This compound was so hygroscopic that optical extinction (ϵ value) could not be obtained, and it was best analyzed as a partially hydrated foam.

Anal. Calcd for $C_9H_{12}N_2O_5S$·½ H_2O: C, 39.70; H, 4.94; N, 10.29; S, 11.78. Found: C, 39.55; H, 4.99; N, 8.90; S, 11.44.

Epimerization of **10** in ~1 N DCl was observed by ^{1}H NMR. Two new signals for H-6 and H-1′ appeared at δ 7.55 and 4.98 ($J_{1',6} \simeq 1.21$ Hz) with concomitant decrease of the corresponding signals of **10**. The epimerization occurred faster than that of pseudoisocytidine, and the α/β ratio reached almost 1. In addition, further DCl treatment of **10** gave a more complicated mixture as observed by NMR probably owing to the formation of the pyranosyl isomers.

5-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)uracil (11). A mixture of pure **5** (544 mg, 0.001 mol) and urea (120 mg, 0.002 mol) in ethanolic sodium ethoxide (prepared by dissolving 46 mg of sodium in 15 ml of ethanol) was refluxed for 3 days. The mixture was concentrated to ~8 ml in vacuo and, after cooling, the concentrated solution was neutralized with 1 N HCl to give a white precipitate which was chromatographed on a silica gel G 60 column (50 g, 40 × 2.5 cm diameter) using benzene–methanol (19:1) as the eluent. Each fraction was checked by TLC. Appropriate fractions were combined and evaporated to dryness to give 300 mg (57%) of a mixture of the α and β isomers (**11** and **12**). This mixture showed only a single spot on TLC in various solvent systems: ^{1}H NMR ($CDCl_3$) δ 1.27 and 1.39 (2 s, isopropylidene CH_3 for **12**, $\Delta\delta$ 12 Hz), 1.32 and 1.56 (2 s, isopropylidene CH_3 for **11**, $\Delta\delta$ 24 Hz). The relative intensity of the isopropylidene methyl signals of **11** to those of **12** was approximately 3 to 1.

Thick layer chromatography (2 mm, 20 × 20 cm) on silica gel GF_{254} by multidevelopment technique (five developments) using ben-

zene–methanol (19:1) gave a partial separation in the form of an elongated band. Removal of the lower portion of this band followed by extraction with methanol–chloroform (1:1) and evaporation of the solvent gave pure β isomer **11** as colorless microcrystals: 95 mg, mp 125–140 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.31 and 1.55 (2 s, 6 H, isopropylidene CH_3), 3.32 (m, 2 H, H-5′,5″), 4.22 (m, 1 H, H-4′), 4.67–4.93 (m, 2 H, H-2′, H-3′), 4.99 (d, 1 H, H-1′).

Anal. Calcd for $C_{31}H_{30}N_2O_6$: C, 70.71; H, 5.74; N, 5.32. Found: C, 70.58; H, 5.80; N, 5.15.

From the upper layer portion of the elongated band in the thick layer chromatogram, only a mixture of the α and β isomers (**12** and **11**) was obtained.

5-(β-D-Ribofuranosyl)uracil (13, Pseudouridine). A mixture of **11** (105 mg, 0.2 mmol) and 10% methanolic HCl (2 ml) was stirred at room temperature for 15 min. During this time, a clear solution was obtained and then crystalline product **13** (20 mg) precipitated. The crystals were collected by filtration and washed with ether, mp 221–222 °C (lit.[15] mp for pseudouridine 220–221 °C). ^{1}H NMR spectrum (D_2O) of this product was identical with that of pseudouridine.[12]

From the filtrate a further quantity of **13** (26 mg) having the same melting point and ^{1}H NMR spectral characteristics was obtained upon dilution with 20 ml of ether. The combined yield was 92%.

Registry No.—**1**, 55726-19-7; **3**, 57100-24-0; **4**, 59464-13-0; **5**, 59464-14-1; **6**, 57100-19-3; **7**, 57100-18-2; **7** HCl, 59464-15-2; **8** HCl, 59464-16-3; **9**, 59464-17-4; **10**, 59464-18-5; **11**, 59464-19-6; **12**, 59464-20-9; **13**, 1445-07-4; (ethoxycarbonylmethylene)triphenylphosphorane, 1099-45-2; guanidine HCl, 15827-40-4; thiourea, 62-56-6.

References and Notes

(1) This investigation was supported in part by funds from the National Cancer Institute, DHEW (Grants CA-08748, -18856, and -17805).
(2) W. E. Cohen, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **16**, 166 (1957); F. F. Davis and F. W. Allen, *J. Biol. Chem.*, **227**, 907 (1957).
(3) R. J. Suhadonik, "Nucleoside Antibiotics", Wiley-Interscience, New York, N.Y., 1970.
(4) K. A. Watanabe, D. H. Hollenberg, and J. J. Fox, *J. Carbohydr., Nucleosides, Nucleotides*, **1**, 1 (1974).
(5) R. Shapiro and R. W. Chambers, *J. Am. Chem. Soc.*, **83**, 3920 (1961); D. M. Brown, M. G. Burdon, and R. P. Slatcher, *J. Chem. Soc.*, 1051 (1968); W. A. Asbun and S. B. Binkley, *J. Org. Chem.*, **31**, 2215 (1966); **33**, 148 (1968); U. Lerch, M. G. Burdon, and J. G. Moffatt, *ibid.*, **36**, 1507 (1971).
(6) S. David and A. Lubineau, *Carbohydr. Res.*, **29**, 15 (1973).
(7) C. K. Chu, K. A. Watanabe, and J. J. Fox, *J. Heterocycl. Chem.*, **12**, 817 (1975).
(8) J. H. Burchenal, K. Ciovacco, K. Kalahar, T. O'Toole, R. Kiefner, M. D. Dowling, C. K. Chu, K. A. Watanabe, I. Wempen, and J. J. Fox, *Cancer Res.*, **36**, 1520 (1976).
(9) H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Bryam, *J. Am. Chem. Soc.*, **97**, 4602 (1975).
(10) J. G. Buchanan, A. R. Edgar, M. J. Power, and P. D. Theaker, *Carbohydr. Res.*, **38**, C22 (1974).
(11) J.-L. Imbach and B. L. Kam, *J. Carbohydr., Nucleosides, Nucleotides*, **1**, 271 (1974).
(12) R. Deslauriers and J. C. P. Smith, *Can. J. Biochem.*, **50**, 766 (1972).
(13) F. E. Hruska, A. A. Gray, and J. C. P. Smith, *J. Am. Chem. Soc.*, **92**, 4088 (1970).
(14) R. W. Chambers, *Prog. Nucleic Acid Res. Mol. Biol.*, **5**, 349 (1966).
(15) W. E. Cohen, *J. Biol. Chem.*, **235**, 1488 (1960); R. W. Chambers, V. Kurkov, and R. Shapiro, *Biochemistry*, **2**, 1192 (1963).
(16) R. S. Klein, H. Ohrui, and J. J. Fox, *J. Carbohydr., Nucleosides, Nucleotides*, **1**, 265 (1974).
(17) The previously reported extinction values for **7** and **8** are incorrect.

Synthesis and Absolute Configuration of Multistriatin

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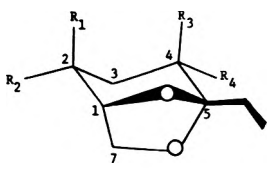
Multistriatin, 2,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane (**1**), was synthesized as a mixture of the four diastereomers **1**α–δ. The key step was the formation of 4,6-dimethyl-7-octen-3-one (**10**) by the alkylation of 3-pentanone with the tosylate (**7**) of 2-methyl-3-buten-1-ol via the metalloenamine synthesis. Epoxidation of **10** with *m*-chloroperoxybenzoic acid and intramolecular ketalization of the 4,6-dimethyl-7,8-epoxyocten-3-one (**11**) with $SnCl_4$ gave **1**, whose **1**α content was maximized by equilibration of **1**γ to **1**α with $SnCl_4$. Acid equilibration of **1** in the presence of excess peroxide leads to the formation of side products at the expense of the multistriatin isomers. Synthesis of **1** from (*S*)-(+)-2-methyl-3-butenoic acid gave (2*R*)-(−)-**1**α, which established the absolute configuration of natural (−)-**1**α as 1*S*:2*R*:4*S*:5*R*. The enantiomeric composition of synthetic (−)- and (+)-**1**α was determined by ^{13}C NMR with the chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III). Natural (−)-**1**α consisted of a single enantiomer.

α-Multistriatin, 2-*endo*,4-*endo*-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane (**1**α), is a novel component of the aggregation pheromone of the European elm bark beetle, *Scolytus multistriatus*.[1] In a previous publication,[2] we have determined the relative stereochemistry for each of the four possible pairs of multistriatin stereoisomers. We report here a synthesis of racemic **1**α–δ designed to confirm the gross structure of multistriatin and provide quantities of **1** sufficient

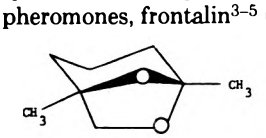


1

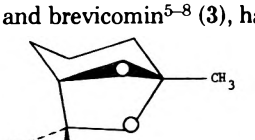
	R_1	R_2	R_3	R_4
1α :	H	CH_3	H	CH_3
1β :	CH_3	H	CH_3	H
1γ :	H	CH_3	CH_3	H
1δ :	CH_3	H	H	CH_3

for field tests. In addition, optically active (+)- and (−)-multistriatin stereoisomers (**1**α–δ) of known absolute configurations were synthesized by inclusion of a chiral intermediate (**5**) of known configuration into the synthetic scheme.

Previous syntheses of the 6,8-dioxabicyclo[3.2.1]octane ring system, including the synthesis of two other bark beetle pheromones, frontalin[3–5] (**2**) and brevicomin[5–8] (**3**), have been



(1*S*) **2**

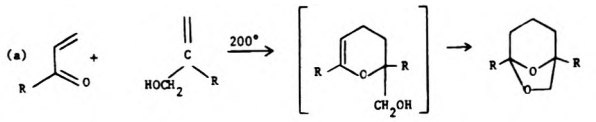


(1*S*) **3**

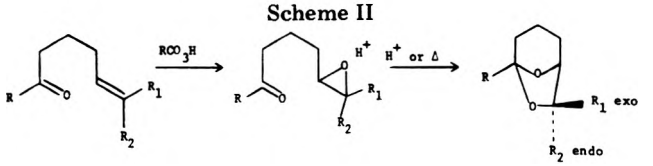
	R_1	R_2
exo :	CH_2CH_3	H
endo :	H	CH_2CH_3

accomplished by two main routes, Schemes I and II. Scheme I involves the Diels–Alder addition of an α,β-unsaturated carbonyl either to an α,β-unsaturated alcohol,[3,4,9] or to another α,β-unsaturated carbonyl that acts as the dienophile.[5,10,11] The first variation of this route (Scheme Ia), is thought to occur via a hydroxy dihydropyran intermediate[9] that cyclizes to the desired product under the conditions of the initial addition.

Scheme I



Scheme II

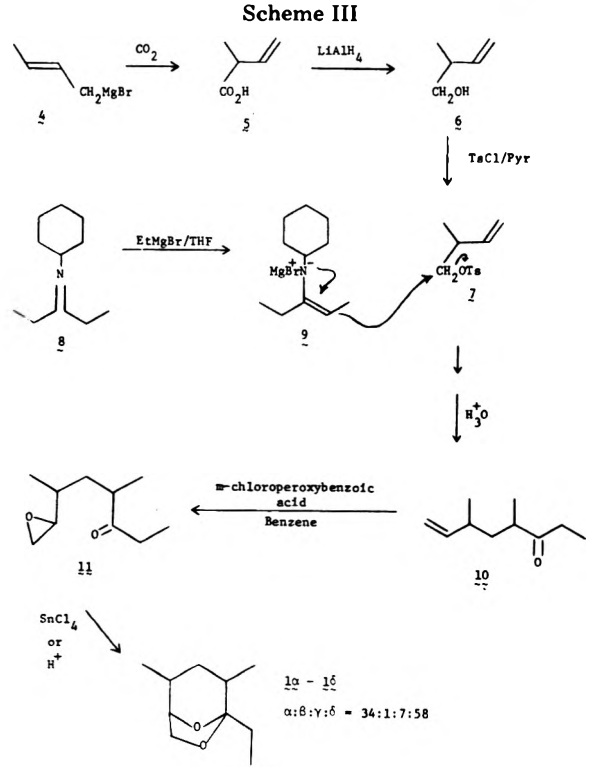


In the second variation (Scheme Ib), the initially formed keto dihydropyran is reduced to the corresponding alcohol, whereupon Lewis acid catalyzed ring closure yields the appropriately substituted 6,8-dioxabicyclo[3.2.1]octane ring. When applied to the synthesis of multistriatin (**1**), this route yielded only small amounts of **1** (5%) in a complex mixture of starting materials and reaction products.[2] Although the stereospecificity of the Diels–Alder reaction was helpful in assigning the relative configurations of the C-1 and C-2 carbons of **1**, this approach was not amenable to a large-scale synthesis.

An alternative approach (Scheme II), which was used in the present synthesis, involves the epoxidation of a δ-keto olefin, followed by thermal or acid-catalyzed cyclization of the keto epoxide.[7,8,12,13] The keto epoxide rearrangement is stereospecific by both thermal and acidic catalysis as evidenced by the stereospecific syntheses of *exo*- and *endo*-brevicomin from the cis and trans epoxides, respectively. This reaction[7,12,13] presumably involves attack of the carbonyl oxygen on the epoxide ring with inversion of the δ carbon.

Synthesis of Racemic Multistriatin. The key intermediate of our synthesis (Scheme III) was the keto olefin, 4,6-dimethyl-7-octen-3-one (**10**). The 2-methyl-3-butenyl moiety

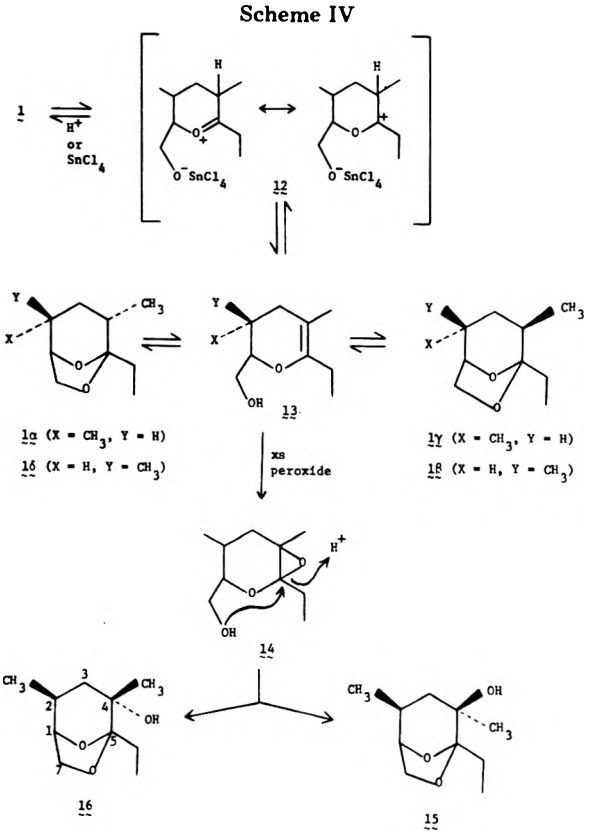
Scheme III



of **10** was introduced as the tosylate (**7**) of 2-methyl-3-butenol (**6**), which was synthesized by the carbonation of butenylmagnesium bromide (**4**) followed by reduction of the resulting 2-methyl-3-butenoic acid (**5**) with lithium aluminum hydride. Alkylation of the magnesium bromide salt (**9**) of the ketimine (**8**) formed from 3-pentanone and cyclohexylamine with the tosylate (**7**) in THF gave, after acid hydrolysis, **10** in 70% yield (distilled) from **6**.[14] The spectra of each of the GLC-purified diastereomers of **10** were nearly identical with minor variations observed only in the ir and NMR spectra. The infrared spectra each exhibited a peak at 1715 cm^{-1} corresponding to the C=O stretching frequency; strong absorptions at 995 and 915 cm^{-1} suggested the presence of a vinyl group, which was confirmed by a two-proton multiplet at 4.85–5.1 ppm and a one-proton multiplet at 5.4–5.8 ppm. The mass spectrum showed a molecular ion (M^+) at *m/e* 154, and an intense McLafferty rearrangement peak at *m/e* 86.

Epoxidation of **10** was accomplished with *m*-chloroperoxybenzoic acid in benzene, but refluxing the reaction mixture[15] gave only a 20–30% yield of cyclized product. Cyclization and equilibration[2] of the α/γ and β/δ pairs were effected by removal of excess peracid and treatment of a benzene solution of crude **11** with $SnCl_4$ (stirring at room temperature for 20 h and refluxing for 1 h). Under these conditions, cyclization occurred rapidly (<30 min), but the acid-catalyzed equilibrations of 1γ to 1α and of 1β to 1δ proceeded slowly, after ketalization was complete. Scheme IV depicts the acid-

Scheme IV



catalyzed cleavage of a C-5–O bond of **1** to give the resonance-stabilized oxonium ion **12** which, following loss of the C-4 proton, forms the hydroxy dihydropyran intermediate **13**.[16] Reversal of this process by reprotonation on either side of the double bond scrambles the stereochemistry at C-4, leaving C-2 unchanged. Thus, the thermodynamically more stable 1α and 1δ isomers predominate.

The MS, ir, and NMR spectra of two of the four synthetic ketal diastereomers separated by preparative GC were identical with those of natural 1α and 1β, while the spectra of the

Table I. Thermal Cyclization of Epoxy Ketones 11α–δ[a]

Time, h	Epoxide 11α, % ketals (α:β:γ:δ)	11γ, % ketals (α:β:γ:δ)	11δ + 11β, % ketals (α:β:γ:δ)
2	29 (87:0:4:9)	73 (11:0:85:4)	64 (4:35:1:59)
11	100 (90:0:7:4)	100 (11:0:85:4)	100 (4:30:1:64)
33	100 (90:0:7:4)	100 (11:0:85:4)	100 (3:8:1:88)

[a] The designations α–δ refer to the multistriatin (1) isomer to which each epoxide cyclizes.

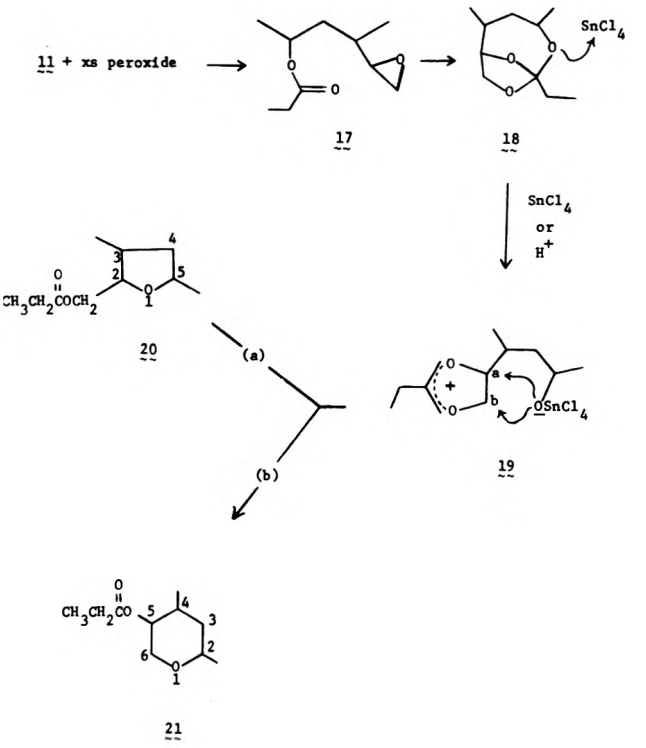
other two synthetic isomers were compatible with structures 1γ and 1δ. The total yield of ketals (1α–δ) from 10 was 63% following fractional distillation, with the biologically active 1α isomer representing 34% of the total multistriatin isomers.

The thermal cyclization of the epoxy ketone 11 was performed at 210 °C in sealed glass tubes on the diastereomers of 11 that were separated by preparative GC. Two of the epoxides were inseparable, and were cyclized as a binary mixture. The ir and NMR spectra of GC-separated samples of the epoxides confirmed that thermal cyclization did not occur on the gas chromatograph. Table I summarizes the results of the thermal cyclization, and shows that each individual epoxide gave mainly one diastereomer of multistriatin. Thus, the thermal ring closure was rapid, even though equilibration of the 1α/1γ pair did not occur and that of the 1β/1δ pair proceeded slowly. These results, in conjunction with those of the acid-catalyzed cyclization of 11, indicate that the initial ring closure in both cases does not affect the configuration of carbons adjacent to the carbonyl. Even though 13 is a likely intermediate in the equilibration process, it is not required in the intramolecular cyclization step.

If an acid catalyst is added to the mixture of crude epoxides without removal of excess peroxide, side products proliferate at the expense of the multistriatin isomers. Four of these side products were purified by preparative GLC and were identified by spectral analysis as 15, 16, 20, and 21. Epoxidation of 13 formed in the presence of acid leads via 14 to the hydroxy ketals 15 and 16 as shown in Scheme IV.[16] Elucidation of the relative stereochemistry of 15 and 16 was aided by the observation that only trace amounts of 1β and 1δ ketals were present in the reaction products relative to 1α and 1γ. The 1β/1δ pair were thus preferentially oxidized, which suggested that the methyl groups on C-2 of 15 and 16 are in the axial position since C-2 should not be affected by the reaction conditions employed. The NMR spectra of 15 and 16 supported this contention since the chemical shifts of the doublets of the methyl groups on C-2 in 15 and 16 (1.23 and 1.14 ppm, respectively) remained in the downfield region characteristic of the axial methyl group signals of 1β and 1δ.[2] In addition, the chemical shifts and splitting patterns for the C-1 and C-7 protons (3.5–3.8 and 4.1 ppm, respectively) closely resembled the C-1 and C-7 proton resonances of 1β and 1δ. The singlet of the methyl group on C-4 of 16 appeared at 0.2 ppm downfield from the same methyl singlet of 15, and is therefore assigned the axial position on the basis of the downfield shifts (0.15–0.2 ppm) observed in NMR spectra of 1α–δ of axial methyl signals relative to equatorial methyl signals.[2] The NMR spectra of 15 and 16 taken in Me_2SO displayed hydroxyl singlets at 4.06 and 4.02 ppm, respectively.

Tetrahydrofuran and pyran ester side products such as 20 and 21 are most likely the ultimate result of a Baeyer–Villiger oxidation by excess peroxide of the epoxy ketone 11 to the epoxy ester 17, which subsequently cyclizes in acid to the intermediate ortho ester 18 (Scheme V). Acid cleavage of 18

Scheme V



results in formation of a resonance-stabilized acetonium ion (19), while oxide attack at carbon a or b of 19 produces 20 or 21, respectively. Because the Baeyer–Villiger oxidation is catalyzed by acids, compounds such as 20 and 21 increased relative to the ketals if acid was applied directly to the epoxidation reaction mixture. These compounds were produced in smaller quantities under the optimum conditions whereby the acid was applied after removal of excess peroxide. The occurrence of side products analogous to 20 and 21 under similar conditions has been reported,[7] and the mechanism of their formation from ortho esters in the presence of Lewis acids has recently been elucidated with the use of ^{18}O-labeled precursors.[17]

Synthesis of Optically Active Multistriatin. Natural α-multistriatin (1α) produced by virgin female elm bark beetles is optically active ($[\alpha]^{25}D$ −47°) and has been shown to be optically pure by the use of the chiral shift reagent $Eu(hfc)_3$ in the ^1H NMR of 1α.[18] In the present study, optically active multistriatin isomers (1α–δ) were synthesized from *S*-(+)- and *R*-(−)-5 (70 and 60% optical purity, respectively), which were obtained by partial resolutions of racemic 5 with (+)- and (−)-α-methylbenzylamine. The absolute configurations of the enantiomers of 5 have been determined.[19] Each of these optically enriched acids was then used in the synthesis of 1α–δ as shown in Scheme VI. The steps employed were identical with those shown in Scheme III for the synthesis of racemic 1.

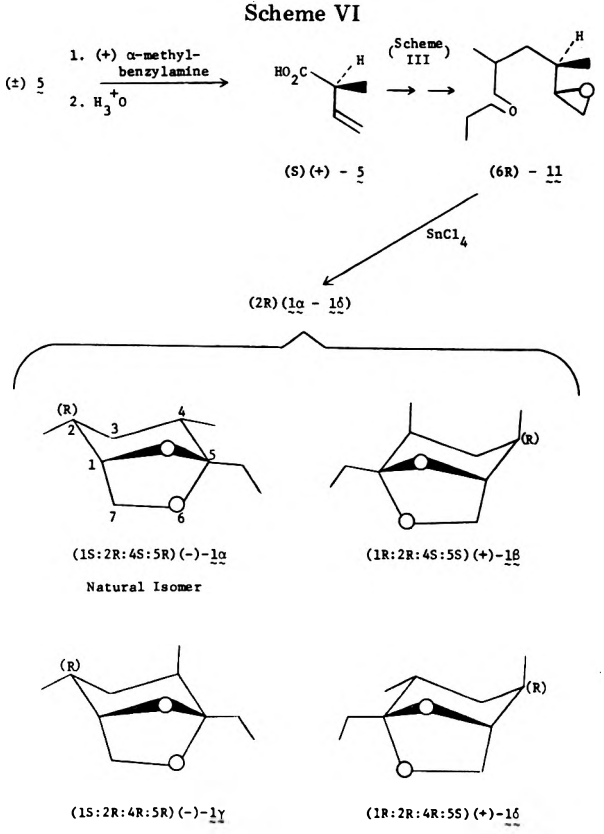
Each isomer of multistriatin (1α–δ) originating from *R*-(−)-5 and *S*-(+)-5 was purified by preparative GLC and shown to be optically active by ORD measurements in *n*-hexane (see Table II). The chiral center of 5 corresponds to C-2 in multistriatin (1), and therefore the multistriatin isomers (1α–δ) synthesized from *S*-(+)-5 all have the *R* configuration at C-2, whereas 1α–δ from *R*-(−)-5 are *S* at C-2. These assignments are based on the reasonable assumption that the configuration at C-2 remained intact because C-2 was not involved in any of the subsequent reactions. Furthermore, C-2 does not racemize during the acid-catalyzed equilibration step, as shown experimentally by the separate equilibrations of the α/γ and β/δ pairs.[2] The thermal conditions employed in the GLC purifications likewise did not lead to racemization at C-2

Table II. Specific Rotations ([α]^{25}D) of Stereoisomers of Multistriatin (1), Frontalin (2),[a] and exo-Brevicomin (3)[a]

	Configuration at chiral carbons				589 nm		365 nm	
	1	2	4	5	Obsd[b]	Calcd[c]	Obsd[b]	Calcd[c]
(−)-1α	S	R	S	R	−26	−47	−79	−142
(+)-1α	R	S	R	S	+21	+44	+62	+132
(−)	1β	S	S	R	R	−34	−73	−114
−242								
(+)-1β	R	R	S	S	+43	+78	+135	+241
(−)-1γ	S	R	R	R	−12	−21	−34	−51
(+)-1γ	R	S	S	S	+10	+21	+35	+75
(−)-1δ	S	S	S	R	−41	−87	−122	−260
(+)-1δ	R	R	R	S	+50	+89	+151	+270
(−)-2	S			R	−52.0			
(+)-2	R			S	+53.4			
(−)-3	S			R	−80.0			
(+)-3	R			S	+84.1			

[a] These values, obtained in ether, were reported by Mori for optically pure enantiomers.[21,22] [b] These values were observed in *n*-hexane for the synthetic stereoisomers of 1 purified by GLC. The concentrations varied between 0.057 and 0.48 M. [c] Calculated values of the optically pure (100%) stereoisomers of 1 based on the observed values, and the optical purities of 56 and 47% for the 2*R* and 2*S* stereoisomers, respectively.

Scheme VI



since each of the pure isomers remained unchanged following reinjection on the GLC column. Assignment of the *R* configuration to C-2 of the synthetic isomers of 1 originating from *S*-(+)-5 established the absolute configuration of all other chiral centers of 1α–δ (C-1, C-4, and C-5) by cognizance of the previously established relative stereochemistry of 1α–δ. Thus, the absolute configuration of both natural and synthetic (−)-α-multistriatin is 1*S*, 2*R*, 4*S*, and 5*R*, as shown in Scheme VI.

The determination of the optical purities of the synthetic (+)- and (−)-α-multistriatin by the use of Eu(hfc)$_3$ in the ^{1}H NMR spectra was not possible. Although natural (−)-1α did appear to be 100% optically pure by qualitative inspection of the Eu(hfc)$_3$-shifted ^{1}H NMR spectrum, a quantitative estimate of the optical purity by peak integration was prohibited by the broadening and multiplicity of the proton signals (C-7) exhibiting the largest enantiomeric split. This technique is of little value for optical purity measurements of synthetic (+)- or (−)-1α in cases of partial enantiomeric enrichment.

The recent report by Fraser[20] on the use of chiral shift reagents in ^{13}C NMR prompted our attempts to use this technique to determine the optical purities of synthetic (+)- and (−)-α-multistriatin. As shown in Figure 1, the noise-decoupled ^{13}C NMR spectra of racemic 1α, (−)-1α, and (+)-1α with Eu(hfc)$_3$ in benzene exhibit observable enantiomeric separations for eight of ten carbons, with the largest differences of 0.7–1.9 ppm observed for the C-1 resonances. The complexity caused by spin–spin splitting often encountered in ^{1}H spectra is absent in the broad-band proton decoupled ^{13}C NMR spectrum. Therefore, the shifted ^{13}C spectrum complements the corresponding ^{1}H spectrum by offering a greater acuity of enantiomeric resolution due to the singlet nature of the carbon-13 signals.

The optical purity of synthetic (+)- and (−)-1α was 47 and 56% respectively, based on peak integration of the ^{13}C NMR signals. Calculation of the specific rotations at 589 and 365 nm for the optically pure isomers of multistriatin (1α–δ) based on the optical purities and observed rotations of the synthetic stereoisomers demonstrated that the values for each pair of enantiomers were in good accord (see Table II). Comparison of the specific rotation of natural (−)-1α ([α]^{25}D −47°) with the values calculated for the optically pure enantiomers of 1α (−47 and +44°, Table II) supports the assignment of full enantiomeric purity for natural (−)-α-multistriatin.

The data of Table II also demonstrate that for all eight optically active stereoisomers of multistriatin, and the enantiomers of frontalin[21] and *exo*-brevicomin,[22] the sign of the plain curve observed in the ORD depends only on the absolute configuration of the 6,8-dioxabicyclo[3.2.1]octane ring system, and is independent of the alkyl substituents. Thus, the 1*S* rings of the multistriatin isomers (1α–δ) all exhibit minus plain curves as do (1*S*)-exo-brevicomin and (1*S*)-frontalin.

Experimental Section

General. Nuclear magnetic resonance spectra were recorded on a Varian XL-100 FT NMR spectrometer or a Varian A-60 NMR spectrometer. Infrared spectra were obtained on a Perkin-Elmer Model 621 spectrophotometer. Solution ir spectra were obtained with 40–60 μg samples in a Barnes 4-μl (1 mm path) ultramicro cavity cell mounted in a Perkin-Elmer 4X refractive beam condenser; a matched cavity cell and beam condenser were used for solvent compensation

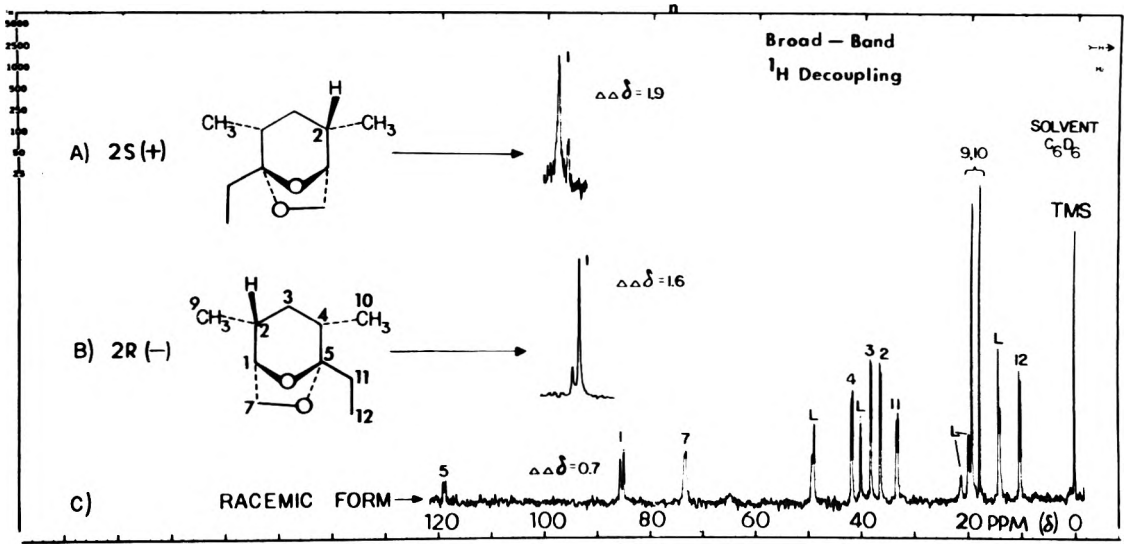


Figure 1. Noise-decoupled ^{13}C NMR spectra of 2*S*-(+)-1α, 2*R*-(−)-1α, and racemic 1α with Eu(hfc)$_3$ in benzene.

of the reference beam. Mass spectra were obtained at 70 eV ionization potential on a Perkin-Elmer Hitachi RMU-6E mass spectrometer modified with a direct inlet sampling system. Gas chromatography was performed on a Varian Aerograph series 2700 gas chromatograph, equipped with a flame ionization detector and modified for preparative GLC with a Brownlee-Silverstein thermal gradient collector. Optical rotary dispersion curves were measured on a JASCO ORD/UV-5 ORD recorder, in conjunction with a metal cylindrical cell (0.5 ml) consisting of a 10-mm metal spacer and pressure-sealed quartz windoes. Unless otherwise stated, all GLC analyses were performed as follows: 4% Carbowax 20M on Chromosorb G, 60/80 mesh, DMCS-AW, 6.3 m × 6 mm o.d., silanized glass; He flow 60 ml/min; column oven temperature, as indicated; detector temperature 200–210 °C; injector temperature 160–200 °C.

Microanalyses were carried out by Galbraith Laboratories, Knoxville, Tenn. All samples of the chiral NMR shift reagent, Eu(hfc)$_3$ (Aldrich Chemical Co.), were sublimed prior to use and prepared in a drybox under a nitrogen atmosphere. Solvents were reagent grade and were dried, when required, over Linde 4A molecular sieves. All reactions described below were performed under a positive pressure of dry nitrogen.

Synthesis of Racemic Multistriatin. 2-Methyl-3-butenoic acid (5) was prepared by the carbonation of butenylmagnesium bromide (4) as described by Lane et al.[23] Distillation of the crude acid gave pure **5**: bp 93–94 °C (33 mm) [lit.[23] bp 95.5 °C (35 mm)].

Anal. Calcd for $C_5H_8O_2$: C, 59.98; H, 8.05. Found: C, 60.02; H, 8.03.

2-Methyl-3-buten-1-ol (6). 2-Methyl-3-butenoic acid (121 g, 1.2 mol) was reduced with $LiAlH_4$ in ether and the crude alcohol was distilled to give 56.5 g (55%) of pure (99% by GC) **6**: bp 116–123 °C (755 mm) [lit.[19] bp 120 °C (756 mm)].

Anal. Calcd for $C_5H_{10}O$: C, 69.72; H, 11.70. Found: C, 69.59; H, 11.57.

2-Methyl-3-butenyl Tosylate (7). A cooled, stirred solution of **6** (65.7 g, 0.763 mol) in 600 ml of dry pyridine was treated with tosyl chloride (295 g, 1.54 mol), and stirring was continued until the tosyl chloride had completely dissolved. The reaction flask was then stoppered and placed in a refrigerator for 70 h. The reaction mixture was divided in half, with each half being poured over 1500 ml of crushed ice and extracted five times with 200 ml of ether. The total ether extracts were each washed three times with 200 ml of 1:1 HCl/H_2O and two times with 200 ml of salt water. The combined ether extracts were dried over K_2CO_3/$MgSO_4$ and concentrated by vacuum until no further weight loss occurred. The final product was 174 g (95%) of **7** as a light tan colored oil that was stored at 10 °C as a solution in 100 ml of dry THF: ir (film) 1190, 1175 cm^{-1} (s, SO_2OR), no O–H stretch absorption.

***N*-(1-Ethylpropylidine)cyclohexylamine (8).**[24] A solution of 3-pentanone (86.1 g, 1.0 mol), cyclohexylamine (99.8 g, 1.0 mol), and toluenesulfonic acid (100–200 mg) in 250 ml of dry benzene was refluxed in a Dean-Stark separator until 17.5 ml of H_2O was liberated (6 days). The benzene was removed, and the crude ketimine was distilled, yielding **8** (142 g, 85%): bp 100–101.5 °C (24 mm) [lit.[24] bp 102–104 °C (26 mm)]; ir (film) 1660 cm^{-1} (s, C=N), no absorption at the N–H or C=O stretching frequencies; NMR ($CDCl_3$) δ 1.06 (t, 3 H, J = 8 Hz), 1.2–1.9 (m, 10 H), 2.23 (q, 2 H, J = 8 Hz), 3.3 (m, 1 H, C=NCH).

Anal. Calcd for $C_{11}H_{21}N$: C, 78.97; H, 12.65; N, 8.37. Found: C, 77.91; H, 12.35; N, 8.08.

4,6-dimethyl-7-octen-3-one (10). A 260-ml solution of ethylmagnesium bromide in THF (2.67 M, 0.696 mol) was added dropwise to a stirred sample of the ketimine **8** (117 g, 0.696 mol) at room temperature followed by heating at reflux for 8 h. The reaction mixture was then cooled to 5 °C and a THF solution (100 ml) of the tosylate **7** (1.67 g, 0.696 mol) was added dropwise, followed by stirring at room temperature for 45 h, and at reflux for 1 h. At the conclusion of the stirring period, a white, milky precipitate had formed which dissolved upon addition of 10% HCl (700 ml, 3 × molar excess). Hydrolysis was continued at reflux temperature for 2.5 h, after which the solution was cooled and the resulting white precipitate was removed by filtration. The filtrate was extracted five times with ether (250 ml), and the combined ether extracts were then washed with 5% $NaHCO_3$ (4 × 250 ml) and salt water (2 × 250 ml). The ether extract was dried over $MgSO_4$, concentrated, and distilled to give pure (99% by GLC) **10** (75.9 g, 71%), bp 81–83 °C (23 mm).

The two diastereomeric forms of **10** were separable by preparative GLC (110 °C; retention times, 17.7 and 19.7 min from injection) and were collected separately for spectral analysis. The data for the second eluted peak are ir (CCl_4) 3080 (s, olefin), 2970 (s), 2935 (m), 2880 (m), 1715 (s, C=O), 1640 (m, C=C), 1460 (m), 1380 (m), 1105 (m), 995 (m, –CH=CH_2), 975 (m), 915 cm^{-1} (s, –CH=CH_2); NMR ($CDCl_3$) δ 0.94–1.12 (two d, one t, 9 H combined, J_d, J_t = 8 Hz), 1.15–1.85 (m, 2 H), 1.9–2.7 (m, 4 H, CH_2=CHCH, $(CH_3)CHCOCH_2CH_3$, CH_2 q visible at 2.46, J = 8 Hz), 4.85–5.1 (m, 2 H, CH=CH_2), 5.4–5.8 (m, 1 H, CH=CH_2); mass spectrum *m/e* (rel intensity) 154 (13) (M^+), 97 (20), 86 (62), 57 (100), 55 (84). The ir, NMR, and mass spectra of the first eluted peak were nearly identical with those cited above.

Anal (distillate). Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.65; H, 11.59.

4,6-Dimethyl-7,8-epoxy-3-one (11). A sample of freshly opened *m*-chloroperoxybenzoic acid (85%, unassayed, 10% molar excess) was added slowly to a cooled (10–15 °C), vigorously stirred solution of the distilled ketone **10** (56.9 g, 0.369 mol) in 1 l. of dry benzene. Stirring of the mixture was continued for 5 h, while the temperature of the reaction mixture rose slowly to room temperature after removal of the ice bath. GLC analysis of a small aliquot of the reaction mixture indicated that 10–15% of the starting ketone **10** remained; an additional 15 g of peracid was added. Following an overnight stirring period, the mixture was cooled to 10 °C, and the precipitated *m*-chlorobenzoic acid was removed by filtration and washed with several portions of cold benzene. The combined filtrates were washed twice with 200 ml of 10% sodium metabisulfite, three times with 200 ml of 5% Na_2CO_3, and three times with 200 ml of salt water, and dried over $MgSO_4$. GLC analysis indicated that no appreciable amount of starting ketone (**10**) remained.

Preparative GLC (170 °C) of a portion of the benzene solution gave three separable peaks corresponding to the four diastereomeric forms of **11** (11α–δ), with the last two eluted epoxides partially coalesced to one peak. The composition, retention time, and percent of total epoxides for each of the collected fractions follow. Fraction 1: a 40/60

mixture of 11γ and an unidentified ester, 17.1–19.2 min, 41%. Fraction 2: pure 11α, 19.2–20.7 min, 15%. Fraction 3: a mixture of 11β and 11δ, 21.3–23.4 min, 43%. The spectral data for the collected fractions follow.

Fraction 1 (11γ): ir (CCl_4) 3040 (w), 2960 (m), 2920 (m), 1735 (s, OC=O), 1710 cm^{-1} (m, C=O), no C=C stretch absorption; NMR ($CDCl_3$) δ 0.9–2.9, complex; no olefin resonances.

Fraction 2 (11α): ir (CCl_4/CS_2) 3040 (w), 2960 (m), 2920 (m), 2870 (w), 1710 (s, C=O), no C=C stretch absorption, 1450 (m), 1370 (m), 1100 (m), 895 (w), 820 cm^{-1} (w); NMR ($CDCl_3$) δ 0.9–1.15 (two d, one t, 9 H combined), 1.15–2.0 (m, 2 H), 2.0–2.9 (m, 6 H combined); mass spectrum *m/e* (rel intensity) 170 (2), 128 (7), 96 (11), 71 (3), 57 (100), 55 (18), 41 (11), 29 (26).

Fraction 3 (11β + 11δ): ir (CS_2) 3040 (m), 2960 (s), 2920 (s), 2865 (m), 1710 (s, C=O), 1500–1400 (CS_2 interference), 1370 (m), 1000 (m), 900 (m), 835 (m); mass spectrum *m/e* (rel intensity) 170 (3), 128 (7), 96 (8), 71 (28), 57 (100), 55 (16), 41 (12), 29 (30).

2,4-Dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane (Multistriatin, 1α–δ). A. Acid-Catalyzed Cyclization of Epoxy Ketone 11. The dried benzene solution of crude epoxy ketone 11 was treated with a benzene solution of $SnCl_4$ (30 ml, 0.43 M, 0.013 mol), and stirring was continued for 20 h. The degree of cyclization and multistriatin isomer ratios were monitored during the reaction by analytical GLC (170 °C) of aliquots (0.5 ml) of the reaction solution, which were worked up according to the procedure given below. Analysis (GLC) of a trial run indicated that complete cyclization occurred in less than 30 min.

The reaction solution was poured over 6 N HCl/ice, and the benzene layer was washed with 5% Na_2CO_3 (3 × 250 ml) and salt water (2 × 250 ml). The above workup procedure produced a white precipitate that was difficult to remove from the organic phase. An improved workup procedure that did not produce this cumbersome precipitate was employed during the synthesis of optically active multistriatin (1) (see below). Fractional distillation of the yellow oil of crude ketals through a 25-cm Vigreux column at 6 mm gave four fractions as follows: fraction 1, bp 27–67 °C, 1.41 g, 88% 1 (by GLC); fraction 2, bp 67–82 °C, 36.4 g, >99% 1; fraction 3, bp 82–91 °C, 2.3 g, 85% 1; fraction 4, bp 91–96 °C, 1.35 g, 8% 1. The total yield of multistriatin isomers (1α–δ) was 39.5 g, or 63% from the keto olefin **10**. The retention times and percent of total 1 for 1α–δ separated by preparative GLC (140 °C) of distillate fraction 2 are 1δ, 14.4 min, 57.5%; 1α, 15.3 min, 34%; 1γ, 16.5 min, 7%; and 1β, 18.0 min, 1.5%. The spectral data for the four isomers of multistriatin (1) have been previously reported.[2]

Anal (fraction 2). Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.32; H, 10.49.

Preparative GLC (170 °C) of distillate fraction 4 gave (retention time, percent of total fraction 4) multistriatin isomers (1α–δ), 7.2–9 min, 8%; 2,4-dimethyl-5-propionoxytetrahydropyran (**21**) (propionoxy group equatorial), 12.0–12.9 min, 30%; unidentified peaks, 12.9–16.8 min, 54%; 3,5-dimethyl-2-(methylpropionoxy)tetrahydrofuran (**20**), 16.8–17.7 min, 8%. The spectral data for **20** and **21** follow.

21: ir (CCl_4) 2970 (s), 2930 (s), 2870 (s), 2840 (s), 1735 (s, OC=O), 1460 (m), 1380 (m), 1355 (m), 1250 (m), 1175 (br, s, OC=O), 1100 (s), 1075 (s, C–O–C), 1020 (s, C–O–C); 885 cm^{-1} (m); NMR (CS_2)[25] δ 0.97 (d, 3 H, J = 6 Hz, C-4 CH_3), 1.07 [t, 3 H, J = 7 Hz, $-OC(=O)CH_2CH_3$], 1.09 (d, 3 H, J = 6 Hz, C-2 CH_3), 1.5–1.8 (m, 2–3 H), 2.21 [q, 2 H, J = 8 Hz, $-OC(=O)CO_2CH_3$], 2.91 (dd, 1 H, C-6 H_{ax}, $J_{gem} = J_{6ax-5ax}$ = 10 Hz), 3.21–3.42 (m, 1 H, C-2 H), 3.67–3.84 (dd, 1 H, C-6 H_{eq}, J_{gem} = 10, $J_{6eq-5eq}$ = 5 Hz), 4.12–4.40 (m, 1 H, C-5 H); mass spectrum *m/e* (rel intensity) no 186 (M^+), 184, 185 (<1), 171 (3), 112 (36), 99 (15), 97 (29), 68 (24), 57 (100), 55 (13), 45 (12), 43 (75), 41 (23), 29 (57).

20: ir (CCl_4) 2970 (s), 2930 (m), 2880 (m), 1738 (s, OC=O), 1455 (m), 1375 (m), 1350 (m), 1175 (s, OC=O), 1100, 1075 (br, m, C–O–C), 1000 cm^{-1} (w); NMR ($CDCl_3$) δ 0.97 (d, 3 H, J = 8 Hz, $CHCH_3$), 1.13 [t, 3 H, J = 8 Hz, $OC(=O)CH_2CH_3$], 1.20 (d, 3 H, J = 8 Hz, $CHCH_3$), 1.6–1.85 (m, 2 H), 2.20–2.6 [m, 3 H, q visible, J = 8 Hz, $OC(=O)CH_2CH_3$], 3.8–4.4 (m, 4 H, C-2 H, C-5 H, $CH_2OC=O$); mass spectrum *m/e* (rel intensity) no 186 (M^+), 171 (<1), 112 (14), 99 (71), 70 (19), 69 (11), 57 (46), 55 (25), 43 (100), 29 (35).

B. Thermal Cyclization of 11. The epoxides (11α–δ, ~100 μg each) were separated by preparative GLC as described above and collected in flame-sealed glass collection tubes (12 in. × 1.5 mm o.d.). The collection tubes were placed in an oven at 210 °C; the products were then rinsed from the tubes following the specified reaction time and analyzed by GLC (170 °C). The results given in Table I demonstrate that complete cyclization occurred within 11 h.

C. Epoxidation of 10 with Excess Peroxide Followed by Acid-Catalyzed Ketalization in Situ. A cooled (10–15 °C), vigorously stirred solution of keto olefin **10** (0.6 g, 3.9 mmol) in methylene chloride (10 ml) was treated with 85% *m*-chloroperoxybenzoic acid (1.0–1.1 g, 30–40% molar excess) and stirred for 5 h while the temperature of the mixture rose slowly to room temperature. The reaction mixture was then treated with two to three crystals of toluenesulfonic acid and heated to reflux for 2 h. The methylene chloride solution was washed with 10% Na_2CO_3, 10% sodium sulfite (2 × 10 ml), 5% Na_2CO_3 (2 × 10 ml), and salt water (2 × 10 ml), and was dried over $MgSO_4$. Preparative GLC (170 °C) of the crude reaction product in methylene chloride gave (retention time, percent of total reaction product) multistriatin isomers, 1α, 1γ, no 1β or 1δ, 7.2–9 min, 41%; tetrahydropyran and furan esters, including **20** and **21**, 12.6–18.0 min, 15%; 4-hydroxy-δ-multistriatin (**15**), 23.7–27.5 min, 21%; 4-hydroxy-β-multistriatin (**16**), 30.6–32.4 min, 23%. The spectral data for **15** and **16** follow.

15: ir (CCl_4) 3580 (m, O–H), 2960 (br, s), 2940 (s), 2880 (s), 1450 (br, m), 1370 (m), 1270 (m), 1180 (s), 1160 (m), 1105 (m), 1045 (s, O–C–O), 1020 (m), 925 cm^{-1} (s); NMR (CS_2)[25] δ 0.78 (t, 3 H, J = 8 Hz, $(O–C–O)CH_2CH_3$), 0.92 (br, s, 3 H, C-4 CH_3), 1.23 (d, 3 H, J = 8 Hz, C-2 CH_3), 1.25–1.95 (m, 6 H), 3.5–3.75 (m, ≈ 2 H, C-7 H_2), 4.10 (m, 1 H, C-1 H); (Me_2SO-d_6) δ 4.06 (s, 1 H, OH); chemical ionization mass spectrum[26] (CH_5^+) *m/e* (rel intensity) 187 (18) $(M + 1)^+$, 186 (2) $(M)^+$, 185 $(M - 1)^+$, 169 (100) $(M + 1 - H_2O)^+$, 123 (29), 69 (25).

16: ir (CCl_4) 3580 (m, OH), 2980 (s), 2940 (s), 2880 (s), 1460 (br, m), 1380 (m), 1355 (m), 1340 (m), 1220 (br, m), 1160 (s), 1130 (m), 1110 (m), 1055, 1050 (s, O–C–O), 1030 (s, O–C–O), 980 (m), 935 (s), 900 cm^{-1} (s); NMR (CS_2)[25] δ 0.78 (t, 3 H, J = 8 Hz, $(O–C–O)CH_2CH_3$), 1.11–1.35 (s, 3 H, C-4 CH_3, overlapping with d, 3 H, C-2 CH_3, J = 8 Hz), 1.3–1.9 (m, 6 H), 3.73 (d, 2 H, J = 3 Hz, C-7 H_2), 4.09 (m, 1 H, C-1 H); (Me_2SO-d_6) δ 4.02 (s, 1 H, –COH); chemical ionization mass spectrum[26] (CH_5^+) *m/e* (rel intensity) 187 (21) $(M + 1)^+$, 186 (3) $(M)^+$, 185 (10) $(M - 1)^+$, 169 (100) $(M + 1 - H_2O)^+$, 151 (22), 123 (42), 69 (32).

Note: The above procedure was carried out with a variety of acids, including H_2SO_4, H_3PO_3, $HClO_4$, and $SnCl_4$, with results that were qualitatively identical with those cited above. Only the ratio of side products and degree of oxidation varied with the acid used. The procedure cited was chosen to illustrate conditions which led to a maximum of side products.

Synthesis of Optically Active Multistriatin. Resolution of 5 with (+)- and (−)-α-Methylbenzylamine. (+)-α-Methylbenzylamine (13.0 g, 0.1 mol) and **5** (11.0 g, 0.1 mol) were dissolved in 80 ml of boiling acetone and allowed to cool to 20 °C and to stand for 14 h. Crystals were filtered from the acetone, washed with a small volume of ethyl ether, and vacuum dried. The amine salt was recrystallized five times from a minimum volume of acetone. The rate of cooling was controlled by placing the flask containing the hot acetone solution in a Dewar flask which contained water at 55 °C. The yield of the partially resolved amine salt was 2.1 g. This resolution process was repeated with (−)-α-methylamine as the resolving reagent, and 4.5 of the amine salt was obtained.

The free acids were recovered by decomposing the salts with 10 ml of 1 M hydrochloric acid for the (+) amine and 20 ml for the (−) isomer. The aqueous solutions were extracted four times with 15-ml portions of ethyl ether, and the extracts were dried with 4 Å sieves. Evaporation of the solvent gave 1.0 g of *S*-(+)-**5**, $[\alpha]^{20}D$ +28.8° (*c* 0.10, hexane), 70% optical purity; the (−) amine extract gave 2.1 g of *R*-(−)-**5**, $[\alpha]^{20}D$ 24.8° (*c* 0.42, hexane), 60% optical purity.

Synthesis of (+) and (−) Isomers of Multistriatin (1α–δ). The synthesis of (2*R*)-multistriatin (1α–δ) from (2*S*)-(+)-**5** (1.0 g, 70% optical purity) and of (2*S*)-multistriatin (1α–δ) from (2*R*)-(−)-**5** (2.1 g, 60% optical purity) was accomplished by the procedure described above (Scheme III). Intermediates were not distilled, and crude reaction products (following workup) were used directly in subsequent reactions. Workup of the final benzene/$SnCl_4$ solutions (35–50 ml) of ketals proceeded as follows. The solutions were washed with 10% NaOH (2 × 10 ml), 10% HCl (2 × 10 ml), 10% Na_2CO_3 (2 × 15 ml), and salt water (2 × 15 ml), dried over $MgSO_4$, and concentrated to give the crude (2*R*)- and (2*S*)-multistriatin isomers: (2*R*)-**1**, 0.73 g, 38% from (*S*)-(+)-**5**, 89% 1α–δ of total products by GLC (170 °C); (2*S*)-**1**, 1.87 g, 46% from (*R*)-(−)-**5**, 87% 1α–δ of total by GLC.

The individual multistriatin isomers (10–80 mg) were separated by preparative GLC (20% FFAP on Chromosorb W AW/DMCS, silanized glass column, 35 ft × 0.375 in. o.d., 120 ml He/min, 170 °C isothermal) and dissolved in *n*-hexane (Baker reagent grade, distilled) for ORD measurements. The ORD curves for all isomers (1α–δ) were plain curves; the quantitative data are given in Table II.

Determination of the Optical Purity of Synthetic (2*R*)-(−)- and (2*S*)-(+)-α-Multistriatin by ^{13}C NMR with the Chiral Shift Reagent Tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) [Eu(hfc)$_3$]. Racemic (2*R*)- and (2*S*)-1α were separated from their respective mixtures of multistriatin isomers by preparative GLC as described above, and prepared for ^{13}C NMR with Eu(hfc)$_3$ in deuteriobenzene as follows: racemic 1α (117 mg),

molar ratio[27] Eu(hfc)$_3$/(2*R*)-1α 0.22, *c* (1α) 0.58 M, 1.2-ml solution in a 12-mm o.d. NMR tube with a vortex plug; (2*S*)-1α (120 mg), molar ratio Eu(hfc)$_3$/(2*S*)-1α 0.29, c (2*S*)-1α 2.2 M, 320 μl total solution in a 5-mm o.d. NMR tube; (2*R*)-1α (78 mg), molar ratio Eu(hfc)$_3$/(2*R*)-1α 0.26, c (2*R*)-1α 2.5 M, 185 μl total solution in a 5-mm o.d. tube.

The ^{13}C NMR spectra were obtained by pulsed Fourier transform NMR as follows: broad-band (noise modulated) ^{1}H decoupling, pulse width 78 μs, acquisition time 0.8 s, no pulse delay; transients, (racemic 1α) 62K; (2*R*)-1α 232K; (2*S*)-1α 71K. The changes in chemical shifts for the C-1 signals[28] in the presence of Eu(hfc)$_3$ were racemic 1α, $\Delta\delta$ 16.9, $\Delta\Delta\delta$ 1.9 ppm; (2*S*)-1$\alpha\Delta\delta$ 14.9, $\Delta\Delta\delta$ 1.6 ppm.

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Registry No.—(±)-1α, 54815-06-4; (−)-1α, 59014-03-8; (+)-1α, 59014-04-9; (±)-1β, 54832-20-1; (−)-1β, 59014-05-0; (+)-1β, 59014-06-1; (±)-1γ, 54832-21-2; (−)-1γ, 54832-22-3; (+)-1γ, 59014-07-2; (±)-1δ, 59014-08-3; (−)-1δ, 59014-09-4; (+)-1δ, 59014-10-7; (±)-**5**, 50304-40-0; (2*S*)-(+)-**5**, 59014-11-8; (2*R*)-(−)-**5**, 20626-49-7; **6**, 59014-12-9; **7**, 58977-11-0; 8, 6125-73-1; **10** isomer I, 58977-12-1; **10** isomer II, 58977-13-2; **11**α, 58977-14-3; **11**β, 59014-13-0; **11**γ, 59014-14-1; **11**δ, 59014-15-2; **15**, 58977-15-4; **16**, 59014-16-3; **20**, 58977-16-5; **21**, 58977-17-6; tosyl chloride, 98-59-9; 3-pentanone, 96-22-0; cyclohexylamine, 108-91-8; (+)-α-methylbenzylamine, 3886-69-9; (−)-α-methylbenzylamine, 2627-86-3.

References and Notes

(1) G. T. Pearce, W. E. Gore, R. M. Silverstein, J. W. Peacock, R. A. Cuthbert, G. N. Lanier, and J. B. Simeone, *J. Chem. Ecol.*, **1**, 115 (1975).
(2) W. E. Gore, G. T. Pearce, and R. M. Silverstein, *J. Org. Chem.*, **40**, 1705 (1975).
(3) G. W. Kinzer, A. F. Fentiman, T. F. Page, R. L. Foltz, J. P. Vité, and G. B. Pitman, *Nature (London)*, **221**, 447 (1969).
(4) T. D. J. D'Silva and D. W. Peck, *J. Org. Chem.*, **37**, 1828 (1972).
(5) B. P. Mundy, R. D. Otzenberger, and A. R. DeBernardis, *J. Org. Chem.*, **36**, 2390 (1971).
(6) T. E. Bellas, R. G. Brownlee, and R. M. Silverstein, *Tetrahedron*, **25**, 5149 (1969).
(7) H. H. Wasserman and E. H. Barber, *J. Am. Chem. Soc.*, **91**, 3674 (1969)
(8) J. O. Rodin, C. A. Reece, R. M. Silverstein, V. H. Brown, and J. I. Degraw, *J. Chem. Eng. Data*, **16**, 380 (1971).
(9) C. W. Smith, D. G. Norton, and S. A. Ballad, *J. Am. Chem. Soc.*, **73**, 5270 (1951).
(10) F. Sweet and R. K. Brown, *Can. J. Chem.*, **46**, 2289 (1968).
(11) Y. Naya and M. Kotake, *Tetrahedron Lett.*, 2459 (1969).
(12) This reaction has also been used in the synthesis of ketals derived from manool: (a) U. Scheidegger, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **45**, 400 (1962); (b) E. Demole and H. Wuest, *ibid.*, **50**, 1314 (1967); (c) R. C. Cambie, K. N. Joblin, and A. F. Preston, *Aust. J. Chem.*, **24**, 2365 (1971).
(13) The synthesis of an analogous system, 2,7-dioxabicyclo[2.2.1]heptane, by acid-catalyzed cyclization of γ,δ-keto epoxides has been reported by Y. Gaoni, *J. Chem. Soc. C*, 2925 (1968).
(14) This alkylation is an example of the metaloenamine synthesis first reported by G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).
(15) This method of cyclization was successful in the synthesis of *exo*-brevicomin; see ref 8.
(16) Intermediates **13** and **14** were not isolated. However, hydroxydihydrofurans have been isolated from the acid-catalyzed cyclization of γ-keto epoxides, as have hydroxy ketals analogous to **15** and **16**; see ref 13.
(17) J. M. Coxon, M. P. Hartshorn, and W. H. Swallow, *J. Chem. Soc., Chem. Commun.*, 261 (1973).
(18) T. E. Stewart, E. L. Plummer, L. McCandless, J. R. West, and R. M. Silverstein, *J. Chem. Ecol.*, in press.
(19) R. Renzo, P. Diversi, and G. Ingrosso, *Gazz. Chim. Ital.*, **98**, 88 (1968).
(20) R. R. Fraser, J. B. Stothers, and C. T. Tan, *J. Magn. Reson.*, **10**, 95 (1973).
(21) K. Mori, *Tetrahedron*, **31**, 1381 (1975).
(22) K. Mori, *Tetrahedron*, **30**, 4223 (1974).
(23) J. F. Lane, J. D. Roberts, and W. G. Young, *J. Am. Chem. Soc.*, **66**, 543 (1944).
(24) R. Mayer, H. J. Hartmann, and J. Jentzsch, *J. Prakt. Chem.*, **31**, 312 (1966).
(25) The NMR spectra of compounds **15**, **16**, and **21** were obtained on a Bruker FT-90 NMR spectrometer (in CS_2 with Me_4Si) through the courtesy of Dr. J. Tumlinson and his staff at the Insect Attractants, Behavior, and Basic Biology Laboratory, USDA, Gainesville, Fla.
(26) The chemical ionization mass spectra were run by Dr. J. Henion and his staff at the Department of Chemistry, Cornell University, Ithaca, N.Y. The system was a Finnigan Model 3300 GC-MS, GC Model 9500, interfaced with a Systems Industries 150 computer.
(27) The optimum molar ratio [Eu(hfc)$_3$/1α] for obtaining good enantiomeric separation was determined by previous runs at (E/1α) = 0.024 and 0.14.
(28) The assignment of the ^{13}C signals of 1α–γ will be discussed in a later publication.

Synthesis and Competitive Mechanism of Formation of Phenyl-Substituted 1,2-Azaborolidines and 1-Aza-5-borabicyclo[3.3.0]octanes[1]

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1,5-Diphenyl-1-aza-5-borabicyclo[3.3.0]octane, 1,2-diphenyl-1,2-azaborolidine, and propene were isolated as the major products of the reaction of triethylamine phenylborane with *N,N*-diallylaniline. These compounds were characterized by nuclear magnetic resonance, infrared, mass spectroscopy, and elemental analyses. Two mechanisms were proposed for the formation of propene and 1,2-diphenyl-1,2-azaborolidine. Triethylamine dideuteriophenylborane reacted with *N,N*-diallylaniline to give 3,7-dideuterio-1,5-diphenyl-1-aza-5-borabicyclo[3.3.0]octane, 3-deuterio-1,2-diphenyl-1,2-azaborolidine, and 3-deuteriopropene. These products are consistent with one of the proposed mechanisms, a concerted, facile elimination of propene. This elimination mechanism was supported by model studies of the transition states. Triethylamine phenylborane reacted with *N,N*-di-3-butenylaniline to give 1,2-diphenyl-1-(3-butenyl)-2-hydroazaboracyclohexane and 1,6-diphenyl-1-aza-6-borabicyclo[4.4.0]decane. No butene gas was eliminated, giving further support for the proposed mechanism. Several substituted derivatives of 1,5-diphenyl-1-aza-5-borabicyclo[3.3.0]octane and 1,2-diphenyl-1,2-azaborolidine were also prepared and characterized.

Previous studies[2,3] in our laboratories showed that the reaction of triethylamine phenylboranes with tertiary diallylamines yielded a new class of compounds, 1-aza-5-borabicyclo[3.3.0]octanes, as well as 1,2-azaborolidines. The formation of the azaborolidines was thought to occur with elimination of an allyl group from nitrogen, although no attempt was made to trap the evolved propene in the earlier work. We would now like to report mechanistic studies on this

Table I

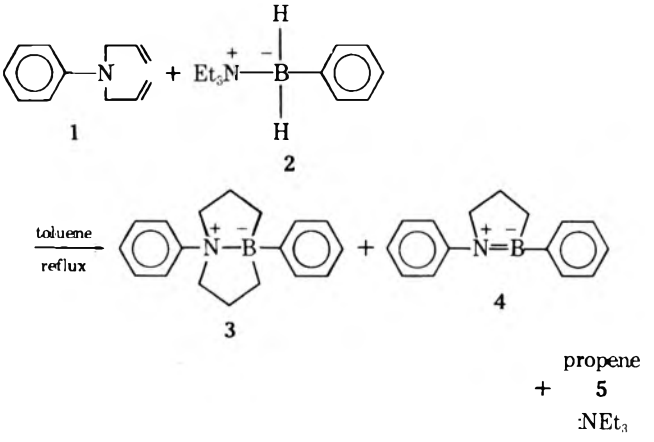
Compd	Name	Formula	%	Mp or bp, °C (mm)	Chemical shift	Anal., %
3	1,5-Diphenyl-1-aza-5-borabicyclo-[3.3.0]octane	$C_{18}H_{22}BN$	51	80–81 (mp)	6.85 (10) 3.3 (4) 2.1 (4) 1.1 (4)	Calcd: C, 82.13; H, 8.42; N, 5.32; B, 4.11 Found: C, 82.15; H, 8.51; N, 5.41; B, 4.21
18	3-Deuterio-1,2-diphenyl-1,2-azaborolidine	$C_{15}H_{15}DBN$	42	50–54 (0.15 mm) (bp)	7.15 (10) 3.75 (2) 2.0 (1) 1.65 (2)	
20	3,7-Dideuterio-1,5-diphenyl-1-aza-4-borabicyclo[3.3.0]octane	$C_{18}H_{20}D_2BN$	53	78–79 (mp)	7.0 (10) 3.45 (4) 2.15 (2) 1.1 (4)	Calcd: C, 81.52; H, 7.60; C, 1.52; N, 5.28; B, 4.08 Found: C, 81.74; N, 5.18; B, 4.20
29	1-(4-Bromophenyl)-5-phenyl-1-aza-5-borabicyclo[3.3.0]octane	$C_{18}H_{21}BNBr$	41	116–118 (mp)	6.9 (9) 3.3 (4) 2.1 (4) 1.1 (4)	Calcd: C, 63.19; H, 6.19; N, 4.09; B, 3.16; Br, 23.36 Found: C, 63.11; H, 6.29; N, 3.96; B, 2.90; Br, 23.24
39	1,2-Diphenyl-1,2-azaborolidine	$C_{15}H_{16}BN$	44	84–86 (0.30 mm) (bp)	7.2 (10) 3.8 (2) 1.8 (4)	Calcd: C, 81.47; H, 7.29; N, 6.34; B, 4.89 Found: C, 81.42; H, 7.31; N, 6.21; B, 5.01
40	1-(4-Bromophenyl)-2-phenyl-1,2-azaborolidine	$C_{15}H_{15}BNBr$	53	120–123 (0.15 mm) (bp)	7.2 (9) 3.8 (2) 1.7 (4)	Calcd: C, 60.03; H, 5.04; N, 4.67; B, 3.61; Br, 26.65 Found: C, 60.14; H, 5.12; N, 4.58; B, 3.64; Br, 26.52

novel elimination as well as details of the synthesis of several of these phenyl-substituted compounds.

Results and Discussion

Equimolar quantities of triethylamine phenylborane (**2**) and *N,N*-diallylaniline (**1**) were dissolved in toluene and slowly heated (Scheme I). Gas samples from the reaction, as

Scheme I

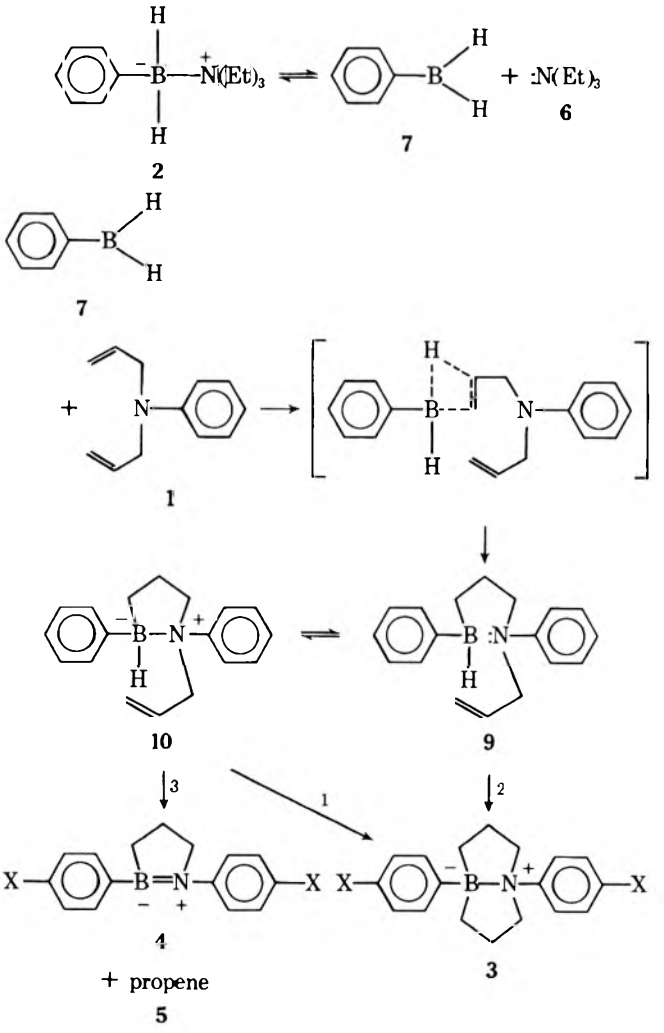


well as solution samples, were monitored by infrared spectroscopy over the temperature range 26–110 °C. The boron–hydrogen bond absorbance at 2340 cm^{-1} was monitored, and it was found that the initial hydroboration occurred near 50 °C. Little change in the intensity was noted up to 95 °C at which point the B–H intensity decreased with time. The infrared spectra began to show traces of propene as indicated by the broad, spiked peak at 910 cm^{-1}. Two products, a colorless liquid and a white solid,[3] were isolated and characterized. A small amount of apparently polymeric, viscous material was also formed; however, attempts to characterize this material were unsuccessful. The liquid was identified as 1,2-diphenyl-1,2-azaborolidine[3] (**4**) and the solid as 1,5-diphenyl-1-aza-5-borabicyclo[3.3.0]octane[3] (**3**).

Several para-substituted derivatives of 1,2-diphenyl-1,2-azaborolidine (**4**) and 1,5-diphenyl-1-aza-5-borabicyclo-[3.3.0]octane (**3**) were prepared by modification of the above procedure as described in the Experimental Section. Physical properties, analyses, and spectral data are given in Table I for selected compounds.[8]

A general mechanism for the formation of **3** and **4** is outlined in Scheme II. The triethylamine phenylborane (**2**) is postu-

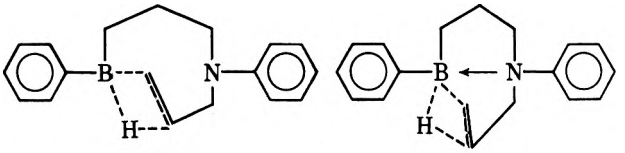
Scheme II



lated to dissociate in solution to give the free phenylborane **7** and triethylamine.

One of the allyl groups of the *N,N*-diallylaniline (**1**) is hydroborated to give the uncoordinated intermediate **9** which would be expected to exist in equilibrium with its coordinated form **10**. The initial hydroboration likely occurs after coordination of the free phenylborane (**7**) with *N,N*-diallylaniline (**1**).

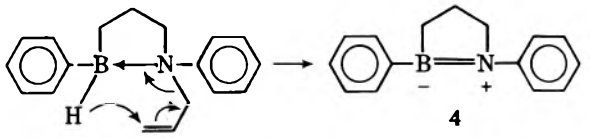
Competitive pathways (Scheme II) could yield products **3** and **4**. The 1,5-diphenyl-1-aza-5-borabicyclo[3.3.0]octane (**3**) could be formed by a second hydroboration with boron adding to the terminal end of the remaining double bond. This might occur by either pathway 1 or pathway 2. Brown[4] has proposed a four-centered transition state for the general process of hydroboration. Following this proposal, the transition state (**11**) for the coordinated form would be much less favorable than that of the uncoordinated form (**12**). This, of course, is



11 **12**

the result of the additional strain imposed by the coordinate bond. Therefore, the second hydroboration should occur along pathway 2.

The formation of the 1,2-diphenyl-1,2-azaborolidine (**4**) is accompanied by the elimination of propene (**5**). Amine boranes have been reported to dealkylate at high temperatures under vacuum.[5] This system, however, appears to be a special one which allows for very facile propene elimination at relatively low temperatures, atmospheric pressure, and mild conditions. The coordinated intermediate (**10**) is well suited for a concerted elimination of propene as shown below:

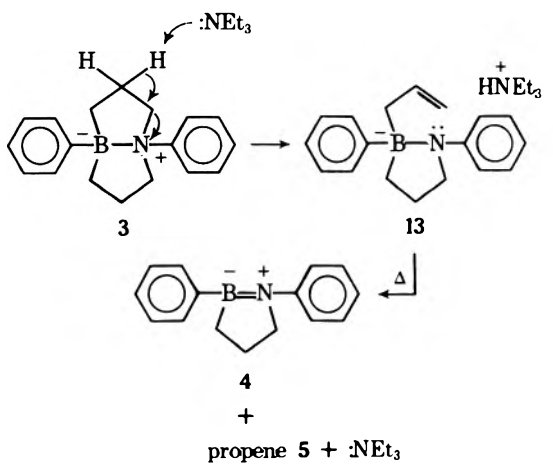


10 **4** + propene **5**

A six-membered transition state would allow for a relatively strain-free addition of hydrogen to the terminal end of the double bond of the allyl group and the ensuing electron shifts.

A second mechanism which might lead to formation of the 1,2-diphenyl-1,2-azaborolidine (**4**) is given in Scheme III. The

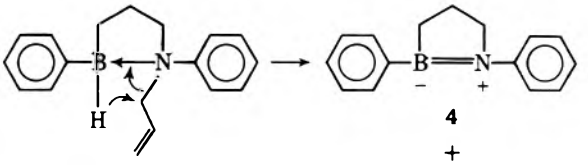
Scheme III



3 **13** **4** + propene **5** + :NEt_3

triethylamine in the refluxing reaction solution could act as the base in a Hofmann-type elimination, abstracting a proton of the 1,5-diphenyl-1-aza-5-borabicyclo[3.3.0]octane (**3**) at either of the two carbon atoms in the β position to the quaternary ammonium group. The resulting allylborane (**13**) then could conceivably undergo thermal cleavage to give 1,2-diphenyl-1,2-azaborolidine (**4**). Alkylboranes have been reported to undergo this type of cleavage.[6]

A third mechanism for formation of **4** could be proposed involving a four-centered reduction of the allyl group of intermediate **10** as shown below:

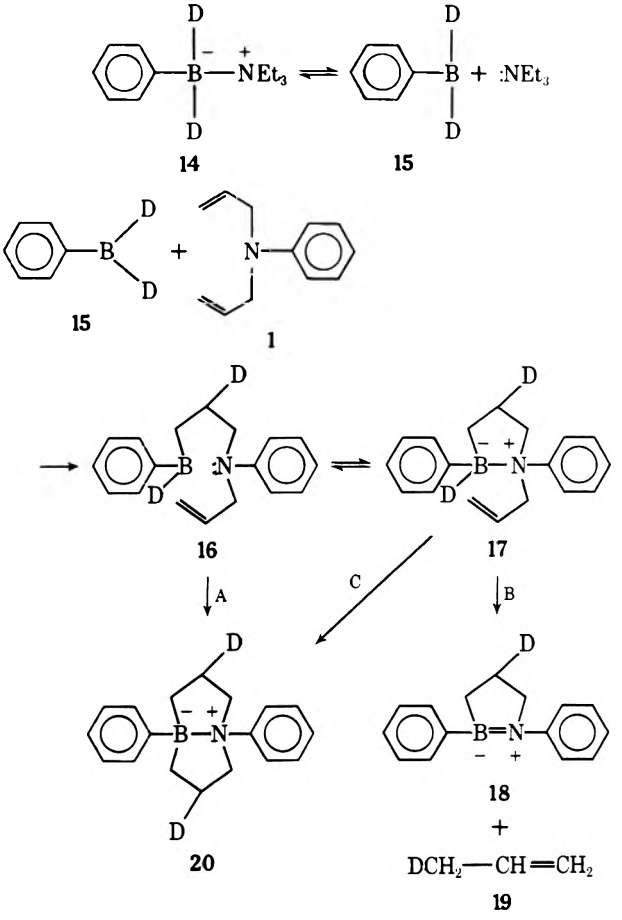


10 **4** + propene **5**

Two separate studies were necessary to give strong support to one of these mechanisms.

Deuterium labeling studies should distinquish quite clearly between the first two proposed mechanisms. The proposed concerted mechanism is shown in Scheme IV. The triethyl-

Scheme IV



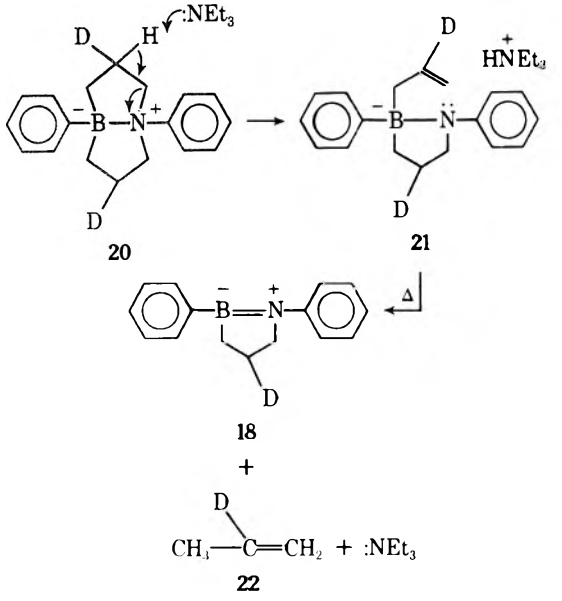
14 **15** **15** **1** **16** **17** **20** **18** + DCH_2—CH=CH_2 **19**

amine dideuteriophenylborane (**14**) would dissociate to give the free dideuteriophenylborane (**15**) which would undergo an initial deuterioboration to give intermediate **16**. An equilibrium would exist between the dissociated form (**16**) and the coordinated form (**17**). Note that the deuterium is in the 2 position of the ring. A second deuterioboration through pathway A would lead to the dideuterated bicyclic product (**20**). A concerted elimination, with deuterium adding to the

terminal end of the double bond in intermediate **17** and the ensuing electron shifts, would yield the monodeuterated azaborolidine (**18**) and 3-deuteriopropene (**19**).

The proposed Hofmann elimination mechanism is shown in Scheme V. Triethylamine would attack **20** at hydrogen or

Scheme V



deuterium on the β carbon to nitrogen. Abstraction of a proton should be favored over deuterium abstraction, owing to an isotope effect. Intermediate **21** could then undergo thermal cleavage to give the monodeuterated azaborolidine (**18**) and 2-deuteriopropene (**22**). If deuterium were abstracted rather than proton, propene gas would be generated.

Triethylamine dideuteriophenylborane (**14**) was prepared by reducing diethyl phenylboronate with lithium aluminum deuteride in ether with triethylamine at low temperature. The triethylamine dideuterioborane structure (mp 64–65 °C, 84%) was characterized by mass spectral, NMR, ir, and elemental analyses. The infrared spectrum showed a broad boron–deuterium absorbance at 1680–1765 cm^{-1}.

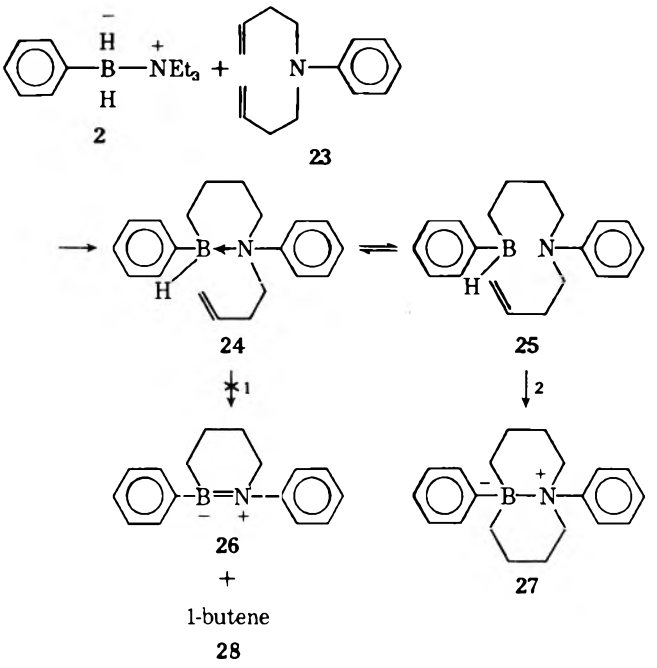
N,N-Diallylaniline (**1**) was added to an equimolar quantity of the triethylamine dideuteriophenylborane (**14**) in *p*-xylene. Above 95 °C deuteriopropene was evolved. The infrared absorbance at 2175 cm^{-1} was consistent with that expected for the allylic carbon–deuterium stretching frequency. NMR, ir, and mass spectral evidence conclusively identified the gas as 3-deuteriopropene rather than 2-deuteriopropene. Final confirmation of structure came from generation of 3-deuteriopropene from the reaction of allylmagnesium bromide with D_2O. The NMR and ir spectra were identical with those of the reaction product.

The structure of 3-deuterio-1,2-diphenyl-1,2-azaborolidine (**18**) was confirmed by mass, NMR, and ir spectra. The structure of **20** was also confirmed by spectral data and elemental analyses (Table I).

Further evidence against the second mechanism (Hofmann-type elimination) was that no propene gas could be generated by heating **3** in toluene with triethylamine; **3** was recovered quantitatively.

Evidence supporting the concerted elimination of propene through a six-centered transition state (Scheme II, path 3) over a four-centered elimination was obtained by the model reaction of *N,N*-di-(3-butenyl)aniline (**23**) with triethylamine phenylborane (**2**) as outlined in Scheme VI. This reaction would be expected to yield 1,6-diphenyl-1-aza-6-borabicyclo[4.4.0]decane (**27**). 1,2-Diphenylazaboracyclohexane (**26**) should not be formed by a concerted mechanism as was the case for the azaborolidines in the previous studies. This compound could, however, conceivably be formed by a four-centered mechanism. The elimination could be tested, as before, by monitoring gases produced from the reaction in *p*-xylene. If the competing pathway 1 (Scheme VI) were followed at the reaction temperature, butene gas would be detected. If only pathway 2 were followed, the bicyclic compound should be formed in relatively higher yield.

Scheme VI



N,N-Di-3-butenylaniline (**23**), triethylamine phenylborane (**2**), and *p*-xylene were slowly heated under nitrogen. Gas samples were taken at various temperatures and time intervals. A bright-green color developed during heating, but no butene gas was evolved during the course of the reaction. A white, crystalline solid was isolated; spectral and analytical results were consistent with the structure of 1,6-diphenyl-1-aza-6-borabicyclo[4.4.0]decane. A second fraction yielded ir and NMR data consistent with the structure 1,2-diphenyl-1-(3-butenyl)-2-hydroazaboracyclohexane (**25**). Spectral data and elemental analyses of these products are detailed in the Experimental Section.

These results offer strong support to the proposed mechanism for facile, concerted elimination of propene in the competitive formation of 1,5-diphenyl-1-aza-5-borabicyclo-[3.3.0]octanes (**3**) and 1,2-diphenyl-1,2-azaborolidine (**4**) (Scheme II).

Experimental Section

Equipment and Data. Nuclear magnetic resonance (NMR) spectra were obtained with a Varian A-60A analytical NMR spectrometer. Chemical shifts were measured in deuteriochloroform, unless otherwise specified, relative to tetramethylsilane. Infrared (ir) spectra were obtained with a Beckman IR-8 infrared spectrophotometer. ^{11}B NMR spectra were obtained with a Varian XL-100 high-resolution NMR spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc. Knoxville, Tenn.

Syntheses of Para-Substituted *N,N*-Diallylanilines. The general procedure for preparation of substituted diallylanilines was a slight modification of that of Butler and Bunch.[7]

Preparation of *N,N*-Di-3-butenylaniline. Aniline (14.0 g, 0.15 mol), sodium carbonate (32.0 g), and 50 ml of water were placed in a 250-ml, three-necked, round-bottomed flask equipped with a me-

chanical stirrer, addition funnel, and cold-water condenser. The mixture was heated to reflux and 4-bromo-1-butene (40 g, 0.30 mol) added dropwise with constant stirring. The reaction was allowed to proceed for 24 h after which the contents were cooled and filtered. The amine layer was separated, dried over sodium sulfate, and distilled under vacuum. A clear, colorless liquid (11.2 g, 37%) was obtained [bp 74–75 °C (0.10 mm)].

Syntheses of Triethylamine Phenylboranes. Para-substituted triethylamine phenylboranes were prepared by modifications of the method of Statton and Butler.[2]

1,2-Diphenyl-1,2-azaborolidine (4) and 1,5-Diphenyl-1-aza-5-borabicyclo[3.3.0]octane (3). These compounds were prepared for purposes of this study by use of the procedure reported by Butler, Statton, and Brey[3] with slight modifications. The spectral data agreed with the literature assignments[3] for these compounds.

A typical procedure for the para-substituted derivatives is given below. (See supplemental tables for other compounds.)

1-(4-Bromophenyl)-2-phenyl-1,2-azaborolidine (28) and 1-(4-Bromophenyl)-5-phenyl-1-aza-5-borabicyclo[3.3.0]octane (29). Triethylamine phenylborane (19.3 g, 0.1 mol) 25.2 g (0.1 mol) of *p*-bromo-*N,N*-diallylaniline, and 1.25 l. of toluene were placed in a 2-l. round-bottomed flask. The toluene was slowly distilled from the flask through a fractionating column. Upon initial heating, the contents of the flask turned bright yellow-green. When the temperature at the distilling head reached 120 °C, the residual green liquid was transferred to a 50-ml round-bottomed flask and distilled on a spinning band column. The lower boiling fraction was a clear to pale yellow, viscous liquid, bp 120–123 °C (0.15 mm), yield 7.8 g. NMR and ir data were consistent with those expected for the azaborolidine (Table III).

The higher boiling fraction, bp 130–132 °C (0.15 mm), was dissolved in acetone and cooled in a dry ice-2-propanol bath to yield 6.7 g of a crystalline compound, mp 116–118 °C. The ir, NMR, and mass spectra and elemental analysis were consistent with the structure 1-(4-bromophenyl)-5-phenyl-1-aza-5-borabicyclo[3.3.0]octane (Tables I and II).

Preparation of Dideuteriophenylborane Triethylamine (14). Lithium aluminum deuteride (3.36 g, 0.08 mol) was added to 200 ml of anhydrous diethyl ether (distilled from lithium aluminum hydride) in a three-necked, 500-ml, round-bottomed flask equipped with mechanical stirrer, addition funnel, condenser with drying tube, low-temperature thermometer, and nitrogen inlet tube. The lithium aluminum deuteride–ether mixture was refluxed for 20 min and then cooled to −72 °C in a dry ice-2-propanol bath. Triethylamine (15.2 g, 0.15 mol) was added in one portion. Diethyl phenylborane (19.0 g, 0.107 mol) was added dropwise with stirring; the temperature was kept below −65 °C during the entire addition. The mixture was allowed to stir until it had warmed to room temperature. The resulting mixture was filtered through a sintered glass funnel to remove the excess lithium aluminum deuteride. The filtrate was cooled in a dry ice-2-propanol bath. White, needlelike crystals of dideuteriophenylborane triethylamine, 17.5 g (84%), were filtered and dried (mp 64–65 °C). The infrared spectrum showed a strong absorbance at 1765 cm^{-1} which was assigned to the B–D stretching frequency. The NMR spectrum exhibited resonances at δ 1.2 (t, 9), 2.75 (quartet, 6), and 7.3 (m, 5). Anal. Calcd for $C_{12}H_{20}D_2BN$: C, 74.63; H, 10.44; N, 7.25; B, 5.60; D, 2.08. Found: C, 73.05; H, 11.12; N, 6.31; B, 5.83.

Preparation and Isolation of 3,7-dideuterio-1,5-diphenyl-1-aza-5-borabicyclo[3.3.0]octane (20), 3-Deuterio-1,5-diphenyl-1,2-azaborolidine (18), and 3-Deuteriopropene (19). Dideuteriophenylborane triethylamine (15.6 g, 0.08 mol), *N,N*-diallylaniline (13.8 g, 0.08 mol), and *p*-xylene (300 ml) were placed in a three-necked, 1-l., round-bottomed flask equipped with a mechanical stirrer, thermometer, and gas outlet. The outlet was connected by Tygon tubing to an infrared gas cell and then to a gas trap cooled by a dry ice-2-propanol mixture. The temperature of the solution was slowly raised and several gas samples were taken at 90, 98, 104, 96, and 97 °C. The infrared spectrum showed absorbances at 912 (s, spike on broad peak), 985 (w), 1002 (w), 1012 (w), 1080 (w), 1140 (s), 1260–1310 (m, broad, detailed), 1350–1400 (m, detailed), 1410–1490 (m, broad, detailed), 1638 and 1655 (double peak, s), 1820 and 1840 (double peak, w), 2175 (spiked peak), 2880 (s), 2940–3020 (s, broad, detailed), and 3090, 3110 cm^{-1} (double peak, s). The peak at 2175 cm^{-1} was consistent with the carbon–deuterium stretching frequency of 3-deuteriopropene. The threshold temperature for propene formation appeared to be 95–96 °C. The liquefied, trapped gas was mixed with deuteriochloroform for analysis by NMR. The NMR spectrum exhibited resonances at δ 1.7 (finely split doublet, 2), 5.0 (finely split triplet), and 5.8 (multiplet with fine splitting). The assignments in the NMR along with comparison with butene as a model, and with 3-deuteriopropene, synthesized for this purpose, confirm the identity of this gas as 3-deuteriopropene. The mass spectrum showed a peak at *m/e* 43. The reaction was allowed to continue for 12 h. The pale green reaction mixture was filtered and the filtrate was evacuated to remove the solvent. The remaining viscous, green liquid was placed in a 50-ml round-bottomed flask and distilled under vacuum on a spinning band column. The first fraction, 1.3 g (bp 50–54 °C, 0.15 mm) gave spectra consistent with 3-deuterio-1,2-diphenyl-1,2-azaborolidine (Table III). The azaborolidine was unstable in air and formed a white, insoluble material (mp 90–100 °C). The other fraction, 1.8 g (bp 64–68 °C, 0.15 mm), was recrystallized from ethanol yielding a white, crystalline compound (mp 77–79 °C). The residue from the distillation flask was recrystallized from ethanol, yielding 3.2 g of white crystals (mp 78–79 °C). Spectral data and elemental analyses confirmed the assignment of the structure for 3,7-dideuterio-1,5-diphenyl-1-aza-5-borabicyclo[3.3.0]octane (Tables I and II).

Reaction of *N,N*-Di-3-butenylaniline (23) with Triethylamine Phenylborane Complex (2). *N,N*-Di-3-butenylaniline (11.2 g, 0.056 mol), triethylamine phenylborane complex (14.1 g, 0.072 mol), and 500 ml of *p*-xylene were placed in a 1-l., three-necked flask equipped with a magnetic stirrer, nitrogen inlet tube, and cold-water condenser. The temperature was varied from 80 to 110 °C. A bright green color developed during heating. Gas samples were taken at regular intervals for infrared analysis. No butene gas was observed during the course of the reaction. The reaction was allowed to proceed for 24 h. The resulting solution was filtered, evaporated, and divided into two portions. The first portion was placed on the spinning band column for distillation. The first fraction (0.8 g, bp 75 °C, 0.5 mm) proved to be unreacted *N,N*-di-3-butenylaniline. The second fraction (1.2 g, bp 75–78 °C, 0.5 mm) gave spectral data consistent with the structure 1,2-diphenylazaboracyclohexane; however, as shown below, the elemental analysis failed to support this structural assignment for this compound. The infrared spectrum exhibited absorbances at 700 (s), 750 (s), 865 (w), 930 (m), 965 (w), 1000 (m), 1048 (m), 1065 (m), 1120 (w), 1280 and 1300 (double peak, m), 1220 (w), 1310 (s), 1400 (s), 1410 (m), 1450 and 1460 (double peak, m), 1515 (s), 1610 (s), and 2900–3150 cm^{-1} (s, broad, detailed). The NMR spectrum gave resonance signals at δ 0.82 (m, 2), 1.5 (m, 4), 3.5 (m, 2), and 7.2 (m, 10.5). The mass spectrum gave a peak at *m/e* 235 ± 1. Anal. Calcd for $C_{16}H_{18}BN$: C, 81.73; H, 7.72; B, 4.60; N, 5.96. Found: C, 78.42; H, 8.19; B, 4.99; N, 3.75 (not consistent with the above structure). The third fraction (1.4 g, bp 90–95 °C, 0.5 mm) gave spectral data consistent with the structure 1,2-diphenyl-1-(3-butentyl)-2-hydroazaboracyclohexane (**25**). The ir exhibited absorbances at 700 (s), 750 and 765 (double peak, s), 800–880 (w, detailed), 890–950 (m, detailed), 1995 (double peak, m), 1028 (m), 1150 (m), 1190 (m), 1325–1450 (broad, s), 1445 (m), 1500 (s), 1600 (s), 2300 (broad, m), and 2900–3100 cm^{-1} (s). The NMR spectrum showed resonance signals at δ 0.8 (m, 2), 1.65 (m, 6), 3.35 (m, 4), 5.1 (m, 1), 5.8 (m, 0.5), and 7.4 (m, 12). The fourth fraction (1.2 g, bp 95–105 °C, 0.50 mm), a light-yellow oil which solidified in the side arm, was recrystallized from ethanol. A white, crystalline solid (mp 140–143 °C) was obtained. The structure assigned was 1,6-diphenyl-1-aza-6-borabicyclo[4.4.0]decane (**27**). The infrared spectrum showed absorbances at 700 (s), 755 (s), 768 (s), 810 (m), 870 (w), 910 (double peak, s), 970 (w), 1000 (s), 1030 (s), 1066 (s), 1180 and 1200 (double peak, s) 1250–1430 (broad, s), 1450 (s), 1510 (s), 1610 (s), 2900–3300 cm^{-1} (broad, s, detailed). The NMR exhibited resonances at δ 0.95 (m, 4), 1.6 (m, 8), 3.5 (m, 4), and 7.3 (m, 10). The mass spectrum gave a parent peak at *m/e* 291 ± 1. Identical spectra were obtained from the second portion of the original reaction solution. The material was chromatographed on a silica gel column in benzene. The eluted solution was evaporated and the residue recrystallized from ethanol. A white, crystalline material (1.1 g, mp 143–145 °C) was obtained. Anal. Calcd for $C_{20}H_{26}BN$: C, 82.48; H, 9.00; B, 3.71; N, 4.81. Found: C, 81.98; H, 8.81; B, 3.64; N, 4.76.

A solid material (1.4 g, mp >350 °C) was recovered from the reaction vessel. The NMR showed only aromatic absorption at δ 7.3. This material was shown to be triphenylcycloborazene.

Preparation of 3-Deuteriopropene (19). Allylmagnesium bromide (20 ml, 0.5 ml/l. in ether) was placed in a 500-ml round-bottomed flask. A few drops of deuterium oxide were added, resulting in gas evolution. The gas was condensed in a trap cooled in dry ice-2-propanol. The condensed gas was mixed with carbon tetrachloride and deuteriochloroform for NMR studies. An infrared gas cell was used to trap some of the gas for analysis. The NMR showed resonance signals at δ 1.65 (finely split signal, 2), 4.8 (finely split triplet, 2), and 5.65 (m, 1). The infrared spectrum exhibited absorbances at 855 and 865 (s, double peak), 940 (broad, s), 1006 (m), 1100 (broad, s), 1330 (s), 1455 (s, spiked), 1675 (m, spiked), 1870 (w), 1995 (s), 2200 (m), 2340 (w), and 2940–3300 cm^{-1} (broad, s, detailed).

Acknowledgment. This work was supported by the National Science Foundation under Grants GH32766 and GH17926 for which we are grateful.

Registry No.—**2**, 15068-65-2; **3** uncoordinated, 4529-26-4; **3** coordinated, 7800-63-7; **14**, 59318-44-4; **18**, 59318-45-5; **19**, 1117-89-1; **20** uncoordinated, 59318-46-6; **20** coordinated, 59350-20-8; **23**, 13369-16-9; **25**, 59318-47-7; **27** uncoordinated, 59318-48-8; **27** coordinated, 59350-19-5; **29** uncoordinated, 59318-49-9; **29** coordinated, 59368-11-5; **30** uncoordinated, 59318-50-2; **30** coordinated, 59349-70-1; **31** uncoordinated, 59318-51-3; **31** coordinated, 59368-12-6; **32** uncoordinated, 59318-52-4; **32** coordinated, 59350-26-4; **33** uncoordinated, 59318-53-5; **33** coordinated, 59350-25-3; **34** uncoordinated, 59318-54-6; **34** coordinated, 59350-24-2; **35** uncoordinated, 59318-55-7; **35** coordinated, 59350-23-1; **36** uncoordinated, 59318-56-8; **36** coordinated, 59350-22-0; **37** uncoordinated, 59318-57-9; **37** coordinated, 59368-09-1; **38** uncoordinated, 59318-58-0; **38**, coordinated, 59350-21-9; **39**, 4529-23-1; **40**, 59318-59-1; **41**, 59318-60-4; **42**, 59318-61-5; **43**, 59318-62-6; **44**, 59318-63-7; aniline, 62-53-3; 4-bromo-1-butene, 5162-44-7; *p*-bromo-*N,N*-diallylaniline, 30438-95-0; triethylamine, 121-44-8; diethylphenylborane, 56797-48-9; *N,N*-diallylaniline, 6247-00-3; *N,N,N',N'*-tetrallyl-*p*-phenylenediamine, 59318-64-8; *p*-phenylenediamine, 106-50-3; 3-bromopropene, 106-95-6; *p*-chloro-*N,N*-diallylaniline, 30438-94-9; *p*-chlorophenylborane triethylamine, 59318-65-9; *p*-methylphenylborane triethylamine, 59318-66-0; *p*-methyl-*N,N*-diallylaniline, 3480-96-4; *p*-ethoxyphenylborane triethylamine, 59318-68-2; *p*-methoxyphenylborane triethylamine, 59318-69-3; *p*-methoxy-*N,N*-diallylaniline, 59318-70-6.

Supplementary Material Available. Tables of physical constants and experimental details on syntheses (16 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Taken from the Ph.D. Dissertation of C. L. McCormick, Department of Chemistry, University of Florida, June 1973.
(2) G. L. Statton and G. B. Butler, *J. Am. Chem. Soc.*, **86**, 518 (1964).
(3) G. B. Butler, G. L. Statton, and W. S. Brey, *J. Org. Chem.*, **30**, 4194 (1965).
(4) H. C. Brown, "Hydroboration", W. A. Benjamin, New York, N.Y., 1962, p 13.
(5) B. M. Mikhailov and F. B. Tutorskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1158 (1961).
(6) E. C. Ashby, *J. Am. Chem. Soc.*, **81**, 4791 (1959).
(7) G. B. Butler and R. L. Bunch, *J. Am. Chem. Soc.*, **71**, 3120 (1949).
(8) See paragraph at end of paper regarding supplementary material.

Investigations on the Photochemical Ring Expansion of Ring Fused β-Lactams

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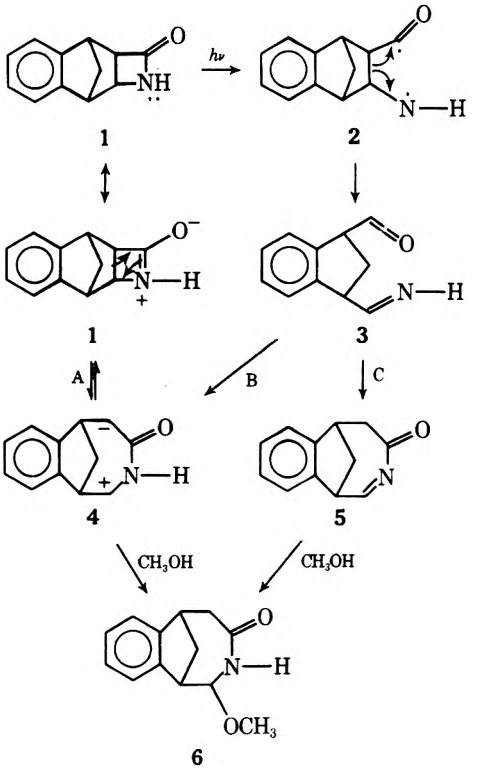
The photochemical ring expansion of exo-3-aza-4-ketobenzotricyclo[4.2.1.$0^{2,5}$]non-7-ene (**1**) in the presence of methanol to *exo*-2-methoxy-3-aza-4-keto-7,8-benzobicyclo[4.2.1]nonene (**6**) was studied. Data on the relative quantum yields for product (**6**) formation and starting material (**1**) disappearance as a function of methanol concentration suggest a dipolar intermediate in the reaction. A variety of other ring fused β-lactams were subjected to the reaction conditions and, of materials studied, only those β-lactams fused to the bicyclo[2.2.1]heptane ring system were found to undergo the rearrangement.

In an earlier report[1] on the photochemical ring expansion of the β-lactam **1**, in alcoholic solution, to the lactam ether **6** a number of mechanistic possibilities were suggested (Chart I). We now report investigations directed at further elucidating the mechanism of this reaction and studies of a series of β-lactams designed to delineate the scope of the reaction.

Chart I



Results and Discussion

The three logical mechanistic routes for the reaction center on the formation of two intermediates (**4** and **5**), one of which, (**4**), is common to two of the routes (A and B). Routes B and C are initiated by C(O)–N bond cleavage[2] to biradical **2** followed by β-bond cleavage to afford the imine ketene[3] **3** which can react either by addition of the N–H across the ketene[4] moiety to afford acylimine **5** or by collapse to zwitterion[5] **4**. A third alternative (path A) involves electrocyclic ring opening to **4**,[7] a route which is difficult to distinguish from path B which we favor. In either case[4,5a,6] addition of methanol to **4** or **5** would afford the observed product. Our discussions will center on path B although it should be kept in mind that path A remains a viable, but perhaps indistinguishable, alternative.

Our first attempt at differentiating paths B and C was based on the fact that, in the formation of acylimine **5**, the N–H must add across the C=C of the ketene moiety, i.e., a proton is transferred from N to C. We reasoned that N-alkylation of **1** would block this path and that the formation of N-alkylated

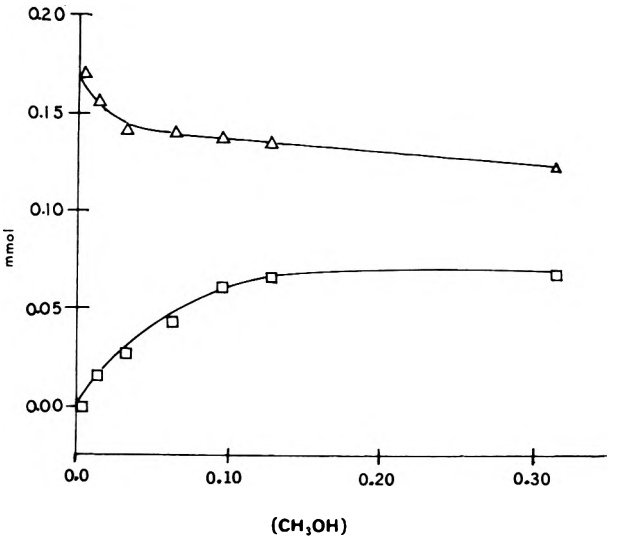
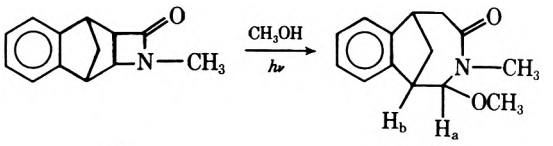


Figure 1. Plot showing dependence of product **6** (□) formation and starting material **1** (△) disappearance on methanol concentration. Unirradiated samples contained 0.216 mmol of **1** in acetonitrile.

product would be convincing evidence that pathway C was not operative.

The required N-methylated derivative **7** was prepared by NaH/DMF/CH_3I alkylation of **1**. Irradiation of **7** in methanol afforded product as evidenced by a doublet at δ 4.6 (H_a in **8**) in the ^1H NMR. Alumina chromatography workup gave material whose NMR and ir spectra were entirely consistent with those expected for a ~60:40 mixture of **8**:**7**. Thus, in addition to peaks assigned to **7** the spectrum showed resonances at δ 2.7 (NCH_3), 3.4 (OCH_3) and a doublet at δ 4.6 (J = 7 Hz, H_a) assigned to **8**. The infrared spectrum showed carbonyl absorptions at 1735 (from **7**) and 1620 cm^{-1} (from **8**) clearly indicating that **8** was a product of the reaction. Unfortunately,



7 **8**

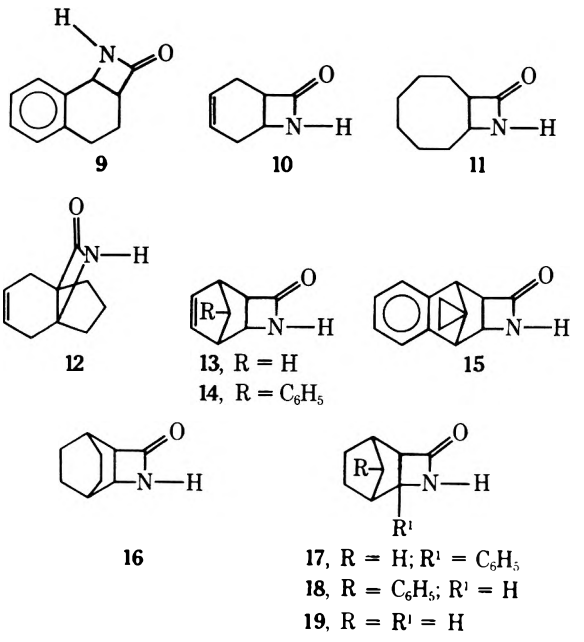
this evidence is inconclusive since repeated purification attempts caused extensive decomposition of the product and we were unable to obtain a pure sample of **8**.[8]

Our second approach was based on the prediction that path B (and A) will be reversible, i.e., intermediate **4** can easily collapse back to starting material (**1**), and methanol addition to give **6** will compete with this reversion to starting material and all other decay processes for **4**. Thus, if the reaction proceeds by either of these routes, the quantum yields for formation of **6** and for the disappearance of **1** should be a function of methanol concentration. Conversely, there is no apparent route for **5** to easily revert to **1** and path C should again show a dependence of product (**6**) quantum yield on methanol concentration but disappearance of **1** should be independent of methanol concentration.

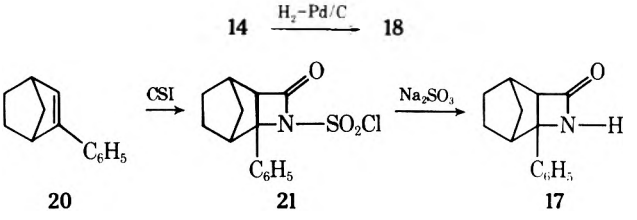
Accordingly, a series of samples of **1** in acetonitrile[9] containing varying amounts of methanol were irradiated in parallel and analyzed via quantitative HPLC for **1** and **6**. The results (Figure 1) indicate a clear dependence of product formation and starting material disappearance on methanol concentration, i.e., they are only consistent with a reaction occurring via path B (or A) and inconsistent with path C.

Scope of the Photorearrangement. Since the formation of **6** occurs with reasonable efficiency it was of interest to determine the scope of this reaction since broad applicability would provide a useful synthetic sequence for the formation of a series of novel ring expanded polycyclic lactams. We wished to investigate two major points concerning the reaction: (1) was the aromatic chromophore necessary to the rearrangement, and (2) was there a ring structural requirement which might limit the potential synthetic utility of the reaction? To this end we investigated the photochemistry of the series of fused β-lactams **9**–**19**[10–15] shown in Chart II.

Chart II

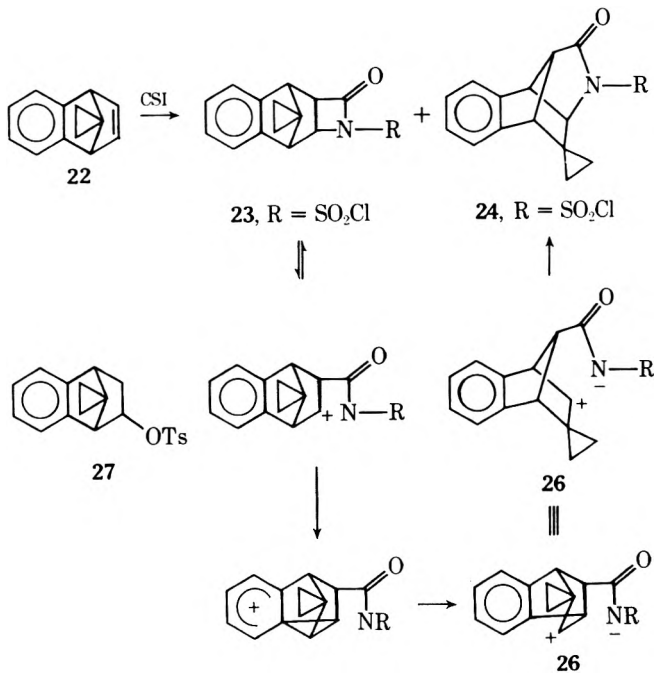


Preparation of β-Lactams. With three exceptions the desired starting materials were prepared by reported routes. Compound **18** was prepared by simple hydrogenation of **14**[14,15] whereas **17** was prepared in 68% overall yield by chlorosulfonyl isocyanate (CSI) addition[16] to **20** followed by removal of the SO_2Cl group according to the procedure of Durst and O'Sullivan.[17] The structures of **17** and **18** follow from their method of synthesis and spectral comparison with the known parent system **19**.[13]



The preparation of **15**, however, was not straightforward. Addition of CSI to **22**[18] in ether gave a 68% yield of a solid material whose infrared spectrum showed absorption at 1825 and 1780 cm^{-1} characteristic of *N*-chlorosulfonyl-β- and γ-lactams,[19d] respectively. Attempts to isolate the desired **23** via silica gel chromatography or crystallization only afforded material enriched with the 1780-cm^{-1} component suggesting that it was being formed by rearrangement of **23**.

An enriched sample (90%) of the rearrangement product was prepared by stirring a sample of the CSI adduct mixture with a slurry of silica gel in chloroform for 24 h. Recrystallization from ether gave pure material which was identified as γ-lactam **24** on the basis of its NMR and ir spectra and those of its reduction product **25**. The NMR spectrum of **24** showed two-proton multiplets centered at δ 0.4 and 1.2 for the cyclopropyl protons and at δ 4.1 (H_d and H_b), 3.65 (H_c), and 2.95 (H_a) in addition to the aromatic resonance at 7.5–7.1 (see structure **25a**, R = SO_2Cl).



Removal of the chlorosulfonyl group[17] gave **25** whose structural assignment is based on ir absorptions at 3420 and 1700 cm^{-1} indicating the presence of a γ-lactam and its ^1H NMR spectrum which showed the expected aromatic, cyclopropyl, and N–H (at δ 6.6) resonances and a unique set of one-proton multiplets (Figure 2) for the ring protons. The

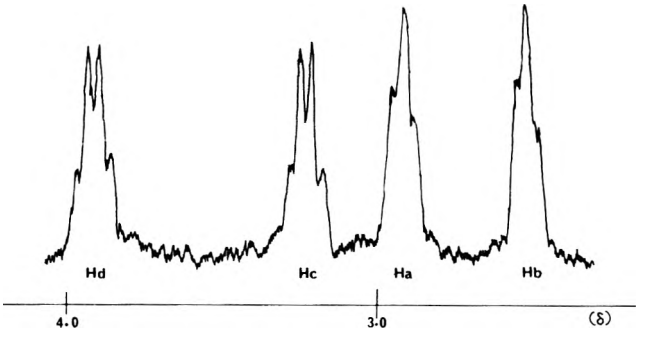
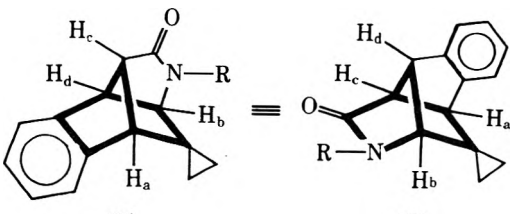


Figure 2. A portion of the NMR spectrum of **25** showing resonances for protons H_a–H_d.

symmetry of the spectrum indicates that there are two pairs of protons with nearly identical couplings. Furthermore, when a decoupling experiment was carried out it was found that irradiation of any of the multiplets caused changes in the other three, i.e., the protons are mutually coupled. These data uniquely fit structure **25.** Protons H_a–H_d are all on the bridgehead positions of bicyclo[2.2.1]heptane systems so that angle factor contributions to couplings should be similar, and they should form two equivalent sets, $H_a + H_b$ and $H_c + H_d$, with essentially equal couplings (see structures **25a** and **25b,**



25a **25b**

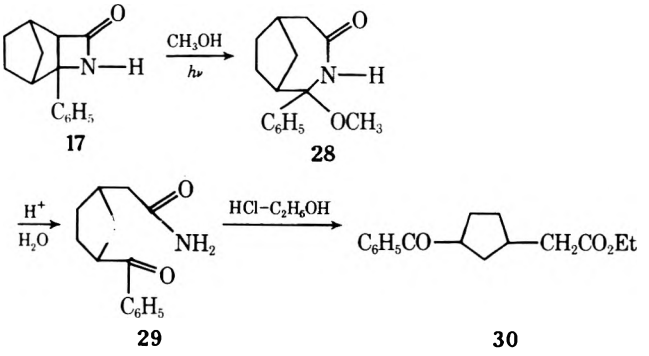
R = H). H_a is vicinally coupled to H_c and W-coupled[20] to H_a and H_d whereas H_b is vicinally coupled to H_d and W-coupled to H_a and H_c. H_c and H_d are vicinally coupled to two protons ($H_a + H_d$ and $H_b + H_c$, respectively) and W-coupled to one proton, H_c to H_b and H_d to H_a. The assignment of H_a to the resonance at δ 2.7 follows from spectral changes occurring on conversion of **24** to **25;** i.e., on removal of the strongly electron-withdrawing chlorosulfonyl group the two-proton multiplet at δ 4.1 in **24** is replaced by a single-proton multiplet at δ 3.9 for H_d and a new multiplet at δ 2.7 for H_b.

There are several analogies to the rearrangements of *N*-chlorosulfonyl-β-lactams[19,21] and the corresponding solvolytic rearrangement of the tosylate **27** has been reported.[22] Apparently, stabilization via the incipient cyclopropylcarbinyl cation in **26** is crucial to the rearrangement since similar treatment of the *N*-chlorosulfonyl derivative of **1** affords no rearranged product.[1]

Finally, reduction of the initial reaction product after careful workup gave the desired β-lactam **15** whose structure was established by comparison of spectral properties with those of **1**.[1]

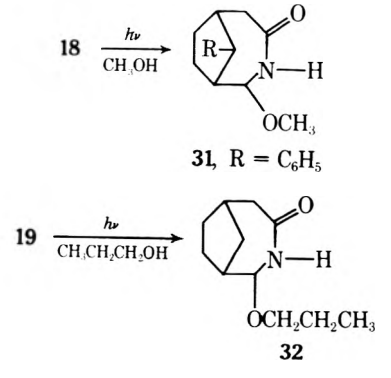
Photolysis of Lactams. Preliminary experiments were run by irradiating the appropriate β-lactam in methanol, carefully evaporating solvent, and examining the ^1H NMR spectrum for a methoxy peak (δ ~3.5) and the proton α to N (H_a in **8** at δ 4.5). Under these conditions **9**–**16** showed no evidence for the occurrence of the ring expansion reaction.[23]

Examination of the photolysate of **17** showed a methoxy methyl resonance at δ 3.1 consistent with ring expansion to **28.** Attempted workup of the reaction mixture by silica gel chromatography afforded a new material, obviously a degradation product of **28.** Analysis of the spectral data suggested that this material was the keto amide **29** and this was established by refluxing this material in ethanol–HCl to convert it to the known keto ester **30**.[24] Presumably **29** arises via acid-catalyzed loss of methanol from **28.**



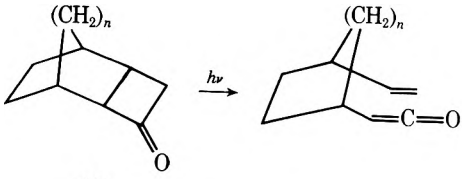
Careful workup of the photolysis mixture by chromatography on neutral alumina gave a 40% yield of **28.** When a sample of **28** was stirred in chloroform containing silica gel it was converted to **29** as expected.

Irradiations of **18** and **19** also proceeded to give the desired products **31** and **32** indicating that the aromatic ring or any



particular orientation of it is not crucial to the ring expansion reaction, i.e., **19** as well as **1, 17,** and **18** gives product. Con-

versely our results indicate that the reaction occurs only when the β-lactam is fused to a bicyclo[2.2.1] system, e.g., it even fails in the closely related [2.2.2] system **16**. This behavior is reminiscent of that observed by Miller and Abraitys[3d] in the corresponding cyclobutanones, e.g., they observed that members of the bicyclo[2.2.1] system (**33**) (n = 1) were efficiently converted to ketene derived products whereas the homologue (n = 2) gave poor yields of those products. They reasoned that the strain inherent to the [2.2.1] system was necessary to cleavage of the second cyclobutanone C–C bond after the initial photochemical α-cleavage reaction. It appears that these considerations also pertain to our system and, in fact, lend further support to the intermediacy of the ketene imine.



33

Experimental Section

Microanalyses were performed by Dr. Franz Kasler of the Department of Chemistry, University of Maryland. The NMR spectra were obtained on a Varian A-60D or XL-100 NMR spectrophotometer with tetramethylsilane as internal standard. Infrared spectra were obtained as a Perkin-Elmer 337 grating infrared spectrometer or a Beckman IR8 infrared spectrometer in a 0.1-mm cell. Mass spectra were determined on a Du Pont 492 spectrometer at 70 eV. Melting points were determined on a Fisher-Johns hot stage apparatus and are uncorrected.

Relative Quantum Yields as a Function of Methanol Concentration. Analyses of photolysis mixtures were carried out on a Du Pont 830 liquid chromatograph with a uv (254 nm) detector at 875 psi column pressure and ambient temperature. A 25 cm × 2.1 mm Zorbax SIL column and a solvent system consisting of 500 parts methylene chloride, 100 parts water, and 15 parts isopropyl alcohol at a flow rate of 0.5 ml/min was employed. Concentrations were calculated from areas obtained by peak integration (disk) using response factors and internal standards. Benzamide was used as an internal standard added to an aliquot of the reaction mixture after irradiation to avoid competition of the standard for the light. Samples were prepared by dilution of a stock solution containing 4.00 g of **1** in 100 ml of the appropriate solvent. Aliquots of 5 ml of this solution were made up to 25 ml by addition of solvent and methanol. Aliquots (5 ml) (40 mg, 0.216 mmol) of these mixtures were placed in 10 × 1 cm quartz tubes sealed with rubber serum caps and purged with pure nitrogen for 5 min before irradiation. Samples were irradiated in a "merry-go-round", in triplicate, for 390 min using a circular bank of ten GE G15T8 lamps. After irradiation 1-ml aliquots were removed and an aliquot of a standard (benzamide) solution added before HPLC analysis.

3-Methyl-*exo*-4-oxo-3-azabenzotricyclo[4.2.1.0^{2,5}]non-7-ene (7). A solution of 1.5 g of **1** in 20 ml of dry DMF was added dropwise to a slurry of 1.5 g of 50% NaH (pentane washed) in 20 ml of DMF. The mixture was stirred under nitrogen at 100 °C for 11 h. The reaction mixture was allowed to cool and the water condenser replaced with a dry ice condenser. Methyl iodide (5.7 g) was added dropwise, the reaction mixture stirred for 30 min, 100 ml of water added, and the mixture extracted with ether. The organic phase was washed with water and dried ($MgSO_4$) and solvent was evaporated. The residual solid was recrystallized from petroleum ether to give 0.7 g (43%) of **7**: mp 114–115 °C; ir ($CHCl_3$) 3000 and 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.9–7.3 (m, 4, aromatic), 3.4–3.6 (broad s, 3, H–C–N and bridgehead H), 3.1 (m, 1, H–C–C=O), 2.85 (s, 3, NCH_3), 1.8–2.0 (m, 2, $-CH_2$).

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.50; H, 6.66; N, 7.13.

Addition of CSI to Spiro[2,3-benzonorbornadiene-7,1′-cyclopropane] (22). To a stirred solution of 4.0 g (0.024 mol) of **22** in 40 ml of anhydrous ethyl ether at −40 °C was added 4 g (0.028 mol) of CSI in 20 ml of ether. The reaction mixture was allowed to warm to room temperature and was stirred for 15 h and then slowly added to 30 g of ice and 20 ml of saturated $NaHCO_3$. Layers were separated and the aqueous phase extracted with three 40-ml portions of ether. The combined organic layer was dried ($MgSO_4$) and the ether evaporated to give 5 g (68%) of a yellow solid, mp 90–100 °C dec.

The infrared spectrum ($CDCl_3$) of the reaction product had two carbonyl absorptions at 1825 and 1780 cm^{-1} due to the presence of **23** and **24**.

The mixture was heated in $CHCl_3$ at 50 °C in the presence of 10 g of silica gel for 24 h. After filtration and evaporation of $CHCl_3$ the resulting solid contained approximately 90% rearrangement product as determined by NMR integration. Recrystallization from ether gave a white solid, mp 165–167 °C, identified as 2-spirocyclopropane-4-chlorosulfonyl-5-oxo-*exo*-4-azabenzotricyclo[4.3.0^{1,6}.0^{3,7}]non-8-ene (**24**): ir 3090, 3010, 1780, 1400, 1280, 1190, 1040 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}NO_3SCl$: C, 54.28; H, 3.87; N, 4.52. Found: C, 54.02; H, 3.93; N, 4.56.

The ^{1}H NMR spectrum ($CDCl_3$) of **23** was obtained by subtracting the resonances due to **24** from the spectrum of the mixture: δ 7.4–7.1 (m, 4, aromatic), 4.45–4.35 (d, J = 4 Hz, 1, H–C–N–SO_2Cl), 3.65–3.50 (d, J = 4 Hz, 1, H–C–C=O), 3.45 (s, 1, bridgehead), 3.1 (s, 1, bridgehead), 1.3–0.1 (m, 4, cyclopropane).

2-Spirocyclopropyl-5-oxo-4-aza-8,9-benzotricyclo[4.3.0^{1,6}.0^{3,7}]non-8-ene (25). To a solution of 0.250 g (0.0081 mol) of **24** in 20 ml of $CHCl_3$ was added 5 ml of 25% Na_2SO_3 solution. The reaction mixture was allowed to stir for 3 h while the pH was adjusted at 7–9 using KOH. The layers were separated and the $CHCl_3$ layer was washed with 30 ml of water, dried ($MgSO_4$), and evaporated. Recrystallization of the resulting solid from THF–petroleum ether gave 85 mg (50% yield) of reduction product **25**, mp 183–185 °C: ir ($CDCl_3$) 3420, 3010, and 1700 cm^{-1}.

Anal. Calcd for $C_{14}H_{13}NO$: C, 79.60; H, 6.20; N, 6.63. Found: C, 79.30; H, 6.38; N, 6.43.

***exo*-4-Oxo-9-spirocyclopropyl-*exo*-3-azabenzotricyclo[4.2.1.0^{2,5}]non-7-ene (15).** Similar treatment of 6 g of the crude CSI–**22** addition product with Na_2SO_3–KOH gave 1.7 g (42%) of **15**, mp 190–192 °C after recrystallization from MeOH–H_2O: ir ($CHCl_3$) 3400 and 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.4–7.1 (m, 4, aromatic), 6.8–6.4 (broad, 1, N–H), 3.7 (d, J = 9 Hz, 1, HC–N), 3.4–3.2 (m, 1, HC–C=O), 3.0–2.8 (m, 2, bridgehead), 1.2–0.1 (m, 4, cyclopropane).

Anal. Calcd for $C_{14}H_{13}NO$: C, 79.60; H, 6.20; N, 6.63. Found: C, 79.31; H, 6.41; N, 6.40.

***endo*-2-Phenyl-3-chlorosulfonyl-*exo*-4-oxo-*exo*-3-azatricyclo[4.2.1.0^{2,5}]nonane (21).** A solution of 2.9 g (20.5 mmol) of CSI in 15 ml of anhydrous ethyl ether was added dropwise to a stirred solution of 3.5 g (20.5 mmol) of 2-phenyl-2-norbornene in 15 ml of anhydrous ethyl ether cooled in an ice water bath. After completion of the addition the reaction mixture was allowed to stir for 1 h. The solid was filtered and washed with cold ether, giving 5.3 g of **21** (85% yield). Recrystallization from ethyl ether gave a white solid, mp 114–116 °C: ir ($CDCl_3$) 3000, 1810, 1410, 1180, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.6–7.3 (m, 5, aromatic ring), 3.5 (s, 1, H–C–C=O), 3.4 (m, 1, bridgehead), 2.7 (m, 1, bridgehead), 2.2–1.0 (m, 6).

Anal. Calcd for $C_{14}H_{14}NO_3ClS$: C, 53.94; H, 4.49; N, 4.49. Found: C, 53.71; H, 4.60; N, 4.52.

***endo*-2-Phenyl-*exo*-4-oxo-3-azatricyclo[4.2.1.0^{2,5}]nonane (17).** Treatment of 1 g (0.0032 mol) of **21** with Na_2SO_3 in the usual manner gave a white solid which was recrystallized from CH_2Cl_2 affording 0.5 g (74%) of **17**, mp 171–172 °C: ir ($CDCl_3$) 3420, 2990, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.3 (s, 5, aromatic), 6.7–6.5 (broad, 1, NH), 3.2 (m, 1, H–C–C=O), 2.7–2.5 (m, 2, bridgehead), 2.2–1.0 (m, 6).

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.88; H, 7.04; N, 6.57. Found: C, 78.93; H, 7.24; N, 6.54.

Photolysis of *endo*-2-Phenyl-*exo*-4-oxo-3-azatricyclo[4.2.1.0^{2,5}]nonane (17) in Methanol. A mixture of 4 g (0.0188 mol) of **17** in 1800 ml of absolute MeOH in a N_2 atmosphere was irradiated for 29 h through a Vycor filter with a 450-W Hanovia medium-pressure mercury lamp. The inner surface of the reaction vessel was coated with a polymeric film after irradiation. Removal of the solvent gave a yellow oil which was dissolved in 1:1 CCl_4–$CHCl_3$ and applied to a neutral alumina column (120 g) and eluted with CCl_4. Fraction 1 (100 ml) contained an unidentified yellow oil. Fraction 2–3 (200 ml each) and fractions 4–6 (1:3-$CHCl_3$–CCl_4, 200 ml) contained product **28**. Fraction 7 contained a mixture of **17** and **28** whereas fractions 8–11 contained only **17**. Recrystallization of **28** from ethyl ether gave 1.43 g (40% based upon recovered starting material), mp 118–120 °C, of *endo*-2-phenyl-*exo*-2-methoxy-4-oxo-3-azabicyclo[4.2.1]nonane (**28**): ir ($CDCl_3$) 3410, 2960, 1650, 1450, 1380, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.16–7.2 (broad s, 5, aromatic), 6.4–6.2 (broad s, 1, NH), 3.1 (s, 3, –OMe), 2.7–2.5 (m, 3, bridgehead + CH_2C=O), 2.5–2.2 (m, 3), 2.0–1.4 (m, 4).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.15; H, 7.87; N, 5.36.

Rearrangement of *endo*-2-Phenyl-*exo*-2-methoxy-4-oxo-3-azabicyclo[4.2.1]nonane (28). To a solution of 650 mg of **28** in 40 ml of $CHCl_3$ was added 30 g of silica gel and 1 ml of water; the mixture was allowed to stir at room temperature for 2 days and filtered, and the silica gel was washed with 300 ml of $CHCl_3$. Evaporation of solvent gave a white solid which was recrystallized from ether to give 200 mg (33%) of 2-(3-benzoylcyclopentyl)acetamice (**29**), mp 108–110 °C: ir ($CDCl_3$) 3550, 3440, 2950, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.1–7.8 (m, 2, aromatic), 7.6–7.2 (m, 3, aromatic), 6.7–5.8 (broad s, 2, NH_2), 4.1–3.6 (m, 1, H-C-C=O), 2.6–1.2 (m, 9, cyclopentane CH_2C=O).

This material was identical with the product obtained via workup of the original photolysis mixture by silica gel chromatography.

A solution of 200 mg (0.87 mmol) of **29** in 15 ml of ethyl alcohol and 5 drops of concentrated HCl was allowed to stir for 2 days at 70 °C. The mixture was filtered and removal of solvent gave a brown solid. The solid was taken up in CCl_4 and unreacted starting material crystallized. The mother liquid was evaporated to give a yellow oil identified as **30**: ir (CCl_4) 2900, 1740, 1680 cm^{-1}; ^1H NMR δ 8.2–7.8 (m, 2, aromatic), 7.6–7.3 (m, 3, aromatic), 4.3–4.0 (q, 2, OCH_2), 4.0–3.7 (m, C-1), 2.7–1.5 (m, 9, cyclopentane CH_2C=O), 1.5–1.3 (t, 3, CH_3). Treatment of the oil with 2,4-dinitrophenylhydrazine reagent gave organge-red crystals which were recrystallized three times from ethyl alcohol to give the 2,4-DNP derivative of mp 81–82 °C (lit. mp 83–85 °C).[24]

The infrared spectrum (KBr) had absorption at 3280, 2960, 1740, 1620, 1595, 1345, 1300, and 1260 cm^{-1}.

***anti*-9-Phenyl-*exo*-4-oxo-3-azatricyclo[4.2.1.$0^{2,5}$]nonane (18).** **14** (4.6 g, 0.022 mol) in 70 ml of ethyl acetate was hydrogenated over 10% palladium on powdered charcoal at an initial pressure of 50 psi in a Parr shaker apparatus. After 5 h the reaction mixture was filtered, solvent removed, and the resulting solid recrystallized from methylene chloride–cyclohexane to give 4.0 g (86%) of **18**, mp 150–152 °C: ir (KBr) 3200, 2970, 2955, 1710, 1335, 1175, 720, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3–7.1 (s, 5, aromatic), 6.3–6.1 (broad, 1, N-H), 3.6–3.5 (d, J = 5 Hz, 1, H-C-N), 3.25–3.1 (s, 1, H-C-C=O), 3.4–3.35 (m, 1, benzylic), 2.9–2.7 (m, 2, bridgehead), 1.65–0.85 (m, 4).

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.56. Found: C, 78.91; H, 7.20; N, 6.47.

Photolysis of 18. A mixture of 600 mg of **18** in 450 ml of absolute MeOH was irradiated for 27 h. Approximately 225 ml of the reaction mixture was evaporated giving a yellow oil. This oil was applied to a dry column of alumina (20 × 1 in.) and eluted with 100 ml of THF. Four bands resulted. The band with R_f ~0.4 was cut from the column, eluted, and recrystallized from THF and petroeum ether (bp 40–60 °C) to give 20 mg of ring-expanded product identified as exo-2-methoxy-4-oxo-*anti*-9-phenyl-3-azabicyclo[4.2.1]nonane (**31**), mp 140–141 °C: ir ($CDCl_3$) 3530, 3410, 2950, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9–7.6 (broad s, 1, NH), 7.4–7.1 (s, 4, aromatic), 4.3–4.1 (t, J = 8 Hz, 1, H-C-OMe), 3.7 (s, 1, benzylic), 3.6–3.4 (s, 3, OMe), 2.8–2.5 (m, 4, bridgehead and CH_2C=O), 2.2–1.6 (m, 4).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.25; H, 7.71; N, 5.48.

Photolysis of 19. A solution of 3 g of **19** in 430 ml of 1-propanol was irradiated for 20.5 h. The residue from evaporation of the photolysate was chromatographed on 250 g of alumina with 3:1 benzene–chloroform and 150-ml fractions taken. Fractions 26–34 were combined and chromatographed on 125 g of silica gel (4:1 benzene–chloroform). Product (**32**, 50 mg) obtained from fraction 23 as an oil showed ir 3400 and 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2 (s, 1, NH), 4.2 (t, 1, J = 5 Hz, H-C-O-), 3.1–3.8 (m, 2, OCH_2) 2.8–1.4 (m, 12), 0.95 (t, 3, $-CH_3$).

Anal. Calcd for $C_{11}H_{19}NO_2$: N, 7.10. Found: N, 7.59, 6.96.

Photolysis of Lactams 9–16. Photolyses were carried out in methanol and monitored by NMR using the prominent H-C-O product resonance to indicate reaction. Compounds **13** and **14** reacted efficiently, presumably via dimerization, as evidenced by the disappearance of olefinic proton resonances. Lactam **15** rapidly disappeared with concomitant decay of the cyclopropyl resonances. Other lactams disappeared slowly with no evidence for product formation.

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Registry No.—**1**, 41326-41-4; **7**, 59433-89-5; **9**, 59433-90-8; **10**, 20205-48-5; **11**, 4946-36-5; **12**, 20824-61-7; **13**, 14805-31-3; **14**, 59433-91-9; **15**, 59433-92-0; **16**, 59433-93-1; **17**, 59433-94-2; **18**, 59433-95-3; **19**, 14805-23-3; **21**, 59433-96-4; **22**, 22003-58-3; **23**, 59433-97-5; **24**, 59433-98-6; **25**, 59433-99-7; **28**, 59434-00-3; **29**, 59434-01-4; **30**, 59434-02-5; **30** 2,4-DNP, 41511-15-3; **31**, 59434-03-6; **32**, 59434-04-7; CSI, 1189-71-5; 2-phenyl-2-norbornene, 4237-08-5.

References and Notes

(1) H. L. Ammon, P. H. Mazzocchi, W. J. Kopecky, Jr., H. J. Tamburin, and P. H. Watts, Jr., *J. Am. Chem. Soc.*, **95**, 1968 (1973).
(2) There are a number of analogies for C(O)–N bond cleavages in lactams: (a) M. Fisher, *Chem. Ber.* **101**, 2669 (1968); (b) *ibid.*, **102**, 342 (1969); (c) *Tetrahedron Lett.*, 2281, 4295 (1969); (d) P. H. Mazzocchi and J. Thomas, *J. Am. Chem. Soc.*, **94**, 8281 (1972); (e) P. H. Mazzocchi, J. J. Thomas, and F. Danisi, *J. Polym. Sci., Part B*, **13**, 737 (1975); (f) Z. Horii, Y. Hori, and C. Iwata, *Chem. Commun.*, 1424 (1969).
(3) The corresponding cleavage of cyclobutanones to alkene ketenes is also well known: (a) W. Hostettler, *Tetrahedron Lett.*, 687 (1965); (b) G. Buchi and E. Burgess, *J. Am. Chem. Soc.*, **84**, 3104 (1962); (c) J. Hurst and G. Whitman, *J. Chem. Soc.*, 2864 (1960); (d) R. D. Miller and V. Y. Abraitys, *J. Am. Chem. Soc.*, **94**, 664 (1972).
(4) J. F. Banfield, G. M. Brown, F. H. Davey, N. Davies, and T. H. Ramsay, *Aust. J. Sci. Res., Ser. A*, 330 (1948).
(5) (a) H. B. Kagan and J. L. Luche, *Tetrahedron Lett.*, 3093 (1970); (b) A. Gomes and M. M. Joullie, *Chem. Commun.*, 935 (1967); (c) R. Huisgen, B. A. Davis, and M. Mazikawa, *Angew. Chem., Int. Ed. Engl.*, **7**, 826 (1968); (d) W. T. Brady and E. D. Dorsey, *J. Org. Chem.*, **35**, 2732 (1970).
(6) W. von E. Doering and M. J. Goldstein, *Tetrahedron*, **5**, 53 (1959).
(7) The thermal analogy of this ring opening in an imino ether is known: L. A. Paquette, M. T. Wyuratt, and G. R. Allen, *J. Am. Chem. Soc.*, **92**, 1763 (1970).
(8) The instability of lactam ethers similar to **8** has been noted: I. Ninomiya, T. Kiyuchi, and T. Naito, *Chem. Commun.*, 81 (1974).
(9) The dielectric constants of acetonitrile (ϵ 36.2) and methanol (ϵ 32.6) are sufficiently close so that there will be no change in solvent polarity on methanol addition.
(10) E. J. Moriconi and P. H. Mazzocchi, *J. Org. Chem.*, **31**, 1372 (1966).
(11) E. Giovannini and W. Wegmuller, *Helv. Chim. Acta*, **41**, 933 (1958).
(12) L. A. Paquette, T. Kakihana, J. F. Hansen, and J. C. Philips, *J. Am. Chem. Soc.*, **93**, 152 (1971).
(13) E. J. Moriconi and W. C. Crawford, *J. Org. Chem.*, **33**, 370 (1968).
(14) Farbwerke Hoechet A.-G, Netherlands Patent Application 6 504 300; *Chem. Abstr.*, **64**, 8135 (1966).
(15) P. H. Mazzocchi, T. Halchak, and H. L. Ammon, Abstracts, First Chemical Congress of North America, Nov 30–Dec 5, 1975, Organic Paper No. 113.
(16) H. Ulrich, *Chem. Rev.*, **65**, 369 (1965).
(17) T. Durst and M. J. O'Sullivan, *J. Org. Chem.*, **35**, 2043 (1970).
(18) B. M. Trost, *J. Org. Chem.*, **34**, 3644 (1969).
(19) (a) T. Sasaki, S. Eguchi, and A. Yamada, *J. Org. Chem.*, **38**, 679 (1973); (b) L. A. Paquette and M. J. Broadhurst, *J. Org. Chem.*, **38**, 1886, 1893 (1973); (c) J. R. Malpass, *Tetrahedron Lett.*, 4951 (1972); (d) G. T. Furst, M. A. Wachsman, J. Pieroni, J. G. White, and E. J. Moriconi, *Tetrahedron*, **29**, 1675 (1973), and references cited therein.
(20) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, 1969, p 334.
(21) A similar rearrangement product has been reportedly formed in 1.6% yield on treatment of *syn*-6,7-benzotricyclo[3.2.2.$0^{2,4}$]nona-6,8-diene with CSI: W. E. Volz and L. A. Paquette, *J. Org. Chem.*, **41**, 57 (1976).
(22) D. Lenoir, P. v. R. Schleyer, and J. Ipaktschi, *Justus Liebigs Ann. Chem.*, **750**, 28 (1971).
(23) In several cases starting material disappeared rapidly but reaction was apparently proceeding via a competing alternate pathway. Thus the NMR of the photolysate of **13** and **14** showed no olefinic absorption suggesting that dimerization had occurred while that of the photolysate of **15** showed no cyclopropyl protons indicating that an alternative process involving the cyclopropyl ring had taken place.
(24) C. L. Stevens, T. A. Treat, P. M. Pillai, W. Schmonsees, and M. D. Glick, *J. Am. Chem. Soc.*, **95**, 1978 (1973).

Diaziridinones (2,3-Diazacyclopropanones). A Cis-Fused Example. Lone Pair–Lone Pair Destabilization[1a]

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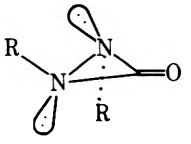
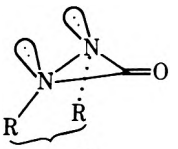
2,2,5,5-Tetramethyl-1,6-diazabicyclo[4.1.0]heptan-7-one (**4**), the first example of a diaziridinone of cis stereochemistry, has been prepared by reaction of the *N*-chloro urea, 1-chloro-4,4,7,7-tetramethyl-1,3-diazacycloheptan-2-one, with either sodium tribenzylmethoxide in tetrahydrofuran or with the potassium salt of the urea 4,4,7,7-tetramethyl-1,3-diazacycloheptan-2-one in dimethoxyethane. Diaziridinone **4** reacts at room temperature with unhindered alcohols by nucleophilic addition and ring opening, with 1,2-disubstituted hydrazines by oxidation–reduction to afford the urea corresponding to **4** and the azo compound corresponding to the hydrazine, and with *p*-nitrophenyl isocyanate to afford the cycloaddition product (a substituted 1,2,4-triazolidine-3,5-dione). Diaziridinone **4** shows a single methyl signal in the NMR, ascribed to rapid interconversion between **4a** and **4b** (eq 3), $\Delta G^{\ddagger} < 5$ kcal/mol. Compound **4** decomposes to carbon monoxide and the azo compound 3,3,6,6-tetramethyl-1,2-diaza-1-cyclohexene ($t_{1/2}$ at 25 °C in CCl_4, 25.1 h; $\Delta H^{\ddagger} = 24.8 \pm 0.4$ kcal/mol; $\Delta S = 1.2 \pm 1.5$ *G*/mol). Comparisons between *cis*-diaziridinone **4** and *trans*-1,2-di-*tert*-butyldiaziridinone indicate that the former is much more reactive than the latter, both in unimolecular reactions (e.g., decarbonylation) and in the bimolecular reactions described above (nucleophilic addition, oxidation–reduction, cycloaddition).

Part A

The synthesis and properties of some *N,N'*-di-*tert*-alkyldiaziridinones (diazacyclopropanones), **1**, have been described.[2] The compounds are thermally rather stable (**1**, R = *tert*-butyl, $t_{1/2} \sim 2$ h at 180 °C), unexpectedly sluggish toward nucleophiles, and show some unusual oxidation–reduction reactions (primarily with hydrogen atom donors such as hydrazines and thiophenols). The physical data (NMR and ir) indicate for the ground state the structure shown in **1a** in which the substituents are trans. Comparison of the carbonyl absorptions (1855–1880 cm^{-1} for diaziridinones, 1837–1850 cm^{-1} for aziridinones, 1813–1840 cm^{-1} for cyclopropanones) indicates a lack of amide-type delocalization of nitrogen lone pair electrons in diaziridinones.

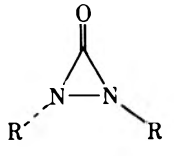


1a

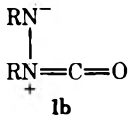


2a

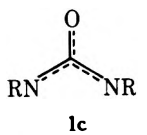
The synthesis and examination of diaziridinones with smaller substituents and of cis diaziridinones (**2a**) has been of interest to us. Such compounds might (a) provide information on the effect of adjacent lone pairs as a function of conformation; (b) indicate whether the low reactivity of **1a** (R = *tert*-alkyl) toward nucleophiles was a steric effect of the substituents or an electronic repulsion effect of the nitrogen lone pairs;[3] (c) provide information on the possible intermediacy of isomeric modifications **1b–e**.[4a] In this paper we report the synthesis of a cis-fused diaziridinone.



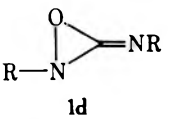
1a



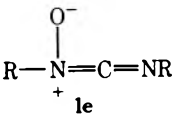
1b



1c



1d

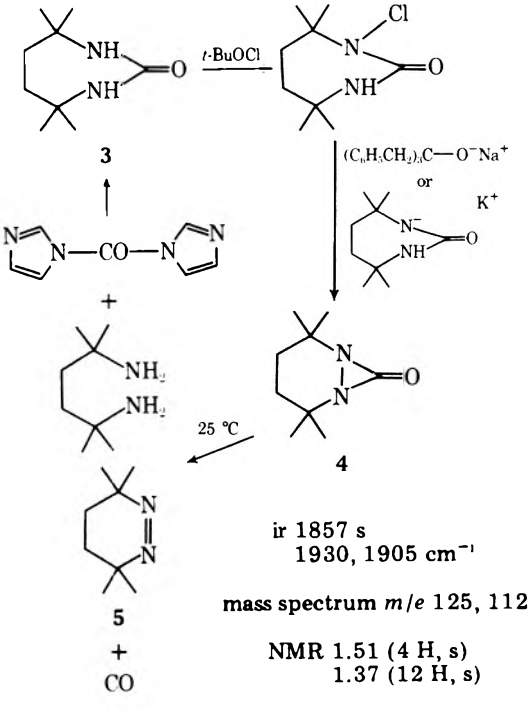


1e

Results

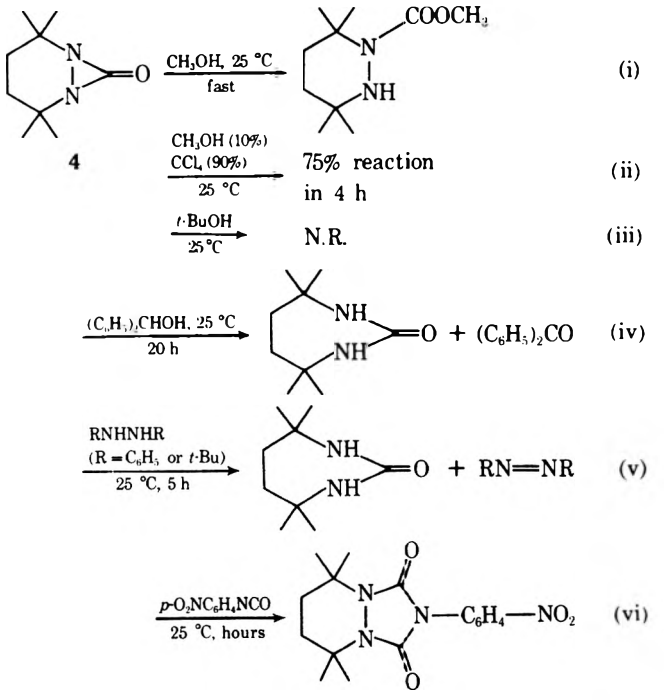
The cis diaziridinone **4**, 2,2,5,5-tetramethyl-1,6-diazabicyclo[4.1.0]heptan-7-one, has been synthesized by the route shown in Scheme I. Choice of base for the conversion of the *N*-chloro urea to diaziridinone **4** was crucial. Use of the hindered base, sodium tribenzylmethoxide, afforded **4** in low, and often variable, yield (15%); use of smaller alkoxides (routinely used for the preparation of di-*tert*-alkyl diaziridinones)[2] afforded carbazates (Scheme II, i). Variation in temperature, solvent, or cation (K^+ instead of Na^+) showed little improvement. Use of the potassium salt of the urea **3** effected the conversion of the *N*-chloro urea to the diaziridinone **4**. The yield was still low but more reproducible than with the tribenzylmethoxide. Of particular interest, this approach has been successful for the synthesis of diaziridinones **1a** in which R = primary and secondary alkyl groups.[4b]

Scheme I



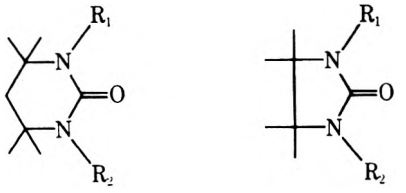
The structural assignment for **4** is based on the physical

Scheme II



data summarized in Scheme I and on the facile decarbonylation of **4** to **5** (3,3,6,6-tetramethyl-1,2-diazacyclohexene).

Efforts to prepare diaziridinones from cyclic ureas **6** and **7** were unsuccessful. Syntheses of the ureas and their *N*-chloro



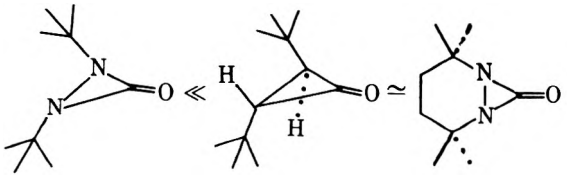
6 **7**

a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = Cl$
c, $R_1 = R_2 = Cl$

and *N,N'*-dichloro derivatives are described in the Experimental Section.

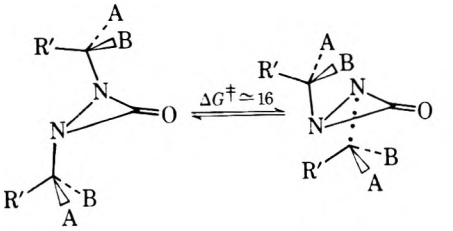
Reactions of Diaziridinone 4. Two aspects of interest are the effect of heat on **4** (consideration of the single methyl and methylene absorptions in the NMR, and the facile decarbonylation) and the effect of attacking agents (nucleophiles, reductants, etc.). In both areas, comparison with *trans*-di-*tert*-butyldiaziridinone is revealing.

The reactions of **4** (Scheme II) include nucleophile addition and ring opening, oxidation–reduction, and "cycloaddition", paralleling related reactions of **1a** (R = *tert*-butyl).[2] In all cases rates are faster for **4** than for **1a** [e.g., requiring a temperature 100 °C higher for **1a** (R = *tert*-butyl) than for **4**]. Particular attention is directed to the facile reduction of **4** by hydrogen transfer from benzhydrol (eq iv)[2] and from hydrazines (eq v).[2] Methanolysis (eq 1) provides a point of comparison of cis and trans diaziridinones with a related trans cyclopropanone: cis diaziridinone **4** and *trans*-di-*tert*-butylcyclopropanone are of comparable (and high) reactivity

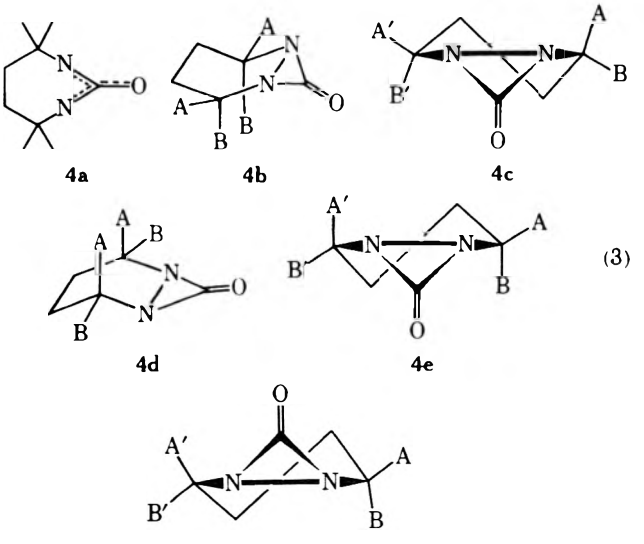

(1)

toward methanol; *trans*-di-*tert*-butyldiaziridinone is much less reactive.[3]

Thermal Behavior of 4. The NMR of **4** shows single methyl and methylene peaks. In comparison, *trans*-di-*tert*-octyldiaziridinone shows separate methyl peaks at 0 °C which coalesce at 35 °C, a $\Delta G^{\ddagger}$ of 16 kcal/mol for equilibration of the magnetic environments of the A and B methyl groups (eq 2).[2]


(2)

There are several possibilities for **4**: (1) the molecule has structure **4a**; (2) the molecule has structure **4b** or **4c** and has accidental equivalence of the methyls (and of the methylene hydrogens); (3) the molecule is rapidly inverting, e.g., between **4b** and **4d** or **4c** and **4f** (eq 3). The close similarity in the ir


4a **4b** **4c**

4d **4e**

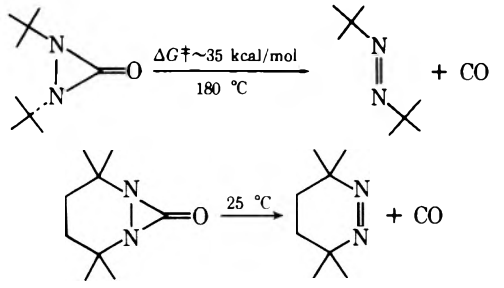
(3)

4f

carbonyl region of **1** and **4** strongly indicates that both possess the diaziridinone ring system, thereby excluding **4a**. The half-chair forms (**4c, 4e, 4f**) are expected to be more stable than the boat forms (**4b, 4d**) by analogy to cyclohexenes.[5] The possibility of accidental equivalence of the methyls in **4c** (or **4b**) is discounted on the following grounds. The spectrum remains two sharp singlets (one for the methyls, one for the methylenes) in several solvents over a broad temperature range: CCl_4 from 0 to 30 °C, CD_3CN from −10 to 30 °C, CH_2Cl_2 from −90 to 30 °C, CCl_2F_2 from −120 to 0 °C, benzene 25 °C. The change from CCl_4 to C_6D_6 results in a modest upfield shift for the methyl resonance (from 1.37 ppm to 1.13) and a larger shift for the methylene (from 1.51 to 1.06), associated with greater anisotropic shielding of the methylene. Preservation of accidental equivalences in two sets of signals in the change from CCl_4 to C_6D_6 is very unlikely. This leaves the third possibility, i.e., **4c, 4e,** and **4f** (or **4b** and **4d**) in rapid equilibrium (eq 3). Efforts to observe a splitting at low temperature in the NMR of **4** were not successful. In CCl_2F_2–CF_3Br (1:1) the spectrum remains two singlets down to −150 °C although considerably broadened at that temperature. Below −150 °C further broadening occurs but with no indication of splitting into different peaks. Clearly, a coalescence peak is not reached even at −150 °C, indicating that the barrier to interconversion of **4a** and **4b** is less than 5–6 kcal/mol, approximately 10 kcal/mol less than the barrier for di-*tert*-octyldiaziridinone.

On standing at room temperature, **4** undergoes quantitative decarbonylation, Scheme I ($t_{1/2}$ at 25 °C in CCl_4 is 25 h). The kinetics of the thermal decomposition were followed by Fourier transform ^1H NMR. [This technique has advantages for kinetics measurements over the usual continuous wave NMR: (a) the greater signal-to-noise ratios, permitting smaller sample size and lower concentrations; (b) the high resolution without "ringing" bands, permitting accurate integration even for absorbances close in chemical shift (an aspect of particular importance in the present study).] Decarbonylation is first order in **4**. Results are summarized in Table I.

Diaziridinone **4** decomposes much more readily than di-*tert*-butyldiaziridinone (**1a**). Decomposition of the latter requires several hours at 180 °C and affords a mixture of products[6a] including carbon monoxide and di-*tert*-butyldiazine. A minimum estimate for the free energy of activation for decarbonylation is thus approximately 35 kcal/mol (eq 4).



(4)

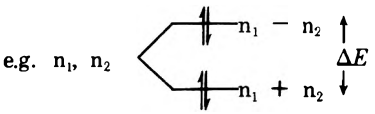
4 **5**

$\Delta G^{\dagger}$ 180 °C (calcd, Table I) ~25 kcal/mol

In summary, both the barriers to "inversion" (eq 2 and 3) and to decarbonylation (eq 4) are approximately 10 kcal/mol smaller for the cis diaziridinone **4** than for the trans diaziridinone **1**. The analysis in the following section is suggestive that in both processes the smaller barriers for **4** may be ascribed, perhaps in large measure, to ground state destabilization associated with the less favorable cis arrangement of the nitrogen lone pairs in **4** than the 120° lone pair–lone pair dihedral angle in **1a**.

The Problem of Adjacent Lone Pairs. Major questions here are the degree of interaction of lone pairs situated on adjacent atoms and total energy as a function of conformation. Theoretical,[7] microwave,[8] NMR,[9] photoelectron spectroscopic,[10] and thermochemical studies[11] provide some information on these questions. Theoretical analyses on hydrazine show a preferred conformation at a lone pair–lone pair dihedral angle $\theta = 90°$.[7] The calculated energies relative to the level for $\theta = 90°$ are (in kcal/mol) 12.2 for $\theta = 0°$, 3.6 for $\theta = 180°$, 1 for $\theta = 120°$. A microwave study on hydrazine indicates the preferred conformation at $\theta = 90°$ and a barrier to rotation of 3 kcal/mol.[8] This number may be too small and has been questioned.[9]

Photoelectron spectroscopy provides a clear indication of lone-pair n_1–lone pair n_2 interactions, and in favorable cases provides a measure of the degree of interaction, ΔE, for the $n_1 + n_2$ vs. the $n_1 - n_2$ levels (eq 5). The interaction is strongly



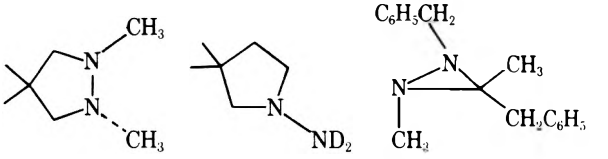
(5)

dependent on the dihedral angle θ (least for $\theta = 90°$, greatest for $\theta = 0$ and 180°).[10a] The largest interaction between adjacent lone pairs might be expected when the pairs are in parallel p orbitals. Strong interaction is seen, by PES, between lone pairs in sp^3 orbitals (e.g., hydrazines)[10a] and in sp^2 orbitals (azo compounds, both cis and trans).[10b] Both "through space" and "through bond" interactions may be important.[10c] The PES data, while providing a good index of lone pair–lone pair interactions, are uninformative on *total* energy differences between conformations as a function of θ (e.g., hydrazines) or between isomers (e.g., cis and trans azo compounds). These total energy differences could be obtained from thermochemical data. Few such data are available for the analysis of the effect of adjacent lone pairs. A recent study on a series of azo compounds (trans acyclic and cis cyclic) indicates that the trans azo linkage is more stable than the cis (in a 1,2-diazacyclohexene-1) by 8 kcal/mol. The rates of decomposition of a series of azo compounds show activation energies that are lower for cis than for trans, also attributed to ground state destabilization from lone pair–lone pair interactions, more unfavorable in cis azo compounds than in trans by ~7 kcal/mol.[12]

Table I. Kinetics Data for Thermal Decomposition of Cis Diaziridinone 4

	CCl_4	CD_3CN (90%)–CCl_4 (10%)
$k_{25\,°C}$	$7.66 \pm 0.07 \times 10^{-6}\ s^{-1}$	$4.26 \pm 0.08 \times 10^{-6}\ s^{-1}$
$k_{50.05\,°C}$	$2.11 \pm 0.03 \times 10^{-4}\ s^{-1}$	$1.28 \pm 0.03 \times 10^{-4}\ s^{-1}$
$\Delta G^{\ddagger}_{298\,K}$	24.4 kcal/mol	24.8 kcal/mol
$\Delta H^{\ddagger}$	24.8 ± 0.4 kcal/mol	25.4 ± 0.6 kcal/mol
$\Delta S^{\ddagger}$	1.2 ± 1.5 *G*/mol	2.5 ± 2.5 *G*/mol

Studies by NMR of conformational changes in hydrazines and related systems have provided some information on lone pair–lone pair interactions.[9] Analysis is frequently complicated by occurrence of both rotational and nitrogen inversion barriers. Comparisons of the type shown by Lehn and Wagner[13a] (**8** and **9**) and by Mannschreck and Seitz (**10**)[13b] are of interest.



8 **9** **10**

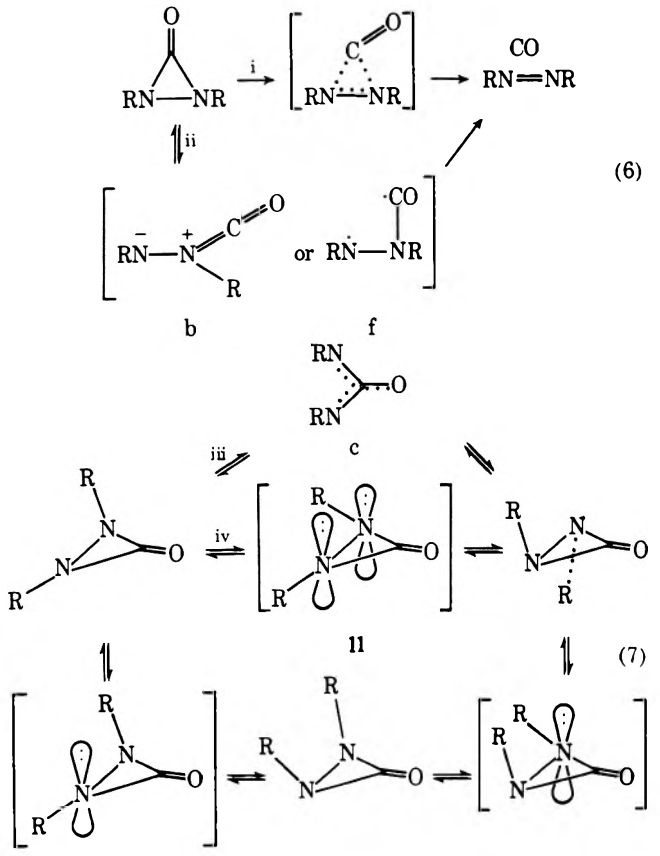
$\Delta G^{\dagger}$ kcal/mol 11.1 8.5 27

In summary, comparisons of the type described above are suggestive that a cis diaziridinone may be less stable than a trans diaziridinone, perhaps by several kcal/mol; the 10 kcal/mol greater reactivity of **4** compared with **1** in decarbonylation and in equilibration of the magnetic environments may be largely due to ground state destabilization of a cis diaziridinone compared to a trans diaziridinone, but other strain effects may also play a role in compound **4**. Additional examples of cis diaziridinones would be helpful.

Part B

What can be said about the mechanisms of the two processes, equilibration of the magnetic environments and decarbonylation, and do the two processes proceed along common paths? On the grounds described in the preceding paragraph, the transition states both for decarbonylation and for equilibration of the magnetic environments of the methyl groups for cis diaziridinone **4** should reflect a major reduction in the lone pair–lone pair interactions.

Decarbonylation, involving cleavage of the C–N bonds, might proceed in two ways: synchronously by a nonlinear cheleotropic process,[14] or stepwise via species b or f (eq 6). Conversion of diaziridinone to azo compound and carbon monoxide by the former path implies a transition state in which the lone pair–lone pair interaction is intermediate between that of reactant and product. The heats of formation for the products of decarbonylation (eq 4) indicate 8.3

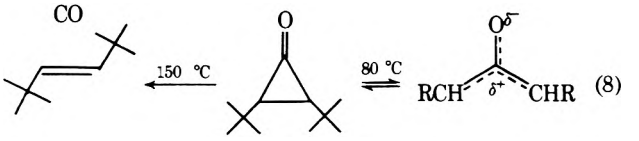


(6)

(7)

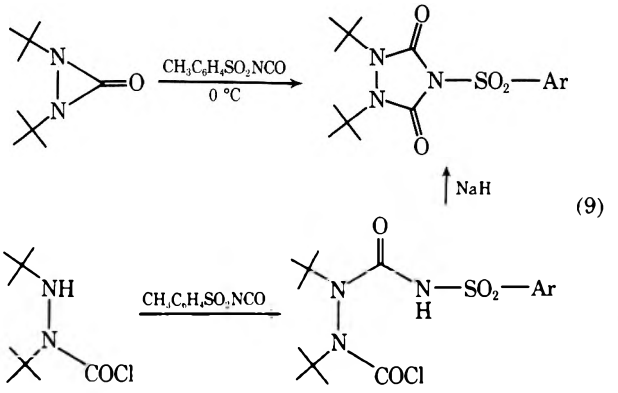
kcal/mol of strain in **5**,[11] ascribed primarily to lone pair–lone pair interactions. Thus decarbonylation by the cheleotropic path would not account for the 10 kcal/mol difference in activation energy between **1** and **4**. Decarbonylation via b or f of eq 6 (in a variety of geometries) could afford the apparently needed reduction in lone pair–lone pair interactions between ground state and transition state.[15] Equilibration of the magnetic environments of the methyl groups in di-*tert*-octyldiaziridinone, $\Delta G^{\ddagger} = 16$ kcal/mol (eq 2),[2] could be achieved by path ii of eq 6 or by paths iii (N–N cleavage), iv (one-step, double N inversion), or v (two-step, single N inversion) of eq 7. Barriers to inversion in acyclic amines are ~5 kcal/mol vs. 17–20 kcal/mol in aziridines.[16] This increase in barrier height is ascribed to angle strain and is comparable to the increase in ring strain (~13 kcal/mol) in a methylenecyclopropane compared with a cyclopropane. Inversion barriers also increase in molecules possessing adjacent heteroatoms, e.g., diaziridine **10**,[13b] ascribed, in part, to unfavorable lone pair–lone pair interactions as a nitrogen is made planar. Calculations indicate a strong preference (>35 kcal/mol)[13b] for nitrogen inversion in **11** proceeding singly (as in path v of eq 7) rather than doubly (as in path iv of eq 7).[17] Thus, angle considerations, lone pair–lone pair interactions (**11** in eq 7 may also be viewed as an "antiaromatic" system), and steric effects all indicate that path iv will not be important. The barrier for path v of eq 7 may be viewed as that for a diaziridine (e.g., **11**, $\Delta G = 27$ kcal/mol) minus the amide resonance associated with making one nitrogen planar (~10 kcal/mol), i.e., 17 kcal/mol vs. the observed barrier of 16 kcal/mol. *Rough* estimates of the energy changes associated with paths ii of eq 6 and iii and v of eq 7 provide no basis for excluding any of these possibilities. Thus for acyclic diaziridinones equilibration (e.g., of the magnetic environments of the methyls in di-*tert*-octyldiaziridinone, eq 2) may be by paths ii, iii, or v.

The very low barrier (<5 kcal/mol) associated with **4** permits the rejection of the nitrogen inversion paths (iv and v of eq 7) for this system: a stepwise, single N inversion process would involve a highly strained transition state resembling a trans diaziridinone fused to a six-membered ring; a one-step, double N inversion process is rejected for **4** on the grounds indicated above for **1a** and **11**. Thus the "equilibration" associated with **4** is ascribed to breaking of a C–N bond (path ii of eq 6) or the N–N bond (path iii of eq 7). Economy of mechanism might lead one to prefer C–N cleavage since the decarbonylation *must* involve these bonds. However, ring opening of **4a** to **4c** (see eq 3) is an allowed process. A related situation of bond changes is found in the racemization (80 °C) and decarbonylation (150 °C) of (+)-*trans*-di-*tert*-butylcyclopropanone for which the evidence favors C_2–C_3 cleavage for the racemization, C_1–C_2 cleavage for decarbonylation (eq 8).[6]



(8)

Efforts to trap potential intermediates such as b or f (eq 6) or c (eq 7, path iii) have afforded several 1:1 adducts; efforts to *prove* the presence of intermediates have been unsuccessful (i.e., in no case has it been possible to demonstrate an independence of adduct formation on concentration of the trapping agent). Urazoles have been obtained from reaction of *p*-nitrophenyl isocyanate with **4** (25 °C, Scheme II, vi) and with di-*tert*-butyldiaziridinone (100 °C). Di-*tert*-butyldiaziridinone also reacts instantly at 0 °C with *p*-toluenesulfonyl isocyanate and with chlorosulfonyl isocyanate to form urazoles (eq 9). The structure of the former adduct was proved by synthesis.



(9)

Experimental Section

4,4,7,7-Tetramethyl-1,3-diaza-2-cycloheptanone (3). A 2-l. Morton flask equipped with two 500-ml pressure-equalizing addition funnels and a fast mechanical stirrer was flamed out under nitrogen. Dry THF (400 ml) was introduced into the flask and heated to just below the boiling point. A solution of 2,5-dimethyl-2,5-diaminohexane (13.84 g, 0.096 mol, Aldrich Chemical Co.) in dry THF (total volume 350 ml) was added to one funnel, and a solution of 1,1′-carbonyldiimidazole[18] (15.50 g, 0.096 mol) in THF (total volume 350 ml) was added to the other funnel. Simultaneous slow addition with rapid stirring under nitrogen was completed in 8 h. After standing overnight the solvent was evaporated. The residue was shaken with 250 ml of water. The resulting solid was collected by filtration, washed with water, air dried, dissolved in 250 ml of THF, and filtered to remove polymer. Evaporation of the THF and sublimation at 150 °C and 0.01 mm provided 6.50 g (40%) of a white solid, **3**, mp 168–170 °C. A resublimed sample had mp 170–171 °C; ir ($CHCl_3$) 3395 (m), 2970 (m), 1645 (vs), 1460 (m), 1445 (m), 1410 (m), 1385 (m), 1365 (m), 1280 (m), 1145 cm^{-1} (m); NMR ($CDCl_3$) 4.45 (b, 2 H), 1.68 (s, 4 H), 1.28 ppm (s, 12 H); mass spectrum *m/e* (rel intensity) 171 (0.5), 170 (M^+, 4), 156 (2), 155 (18), 141 (0.5), 140 (1.5), 113 (2), 112 (18), 107 (2), 95 (13), 58 (100), 55 (13), 42 (25), 41 (26).

Anal. Calcd for $C_9H_{18}N_2O$: C, 63.49; H, 10.65; N, 16.46. Found: C, 63.33; H, 10.90; N, 16.08.

The residue from the sublimation, 2.00 g, was assumed to be low polymer of **3** on the basis of the physical data: mp 250 °C dec; ir ($CHCl_3$) 3430 (m, b), 1680 (s, b), 1520 (s, b), 1385 (m), 1365 (m), 1245 cm^{-1} (s); NMR ($CDCl_3$) 4.00 (b), 1.76 (b), 1.21 ppm (b); mass spectrum *m/e* (rel intensity) 341 (3), 340 (M^+, 10), 312 (2), 287 (4), 265 (5), 264 (5), 186 (3), 171 (5), 170 (13), 156 (5), 155 (41), 149 (17), 95 (13), 70 (10), 58 (100), 57 (10), 56 (10), 42 (25), 41 (20). The mass spectrum appears to show only the dimer of **3**, 4,4,7,7,11,11,14,14-octamethyl-1,3,8,10-tetrazatetradecane-2,9-dione; higher analogues may not have had enough volatility to be seen. This polymeric material could be cracked in 60–75% yield to the monomer at 300 °C.

1-Chloro-4,4,7,7-tetramethyl-1,3-diazacycloheptan-2-one. Tetramethyldiazacycloheptanone (0.023 g, 0.135 mmol) was dissolved in 2 ml of methylene chloride. To this stirred solution was added *tert*-butyl hypochlorite (0.030 g, 0.27 mmol); the reaction was protected from light. After 4 h the solvent was evaporated affording a slightly yellow solid: mp 80 °C dec; ir ($CHCl_3$) 3400 (m), 1680 (s), 1450 cm^{-1} (w); NMR ($CDCl_3$) 5.00 (b, 1 H), 1.80 (m, A_2B_2, 4 H), 1.40 (s, 6

H), 1.26 ppm (s, 6 H). This reaction failed when THF was the solvent.

2,2,5,5-Tetramethyl-1,6-diazabicyclo[4.1.0]heptan-7-one (4). A. A solution of sodium tribenzylmethoxide was prepared by heating at reflux for 24 h under nitrogen a solution of tribenzylcarbinol[19] (0.674 g, 2.23 mmol) in 25 ml of dry THF with sodium hydride [0.115 g (57% dispersion), 2.70 mmol; washed twice with 15 ml of THF]. 1-Chloro-4,4,7,7-tetramethyl-1,3-diaza-2-cycloheptanone prepared from the urea (0.400 g, 2.35 mmol) and *tert*-butyl hypochlorite (0.50 g, 4.5 mmol) was dissolved in 15 ml of THF. To this solution, stirred under nitrogen, was added by cannula the solution of sodium tribenzylmethoxide in 15 min; a fine white precipitate formed during the addition. The solvent was removed at aspirator pressure. The residue was washed with 20 ml of pentane, and the pentane evaporated to give a viscous liquid whose ir spectrum had a strong carbonyl band at 1860 cm^{-1}. The product was collected by sublimation at 0.01 mm through a 5-mm U-tube collector cooled at −78 °C. A colorless, crystalline solid collected in the tube just above the cooling bath, and a yellow liquid collected at the bottom. The colorless solid, 37 mg (14%), was found to be pure diaziridinone **4**: mp 30 °C; ir (CCl_4) 2980 (s), 1930 (m), 1905 (m), 1857 (vs), 1460 (m), 1390 (m), 1370 (m), 1130 (m), 1100 (m), 1080 cm^{-1} (m); NMR (CCl_4) 1.51 (s, 4 H), 1.37 ppm (s, 12 H); NMR (C_6D_6) 1.13 (s, 12 H), 1.06 ppm (s, 4 H); mass spectrum *m/e* (rel intensity) 125 (2), 113 (1), 112 (11), 69 (8), 57 (23), 56 (100), 55 (12), 41 (43), 39 (12). The yellow liquid was found to consist mainly of 3,3,6,6-tetramethyl-1,2-diazacyclohexene (**5**), ir 1560 (m), 1465 (m), 1455 (m), 1380 (m), 1360 (m), 1340 cm^{-1} (m), and a small amount of diaziridinone **4**; in addition weak unidentified absorbances were noted at 2250, 1780, 1735, and 1710 cm^{-1}. the yields for this reaction are variable.

B. The potassium salt of 4,4,7,7-tetramethyl-1,3-diaza-2-cycloheptanone was prepared from the urea (168 mg, 0.99 mmol) and potassium hydride (39 mg, 0.98 mmol) in 10 ml of DME; the salt formed rapidly and was largely insoluble. 1-Chloro-4,4,7,7-tetramethyl-1,3-diaza-2-cycloheptanone, prepared from the urea (168 mg, 0.99 mmol) and *tert*-butyl hypochlorite (142 mg, 1.3 mmol), was dissolved in 7 ml of DME and added by cannula to the urea salt stirred under nitrogen. Within a few minutes all the anion had dissolved, and a new fine white precipitate formed. The solvent was evaporated at aspirator pressure. Sublimation (3 h) at 0.001 mm through a U-tube collector cooled at −78 °C afforded again colorless crystals of diaziridinone **4** (38 mg, 23%) in the tube just above the cooling bath, and a small amount of yellow liquid, azo compound **5** (5 mg), at the bottom of the tube; the products were identified by ir and NMR. When the scale of the reaction was doubled the yield of diaziridinone was 15%.

Thermal Decomposition of 2,2,5,5-Tetramethyl-1,6-diazabicyclo[4.1.0]heptan-7-one (4). Product Study. When samples of diaziridinone **4** were heated, or allowed to stand at room temperature for extended periods, they were transformed quantitatively into a fragrant yellow liquid, 3,3,6,6-tetramethyl-1,2-diazacyclohexene (**5**): ir (CCl_4) 2960 (s), 1560 (w), 1465 (m), 1455 (m), 1380 (m), 1360 (m), 1340 (m), 850 cm^{-1} (m); NMR (CCl_4) 1.45 (s, 4 H), 1.25 ppm (s, 12 H); mass spectrum *m/e* (rel intensity) 112 (3), 84 (10), 70 (6), 69 (13), 57 (27), 56 (76), 55 (20), 43 (25), 42 (20), 41 (100), 40 (10), 39 (40). The ir and NMR spectra were identical with those already reported for this compound.[20] Decomposition of a sample of diaziridinone **4** in a sealed capillary, and mass spectral analysis of the contents established the presence of carbon monoxide (*m/e* calcd, 27.9946; obsd, 27.9946) and azo compound **5** (*m/e* calcd, 140.1313; obsd, 140.1313) and the absence of carbon dioxide and cyclic hydrazine 3,3,6,6-tetramethyl-1,2-diazacyclohexane (possible products of hydrolysis and decarboxylation of diaziridinone **4**).

Kinetics Method. Preparation of Samples. Carbon tetrachloride was distilled from P_2O_5 and then K_2CO_3. Acetonitrile-d_3 was distilled from P_2O_5. The NMR tubes were washed with basic detergent, repeatedly rinsed with distilled water, acetone, and methylene chloride, placed in a drying oven at 125 °C for 24 h, and flame dried under nitrogen immediately before use. To each of three NMR tubes was added 35 μl of a carbon tetrachloride solution of the diaziridinone (ca. 29%). Carbon tetrachloride (300–400 μl) was added to two of the tubes. Acetonitrile-d_3 (300 μl) was added to the third. The samples were degassed by four consecutive freeze–pump–thaw cycles, and sealed under vacuum.

A 20-s warm-up period was allowed each time the tube was submerged in the constant-temperature bath. Quenching of the reaction was accomplished by submerging the tube in a dry ice–2-propanol bath. The interval time was taken at the point at which the tube was submerged.

The reaction was followed by NMR. The Fourier transform spectra were determined at 60 MHz and −5 to 0 °C using a Perkin-Elmer Model R-20B spectrometer interfaced with a Digilab FTS/NMR-3 data system.[21] The significant pulsing parameters were irradiation frequency, 60015150 Hz; band width, 400 Hz; nutation angle, ca. 40°; transform size, 4096 points; computer resolution, 0.196 Hz; time between pulses, 5.10 s; number of pulses per spectrum, 60 (decomposition in CCl_4); 120 (decomposition in CD_3CN). Observed resolution varied between 0.3 and 0.5 Hz. The integrals were calculated by the computer and recorded on fine-lined (1 mm spacing) spectral paper. Integrals were standardized and normalized by having the computer set the total integral of the two diaziridinone resonances plus the two product resonances in each spectrum equal to the same value, 240 mm. The results are summarized in Table I.

Reactions of 2,2,5,5-Tetramethyl-1,6-diazabicyclo[4.1.0]-heptan-7-one (Cis-Diaziridinone 4). See Scheme II. A. With *p*-Nitrophenyl Isocyanate. A solution of freshly sublimed *p*-nitrophenyl isocyanate (4 mg, 0.024 mmol) and 2,2,5,5-tetramethyl-1,6-diazabicyclo[4.1.0]heptan-7-one (**4**, 5 mg, 0.03 mmol) in 100 μl of CCl_4 was allowed to stand at room temperature (reaction was complete after 24 h). The solvent was evaporated and the crude product triturated with CH_2Cl_2; evaporation of the CH_2Cl_2 gave a yellow solid, ir (CCl_4) 1815, 1775, 1715–1685 cm^{-1}. Analysis by TLC indicated two products. Purification was accomplished by TLC on Baker-flex silica gel plate, CH_2Cl_2 eluent. The major product, which had the higher R_f, was assigned the urazole structure 2,2,5,5-tetramethyl-8-*p*-nitrophenyl-1,6,8-triazabicyclo[4.3.0]nonane-7,9-dione (Scheme II, eq vi) on the basis of the physical data: mp 98–107 °C; ir (CCl_4) 1775 (m), 1715 (s), 1595 (m), 1528 (s), 1500 (s), 1400 (m), 1335 cm^{-1} (s); NMR (CCl_4) 7.86 (m, 4 H), 1.70 (s, 4 H), 1.53 ppm (s, 12 H); mass spectrum *m/e* (rel intensity) 333 (14), 332 (M^+, 72), 317 (3), 307 (12), 306 (53), 292 (4), 291 (20), 264 (15), 263 (100), 238 (6), 237 (50), 222 (2), 221 (2), 179 (6), 164 (3), 154 (4), 153 (42), 149 (18), 141 (22), 139 (10), 138 (8), 127 (12), 125 (8), 113 (3), 112 (3), 111 (42), 110 (12), 99 (26), 90 (10), 69 (62), 57 (16), 56 (40), 55 (34), 43 (20), 42 (16), 41 (50), 39 (10). Only a small amount of the second product was obtained: ir (CCl_4) 1815 (m), 1335 (s), 1260 cm^{-1} (m).

Solutions of **4** in CCl_4 showed no reaction with phenyl isocyanate or with dimethyl acetylenedicarboxylate after 10 h at 25 °C.

B. With Ethanol. A solution of 1 μl of diaziridinone **4**, 5 μl of absolute ethanol, and 20 μl of carbon tetrachloride at 25 °C showed slow disappearance of the diaziridinone carbonyl band at 1860 cm^{-1}; after 24 h about 5% of the diaziridinone remained. New carbonyl bands were observed at 1690 and 1650 cm^{-1}.

C. With Methanol. A solution of 5 mg of diaziridinone **4**, 40 μl of absolute methanol, and 400 μl of carbon tetrachloride at 25° showed (ir) approximately 10% of the diaziridinone still present after 4 h; new carbonyl bands were observed at 1690 and 1650 cm^{-1}; a moderate band at 1560 cm^{-1} indicated the presence of azo compound **5**.

D. With Benzhydrol. A solution of 0.5 mg of diaziridinone **4** and 1 mg of benzhydrol in 25 μl of CCl_4 at 25 °C showed (ir) disappearance of the carbonyl band at 1860 cm^{-1} and appearance of two new bands at 1665 (benzophenone) and 1650 cm^{-1} (4,4,7,7-tetramethyl-1,3-diaza-2-cycloheptanone, **3**). The reaction was essentially complete after 20 h. Analysis by TLC, on both alumina and silica gel, confirmed the presence of benzophenone and cyclic urea **3**. No other product was detected.

E. With Hydrazobenzene. A solution of hydrazobenzene (1 mg) and diaziridinone **4** (0.5 μl) in 20 μl of $CHCl_3$ showed (ir) disappearance of the diaziridinone carbonyl at 1860 cm^{-1} and appearance of the carbonyl of 3,3,7,7-tetramethyl-1,3-diaza-2-cycloheptanone at 1645 cm^{-1} (time for 50% reaction, 3000 s). Analysis by TLC showed that **3** and azobenzene were present.

F. With *N,N'*-Di-*tert*-butylhydrazine. A solution of *N,N'*-di-*tert*-butylhydrazine (0.5 μl) and diaziridinone **4** (0.5 μl) in 20 μl of CCl_4 showed (ir) disappearance of the diaziridinone carbonyl at 1860 cm^{-1} and appearance of the carbonyl of 3,3,7,7-tetramethyl-1,3-diaza-2-cycloheptanone at 1650 cm^{-1} (time for 50% reaction, 500 s). Analysis by TLC confirmed the presence of cyclic urea **3**.

Reaction of Di-*tert*-butyldiaziridinone with Isocyanates. A. With *p*-Toluenesulfonyl Isocyanate.[22] Addition of a solution of the isocyanate (1 equiv) in pentane to a solution of the diaziridinone (1 equiv) in pentane at 0 °C resulted in immediate reaction. Analysis by TLC and NMR indicated one major and two (or more) minor products. Removal of the solvent and recrystallization from hexane afforded the major product, 1,2-di-*tert*-butyl-4-*p*-toluenesulfonyl-1,2,4-triazolidine-3,5-dione, in good yield: mp 121–122 °C; ir ($CHCl_3$) 1785 (m), 1740 (vs), 1285 (s), 1170 cm^{-1} (s); NMR ($CDCl_3$) 1.19 (s, 18 H), 2.47 (s, 3 H), 7.25–8.25 ppm (m, 4 H); shown to be identical with an authentic sample (see below).

Anal. Calcd for $C_{17}H_{25}N_3O_4S$: C, 55.53; H, 6.82; N, 11.43. Found: C, 55.38; H, 6.89; N, 11.51.

B. With *p*-Nitrophenyl Isocyanate. A solution of di-*tert*-butyldiaziridinone (0.65 g, 3.8 mmol), *p*-nitrophenyl isocyanate (0.60 g, 3.6

mmol), and 5 ml of isooctane was heated at 100 °C. A yellow precipitate slowly formed and the reaction was followed by ir. After 48 h all the diaziridinone had been consumed. Evaporation of the solvent gave a yellow powder: ir ($CHCl_3$) 1790, 1775, 1730, 1665 cm^{-1}. A portion of the product was purified by preparative TLC (alumina, CH_2Cl_2). The main product, which possessed the highest R_f, was recrystallized from THF–heptane to give colorless needles, assigned the urazole structure, 1,2-di-*tert*-butyl-4-*p*-nitrophenyl-1,2,4-triazolidine-3,5-dione, on the basis of the physical data: mp 158–159.5 °C; ir ($CHCl_3$) 1775 (w), 1730 (s), 1595 (w), 1525 (m), 1495 (m), 1390 (m), 1375 (m), 1345 cm^{-1} (m); NMR ($CDCl_3$) 7.97 (A_2B_2, $\Delta\nu$ 39 Hz, J = 9 Hz, 4 H), 1.37 ppm (s, 18 H); mass spectrum *m/e* (rel intensity) 334 (M^+, 1.5), 280 (1), 279 (5), 278 (25), 263 (3), 248 (2), 224 (2), 223 (7), 222 (50), 192 (4), 176 (2), 165 (2), 149 (7), 115 (9), 57 (100), 41 (30), 29 (25), 28 (15).

2,3 Di-*tert*-butylcarbazyl Chloride. Phosgene (0.95 g, 9.5 mmol) in 20 ml of anhydrous ether was added by cannula to a stirred solution under nitrogen of 1,2-di-*tert*-butylhydrazine (1.30 g, 9.0 mmol) and triethylamine (0.95 g, 9.0 mmol), in 200 ml of ether. A copious precipitate was observed on completion of the addition. Filtration followed by evaporation of the filtrate, and trituration with 20 ml of pentane, filtering, and evaporation of the pentane afforded 1.60 g (86%) of a fragrant, faintly yellow liquid: ir (CCl_4) 3440 (w), 3350 (w), 1745 cm^{-1} (s); NMR (CCl_4) 1.20 (s, 9 H), 1.43 (s, 9 H), and 4.02 ppm (b, 1 H). This material is identical with that obtained by reaction of di-*tert*-butyldiaziridinone with dry HCl. In the absence of moisture it decomposes slowly to a white solid: ir (CCl_4) 3500–2500 (m), 1700 (m, b), 1710 cm^{-1} (s, b).

1,2-Di-*tert*-butyl-4-*p*-toluenesulfonyl-1,2,4-triazolidine-3,5-dione. A solution of 2,3-di-*tert*-butylcarbazyl chloride (0.477 g, 2.30 mmol) and *p*-toluenesulfonyl isocyanate (0.446 g, 2.26 mmol) in 10 ml of dry hexane was refluxed for 14 h. Infrared spectra showed weakening of the isocyanate band plus appearance of a new one at 1715 cm^{-1}. Sodium hydride [0.090 g (57%), 2.1 mmol] was added and the solution refluxed for 6 days. The hexane was evaporated leaving white crystals and an oil. This was extracted with 30 ml of pentane, followed by 25 ml of boiling hexane. Evaporation of the pentane afforded mainly *p*-toluenesulfonamide. Evaporation of the hexane afforded 0.078 g (10%) of essentially pure urazole: mp 120–122 °C, shown to be identical by mixture melting point and ir spectra with the product of reaction of di-*tert*-butyldiaziridinone and *p*-toluenesulfonyl isocyanate (see above).

2,2,4,4-Tetramethylglutaric Acid. Isobutyric acid (88.0 g, 1.00 mol) (dried over $MgSO_4$) was added, slowly at first, to lithium wire (7.12 g, 1.01 mol) in 800 ml of dry THF.[23] The mixture was refluxed for 36 h, during which time the lithium was consumed and a white precipitate formed. To this mixture under nitrogen, cooled in an ice bath, was added by cannula 1 mol of lithium diisopropylamide [made from diisopropylamine (102 g, 1.01 mol) and 1 mol of *n*-butyllithium (Ventron) in hexane]. The precipitate dissolved during the addition. After stirring for 3 h diiodomethane (130 g, 0.485 mol) was added with cooling; the reaction is exothermic. The mixture was stirred for 21 h at room temperature and heated at reflux for 5 h. The reaction mixture was evaporated to a volume of 500 ml and then poured into 400 ml of ice and acidified with 180 ml of concentrated hydrochloric acid. This was extracted five times with 250-ml portions of ether. The combined ether was dried ($MgSO_4$) and evaporated to give crystals with highly colored impurities. Recrystallization from water gave 39.3 g (43%) of colorless crystals: mp 187–189 °C (lit.[24] 185–186 °C); ir ($CHCl_3$) 3500–2500 (b), 1715 cm^{-1} (s); NMR ($CDCl_3$) 1.86 (s, 2 H), 1.30 ppm (s, 12 H).

2,2,4,4-Tetramethylglutaryl Dichloride. The procedure followed was adapted from Cason and Reist's preparation of glutaryl dichloride.[25] Thionyl chloride (80 g, 0.68 mol) was added to 2,2,4,4-tetramethylglutaric acid (10.00 g, 0.53 mol) and 0.15 ml of pyridine. After the vigorous initial reaction had subsided, the mixture was heated at reflux for 4 days. The solvent was evaporated and the residue sublimed at 30 °C and 0.005 mm to give 9.12 g (76%) of a white solid which had mp 38–39.5 °C; ir (CCl_4) 1810 (s), 1785 (vs), 1765 (m), 940 (m), 900 (w), 865 (m), 850 cm^{-1} (s); NMR (CCl_4) 2.34 (s, 2 H), 1.33 ppm (s, 12 H).

Anal. Calcd for $C_9H_{14}Cl_2O_2$: C, 48.02; H, 6.27. Found: C, 47.95; H, 6.19.

4,4,6,6-Tetramethyltetrahydro-2-pyrimidone (6a) was prepared in three consecutive steps starting with 2,2,4,4-tetramethylglutaryl dichloride. To a solution of sodium azide (23 g, 0.35 mol) in 75 ml of water, cooled in ice and rapidly stirred, was added slowly by pipet 2,2,4,4-tetramethylglutaryl dichloride (5.00 g, 22.3 mmol) in 15 ml of THF. After stirring for 100 min, 100 ml of water was added and the resulting solution extracted four times with 75 ml of benzene. The combined benzene solution was dried ($MgSO_4$). A small aliquot was evaporated to give 2,2,4,4-tetramethylglutaryl diazide: ir (CCl_4) 2135 (vs), 1710 (s), 1170 (s), 1135 (m), 1035 (s), 1005 cm^{-1} (m); NMR (CCl_4) 1.94 (s, 2 H), 1.13 ppm (s, 12 H). The azide solution was slowly heated to the boiling point of benzene, then refluxed for 1 h; gas evolution began at 65 °C. The benzene was evaporated to give 2,4-dimethyl-2,4-pentyl diisocyanate. A sample purified by GC had ir (CCl_4) 2250 (vs), 1225 (w), 1180 cm^{-1} (m); NMR (CCl_4) 1.71 (s, 2 H), 1.47 ppm (s, 12 H); mass spectrum *m/e* (rel intensity) 168 (1), 127 (3), 85 (6), 84 (100), 83 (3), 76 (4), 56 (12), 55 (3), 54 (2), 53 (1), 42 (5), 41 (6), 40 (2), 39 (3).

Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.10; H, 7.54; N, 15.09.

The crude diisocyanate was dissolved in 250 ml of THF containing 5 ml of water and refluxed for 3 days. The solvent was evaporated and the resulting solid dried for 1 h at 90 °C and 20 mm. Sublimation at 130 °C and 0.01 mm gave 3.05 g of a white powder, mp 213–216 °C. This was dissolved in 200 ml of methylene chloride, extracted four times with 15-ml portions of saturated $NaHCO_3$ solution, and evaporated to give 2.65 g (76%) of 4,4,6,6-tetramethyltetrahydro-2-pyrimidone (**6a**), mp 216–219 °C. Sublimation at 100 °C and 0.005 mm gave analytically pure material: mp 219–220.5 °C; ir ($CHCl_3$) 3420 (w), 1655 (s), 1480 (m), 1460 cm^{-1} (m); NMR ($CDCl_3$) 5.15 (b, 2 H), 1.69 (s, 2 H), 1.28 ppm (s, 12 H); mass spectrum *m/e* (rel intensity) 156 (M^+, 3), 142 (10), 141 (25), 99 (4), 98 (28), 85 (5), 84 (70), 63 (23), 62.5 (7), 59 (8), 58 (58), 57 (33), 56 (28), 55 (8), 43 (7), 42 (100), 41 (33), 40 (5), 39 (14).

Anal. Calcd for $C_8H_{16}N_2O$: C, 61.51; H, 10.33; N, 17.92. Found: C, 61.28; H, 10.10; N, 17.70.

General Method for the Preparation of *N*-Chloro Ureas. The urea to be chlorinated was dissolved or suspended in a minimal amount of methylene chloride (typically 5–10 ml per gram of urea) containing 1 equiv of *tert*-butyl hypochlorite. After several hours (protected from light) the solvent was evaporated at aspirator pressure and the crude product placed under 0.005 mm vacuum for 10 min in order to remove any residual *tert*-butyl alcohol. An excess of *tert*-butyl hypochlorite should be avoided with the cyclic ureas as dichlorination may occur.

For preparation of the *N,N'*-dichloro ureas, longer reaction times and a severalfold excess of *tert*-butyl hypochlorite were used. Dichlorination was not observed with *N,N'*-di-*tert*-butylurea.

1-Chloro-4,4,6,6-tetramethyltetrahydro-2-pyrimidone (6b) was prepared from 4,4,6,6-tetramethyltetrahydro-2-pyrimidone (0.205 g, 1.31 mmol) and *tert*-butyl hypochlorite (0.150 g, 1.37 mmol) in 5 ml of methylene chloride by the above procedure: 0.253 g (~100%) of white crystals; mp 135–138 °C; ir (CCl_4) 3210 (m), 2960 (m), 1680 (s), 1390 (m), 1365 (m), 1190 cm^{-1} (w); ir ($CHCl_3$) 3410 (m), 1660 cm^{-1} (s); NMR ($CDCl_3$) 5.00 (b, 1 H), 1.96 (s, 2 H), 1.40 (s, 6 H), 1.30 ppm (s, 6 H); mass spectrum *m/e* (rel intensity) 192 (M^+, 1), 190 (M^+, 2), 177 (3), 176 (1), 175 (10), 157 (2), 142 (5), 141 (4), 134 (6), 133 (1), 132 (17), 125 (2), 98 (15), 97 (17), 94 (10), 58 (65), 57 (25), 56 (63), 55 (20), 42 (100), 41 (50), 39 (22).

1-Chloro-4,4,5,5-tetramethyl-2-imidazolidone (7b) was prepared from 4,4,5,5-tetramethyl-2-imidazolidone[26] (0.312 g, 2.20 mmol) and *tert*-butyl hypochlorite (0.242 g, 2.21 mmol) in 12 ml of methylene chloride by the above procedure: 0.375 (97%) of white crystals; mp >100 °C dec; ir (CCl_4) 3200 (m, b), 1730 cm^{-1} (s); NMR (CCl_4) 7.05 (b, 1 H), 1.25 (s, 6 H), 1.19 ppm (s, 6 H).

1,3-Dichloro-4,4,5,5-tetramethyl-2-imidazolidone (7c) was prepared from 4,4,5,5-tetramethyl-2-imidazolidone[26] (142 mg, 1.00 mmol) and *tert*-butyl hypochlorite (300 mg, 2.75 mmol) in 2 ml of methylene chloride by the above procedure: 211 mg (100%) of a white, crystalline solid: mp 92–96 °C; ir (CCl_4) 1775 (s), 1735 (sh), 1385 (m), 1375 (m), 1275 cm^{-1} (m); NMR (CCl_4) 1.24 ppm (s).

Anal. Calcd for $C_7H_{12}N_2OCl_2$: C, 39.78; H, 5.73. Found: C, 40.04; H, 5.93.

1,3-Dichloro-4,4,7,7-tetramethyl-1,3-diaza-2-cycloheptanone was prepared from 4,4,7,7-tetramethyl-1,3-diaza-2-cycloheptanone (81 mg, 0.48 mmol), dissolved in 1 ml of *tert*-butyl hypochlorite and allowed to stand for 48 h protected from light. Removal of solvent afforded 112 mg (100%) of a white, crystalline solid: mp 88–91 °C; ir (CCl_4) 1705 (s), 1455 (m), 1385 (m), 1365 (m), 1275 (m), 1250 (m), 1140 (m), 1120 cm^{-1} (m); NMR (CCl_4) 1.35 (s, 12 H), 1.88 ppm (s, 4 H); mass spectrum *m/e* (rel intensity) 242 (M^+, 0.5), 240 (M^+, 3), 238 (M^+, 5), 225 (0.5), 223 (2), 149 (3), 148 (19), 147 (6), 146 (60), 112 (11), 111 (9), 110 (9), 96 (9), 95 (28), 93 (26), 92 (77), 84 (23), 70 (31), 69 (50), 68 (11), 67 (11), 58 (60), 57 (12), 56 (70), 55 (65), 54 (12), 53 (11), 43 (19), 42 (77), 41 (100), 40 (15), 39 (40).

Anal. Calcd for $C_9H_{16}N_2OCl_2$: C, 45.19; H, 6.74. Found: C, 45.51; H, 6.89.

1,3-Dichloro-4,4,6,6-tetramethyltetrahydro-2-pyrimidone (6c)

was prepared from 4,4,6,6-tetramethyltetrahydro-2-pyrimidone (27 mg, 0.17 mmol) and *tert*-butyl hypochlorite (150 mg, 1.4 mmol) in 1 ml of methylene chloride: 39 mg (100%) of a white, crystalline solid; mp 90 °C dec; ir (CCl_4) 1705 (s), 1385 (w), 1370 (w), 1290 (m), 1215 cm^{-1} (m); NMR (CCl_4) 1.39 (s, 12 H), 2.15 ppm (s, 2 H).

1,3-Dichlorotetrahydro-2-pyrimidone. Tetrahydro-2-pyrimidone (Aldrich, 1.00 g, 10.0 mmol) and *tert*-butyl hypochlorite (3 ml) in 25 ml of methylene chloride were allowed to stand for 14 h protected from light. The solvent was evaporated to give 1.75 g (~100%) of a white solid: mp 68–70 °C; ir (CCl_4) 1710–1715 (s), 1475 (m), 1395 (m), 1270 (m), 1200 (m), 1165 cm^{-1} (m); NMR (CCl_4) 2.38 (t, J = 6 Hz, 4 H), 1.00 ppm (quintet, J = 6 Hz, 2 H). Samples were observed to decompose spontaneously and exothermically.

Attempted Preparation of Diaziridinones from 6 and 7. Reaction of 1-chloro-4,4,6,6-tetramethyltetrahydro-2-pyrimidone with the potassium salt of 4,4,6,6-tetramethyltetrahydro-2-pyrimidone in DME, or with the potassium salt of 1,1-diethyl-3-*tert*-butylurea in DME, or with sodium tribenzylmethoxide in THF provided no ir evidence even for the transient existence of a diaziridinone. Addition of 1 equiv of bromine to a suspension of 2 equiv of the potassium salt of tetramethyltetrahydropyrimidone in DME gave an immediate precipitation of potassium bromide, and after workup 80% recovery of the urea.

During the reaction of 1,3-dichloro-4,4,6,6-tetramethyltetrahydro-2-pyrimidone with potassium hydride in THF, and with potassium triethylmethoxide in THF, transient weak carbonyl bands were observed at 1915 and 1865 cm^{-1}.

Reaction of the chloro urea with potassium dispersion in benzene was immediate and vigorous; a moderate carbonyl band was seen at 1865 and a weaker one at 1915 cm^{-1}. These absorptions disappeared before isolation could be attempted.

No reaction was observed by ir between 1-chloro-4,4,5,5-tetramethyl-2-imidazolidone and potassium *tert*-butoxide in ether.

Registry No.—**3**, 58816-12-9; **3** dimeric derivative, 59169-67-4; **3** potassium salt, 58816-14-1; **4**, 58816-15-2; **5**, 19403-24-8; **6a**, 58816-16-3; **6b**, 58816-17-4; **6c**, 58816-18-5; **7a**, 3964-19-0; **7b**, 58816-19-6; **7c**, 58816-20-9; 2,5-dimethyl-2,5-diaminohexane, 23578-35-0; 1,1′-carbonyldiimidazolo, 530-62-1; 1-chloro-4,4,7,7-tetramethyl-1,3-diazacycloheptan-2-one, 58816-21-0; *p*-nitrophenyl isocyanate, 100-28-7; 2,2,5,5-tetramethyl-8-*p*-nitrophenyl-1,6,8-triazabicyclo[4.3.0]nonane-7,9-dione, 58816-22-1; ethanol, 64-17-5; methanol, 67-56-1; benzhydrol, 91-01-0; hydrazobenzene, 122-66-7; *N,N′*-di-*tert*-butylhydrazine, 13952-69-7; *p*-toluenesulfonyl isocyanate, 4083-64-1; 1,2-di-*tert*-butyl-4-*p*-toluenesulfonyl-1,2,4-triazolidine-3,5-dione, 58816-23-2; 1,2-di-*tert*-butyl-4-*p*-nitrophenyl-1,2,4-triazolidine-3,5-dione, 58816-24-3; 2,3-di-*tert*-butylcarbazyl chloride, 58816-25-4; 2,2,4,4-tetramethylglutaric acid, 1189-82-8; isobutyric acid, 79-31-2; 2,2,4,4-tetramethylglutaryl dichloride, 58816-26-5; 2,4-dimethyl-2,4-pentyl diisocyanate, 58816-27-6; 1,3-dichloro-4,4,7,7-tetramethyl-1,3-diaza-2-cycloheptanone, 58816-28-7; 1,3-dichlorotetrahydro-2-pyrimidone, 58816-29-8; tetrahydro-2-pyrimidone, 1852-17-1; 2,2,4,4-tetramethylglutaryl diazide, 58816-30-1; di-*tert*-butyldiaziridinone, 19656-74-7.

References and Notes

(1) (a) Supported, in part, by Public Health Service Research Grant CA-16592 from the National Cancer Institute. (b) National Science Foundation Predoctoral Fellow.

(2) F. D. Greene, J. C. Stowell, and W. R. Bergmark, *J. Org. Chem.*, **34**, 2254 (1969); F. D. Greene, W. R. Bergmark, and J. G. Pacifici, *ibid.*, **34**, 2263 (1969).

(3) *trans*-Di-*tert*-butyldiaziridinone is much less reactive toward nucleophiles than is di-*tert*-butylcyclopropanone in spite of the infrared indication of a lack of amide-type resonance in the former.

(4) (a) Some evidence has been obtained for the transient existence of forms **1d** and **1e**: F. D. Greene and J. F. Pazos, *J. Org. Chem.*, **34**, 2269 (1969). (b) C. A. Renner, J. P. Cross, and F. D. Greene, *ibid.*, in preparation.

(5) N. L. Allinger and J. T. Sprague, *J. Am. Chem. Soc.*, **94**, 5734 (1972). See M. Bernard and M. St. Jacques, *Tetrahedron*, **29**, 2539 (1973), for an NMR study on 3,3,6,6-tetramethylcyclohexene and related compounds. See also F. R. Jensen and C. H. Bushweller, *J. Am. Chem. Soc.*, **91**, 5774 (1969), and references cited therein.

(6) (a) F. D. Greene, R. L. Camp, L. Kim, J. F. Pazos, D. B. Sclove, and C. J. Wilkerson, "XXIII International Congress of Pure and Applied Chemistry", Vol. 2, 1971, p 325; (b) D. B. Sclove, J. F. Pazos, R. F. Camp, and F. D. Greene, *J. Am. Chem. Soc.*, **92**, 7488 (1970).

(7) L. Radom, W. J. Hehre, and J. A. Pople, *J. Am. Chem. Soc.*, **94**, 2371 (1972).

(8) T. Kasuya and T. Kojima, *J. Phys. Soc. Jpn.*, **18**, 364 (1963).

(9) M. J. S. Dewar and W. B. Jennings, *J. Am. Chem. Soc.*, **95**, 1562 (1973), and references cited therein.

(10) (a) S. F. Nelson and J. M. Buschek, *J. Am. Chem. Soc.*, **96**, 6982, 6987 (1974); (b) K. N. Houk, Y-M. Chang, and P. S. Engel, *ibid.*, **97**, 1824 (1975); (c) F. Brogli, W. Eberbach, E. Haselbach, E. Heilbronner, V. Hornung, and D. M. Lemal, *Helv. Chim. Acta*, **56**, 1933 (1973).

(11) Paul S. Engel, private communication; also P. S. Engel, R. A. Melaugh, A. W. Garner, F. D. Rossini, M. Manson, and J. W. Timberlake, *J. Chem. Thermodyn.*, submitted for publication. Direct comparison of acyclic cis and trans azo compounds, e.g., *cis*- and *trans*-diisopropyldiazene ("azoisopropane"), has been unsuccessful because of difficulties with the cis isomer [P. S. Engel, private communication; see also the earlier report of P. S. Engel, J. L. Wood, J. A. Sweet, and J. L. Margrave, *J. Am. Chem. Soc.*, **96**, 2381 (1974)].

(12) P. S. Engel and D. J. Bishop, *J. Am. Chem. Soc.*, **97**, 6754 (1975).

(13) (a) J. M. Lehn and J. Wagner, *Tetrahedron*, **26**, 4227 (1970); (b) A. Mannschreck and W. Seitz, "XXIII International Congress of Pure and Applied Chemistry", Vol. 2, 1971, p 308; *Angew. Chem.*, **81**, 224 (1969).

(14) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, N.Y., 1970, pp 152–163.

(15) Evidence exists in other three-ring systems for nonconcerted fragmentation; e.g., episulfoxides [J. E. Baldwin, G. Hofle, and S. C. Choi, *J. Am. Chem. Soc.*, **93**, 2810 (1971); D. M. Lemal and P. Chao, *ibid.*, **95**, 922 (1973)] and cyclopropanimines (D. B. Sclove, Ph.D. thesis, Massachusetts Institute of Technology, 1972, p 89).

(16) See reviews by H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970); A. Rank, L. C. Allen, and K. Mislow, *ibid.*, **9**, 400 (1970).

(17) One-step, double nitrogen inversion in diaziridines is costly both in terms of angle strain and of lone pair–lone pair interactions. For a case of some relevance in this connection, involving an *N,N′*-diacyldiaziridine, see H. W. Heine, R. Henrie, II, L. Heitz, and S. R. Kovvali, *J. Org. Chem.*, **39**, 3187 (1974).

(18) H. A. Staab and K. Wendel, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 201.

(19) P. R. Austin and J. R. Johnson, *J. Am. Chem. Soc.*, **54**, 647 (1932). The sample used in our study was prepared from benzylmagnesium chloride and diethyl carbonate.

(20) N. A. Porter, Ph.D. Thesis, Harvard University, Cambridge, Mass., 1969.

(21) D. D. Traficante and J. A. Sims, *Rev. Sci. Instrum.*, **45**, 1063 (1974).

(22) We wish to thank Dr. Edward J. Walsh for this experiment.

(23) P. L. Creger, *J. Am. Chem. Soc.*, **89**, 2500 (1967); *Org. Synth.*, **50**, 58 (1970).

(24) J. Michailenko and W. Jaworski, *Chem. Zentralbl.*, II, 529 (1900); *Beilstein*, II, 717.

(25) J. Cason and E. J. Reist, *J. Org. Chem.*, **23**, 1675 (1958).

(26) R. Sayre, *J. Am. Chem. Soc.*, **77**, 6689 (1955).

Carbon-13 and Proton Nuclear Magnetic Resonance Spectroscopic Study of Protonated Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one, a Model 1,3-Bishomocubyl Cation. Attempted Preparation of the Parent and Alkyl- (Aryl-) Substituted Ions and Their Opening to 3-Substituted *endo*-Tricyclo[5.2.1.0^{2,6}]deca-4,8-dienyl Cations[1]

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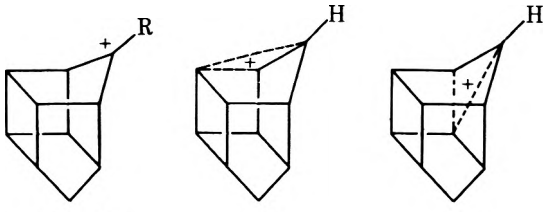
Protonation of pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one in FSO_3H/SO_2ClF at −78 °C gave the 6-hydroxypentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-6-yl cation. 6-Methyl- and 6-phenylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-6-ol (syn and anti) in FSO_3H/SO_2ClF at −78 °C gave ring-opened allylic 3-methyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-yl cation and 8- or 9-fluorosulfonated allylic 3-phenyl-*endo*-tricyclo[5.2.1.0^{2,6}]dec-4-en-3-yl cations. The structure of these ions was proved by ^{13}C and ^1H NMR spectroscopy and by the ionization of 3-methyl- and 3-phenyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ols in FSO_3H/SO_2ClF at −90 °C. Ionization of 6-phenylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]-dec-6-ol and 3-phenyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ols in HF/SO_2ClF at −78 °C gave the same allylic 3-phenyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-yl cation. All attempts to prepare the parent secondary or tertiary 1,3-bishomocubyl cations as well as the parent secondary *endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dienyl cation were unsuccessful.

Dilling and co-workers[2a] have carried out extensive investigations to determine the nature of 1,3-bishomocubyl cations in solvolytic and related reactions. In their solvolytic studies it was indicated that stereochemical and kinetic data seemed most consistent in secondary systems with the bridged ions **4** and **5**, but the classical ion **1** was not completely ruled out.



1, R = H
2, R = Ph
3, R = CH_3

4 **5**

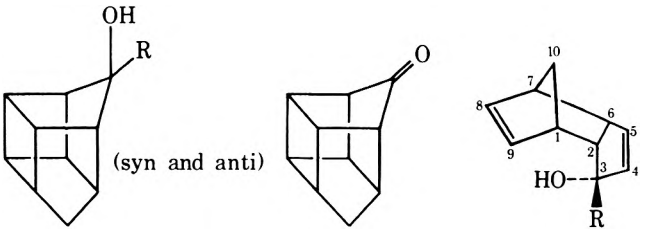
They also pointed out, however, that formation of bridged ions in the tertiary systems is ambiguous.[2,a,e] In a subsequent paper[3] they reported their attempts to observe the secondary and tertiary 1,3-bishomocubyl cations **1** and **3** in superacidic media by ^1H NMR spectroscopy and also carried out some related reactions to reveal the nature of these ionic species. They were not successful either in observing the 1,3-bishomocubyl cations nor in confirming the structure of ions obtained, based on ^1H NMR spectroscopic studies.

In our continued studies on carbocations, we now would like to report our studies relating to 1,3-bishomocubyl cations.

Results

We have investigated carbocations formed under stable ion conditions from both pentacyclic and tricyclic precursors **6–13** which were synthesized starting from dicyclopentadiene by reported methods.[2a,b,c,e] Alcohol **14** was prepared by the reaction of phenyllithium on **12** in ether.

Treatment of pentacyclic ketone **9** in FSO_3H/SO_2ClF at −78 °C gave a yellow-colored solution whose ^{13}C and ^1H NMR spectra were consistent with the protonated ketone **15**. **15** can be considered a model for a 1,3-bishomocubyl cation. **12** under similar conditions gave a species whose spectral data were in accordance with 8- or 9-fluorosulfonated protonated ketonic species **18**. However, in HF/SO_2ClF solution protonated ketone **19** was obtained.

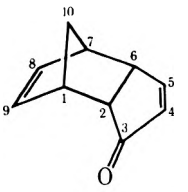


(syn and anti)

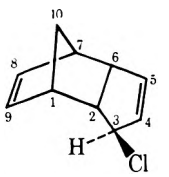
6, R = H
7, R = CH_3
8, R = Ph

9

10, R = CH_3
11, R = H
14, R = Ph



12



13

A mixture of syn and anti alcohols **7** with FSO_3H/SO_2ClF at −78 °C gave a clean, yellowish brown solution, whose ^1H NMR spectrum was identical with that reported by Dilling.[3] The solution was stable up to −30 °C. Ionization of **7** even at −120 °C gave the same ion. The tricyclic alcohol **10** under similar conditions at −90 °C gave a similar solution whose ^1H NMR spectrum was identical with that of the former ion generated from **7**. The ^{13}C NMR spectra for both solutions were also identical, indicating that both pentacyclic and tricyclic precursors **7** and **10** gave the same ion under these conditions. The ^1H and ^{13}C NMR spectra of the ion are shown in Figure 1.

Ionization of pentacyclic and tricyclic precursors **8** and **14**, respectively, in FSO_3H–SO_2ClF at −78 °C gave rise to solutions which showed similar but more complicated ^1H NMR spectra indicating formation of a mixture of ions. ^{13}C NMR spectra of the ions showed them to be a mixture of two species. However, ionization of the same precursors in HF/SO_2ClF at −78 °C gave rise to solutions whose ^1H and ^{13}C NMR spectra indicated the formation of the same single ion. The spectra are shown in Figure 2.

Dissolution of the pentacyclic secondary alcohol **6** in FSO_3H/SO_2ClF at −78 °C gave a light yellow colored solution whose ^1H NMR spectrum was identical with that of the pre-

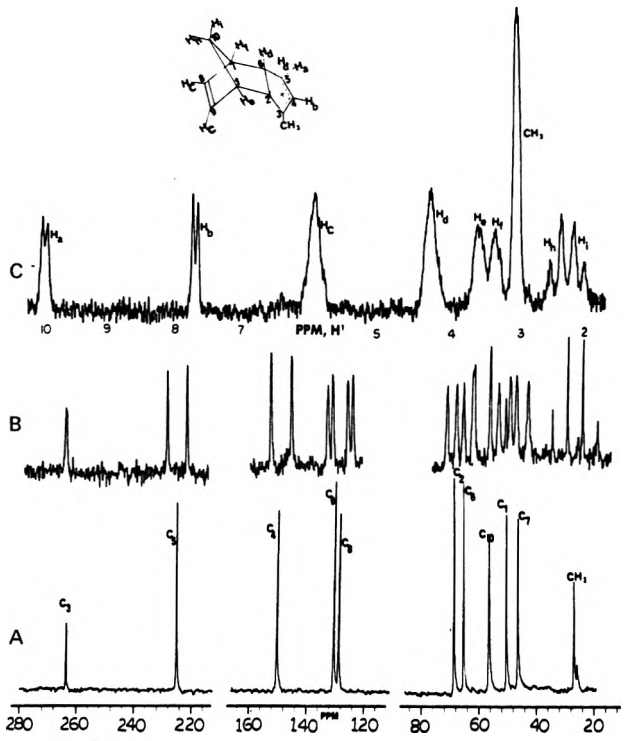


Figure 1. ^{1}H (C) and ^{13}C (A, B) NMR spectra of 3-methyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-yl cation in FSO_3H/SO_2ClF solution at −70 °C: A, proton noise decoupled; B, proton noise coupled.

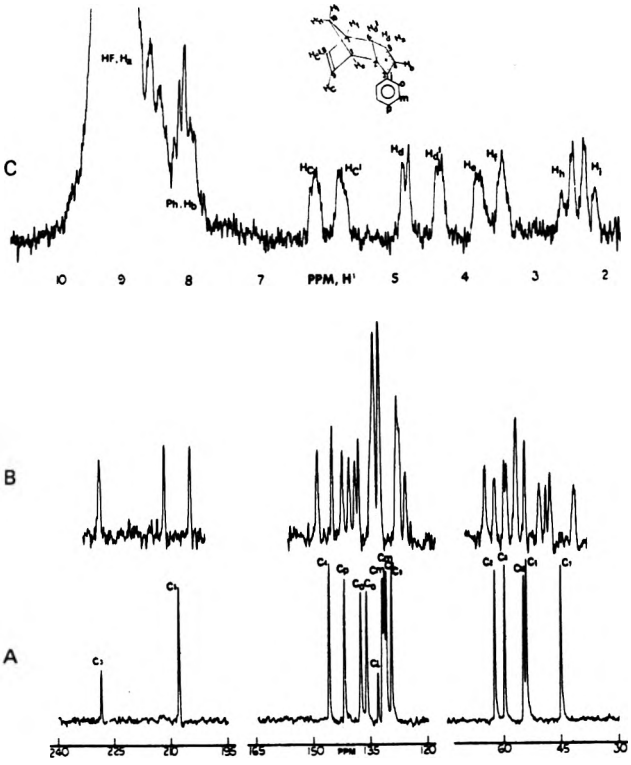


Figure 2. ^{1}H (C) and ^{13}C (A, B) NMR spectra of 3-phenyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-yl cation in HF/SO_2ClF solution at −70 °C: A, proton noise decoupled; B, proton noise coupled.

Table I. ^{1}H NMR Parameters of Ions[a]

22	8.4–9.4 broad (HF, H_a), 7.65–8.4 broad (aromatic protons, H_b), 6.1 broad (1 H, H_c), 5.7 broad (1 H, H'_c), 4.7 (d, 1 H, H_d, J_{HH} = 5 Hz), 4.2 (d, 1 H, H'_d, J_{HH} = 3.5 Hz), 3.7 (b, 1 H, H_e), 3.3 (b, 1 H, H_f), 2.5 (t, 1 H, H_h, J_{HH} = 9 Hz), 2.1 (2, 1 H, J_{HH} = 9 Hz) Fluorosulfonated ion ^{19}F shift −38.1
20	9.7 (d, 1 H, H_a), 7.6 (d, 1 H, H_b), 5.88 (2 H, H_c), 4.23 (2 H, H_d), 3.55 (1 H, H_e), 3.22 (1 H, H_f), 3.02 (3 H, CH_3), 2.40 (d, 1 H, H_h), 2.03 (d, 1 H, H_i)
23	5.4 (s, 1 H, $CHOH_2^+$), 2.9–3.0 (m, 8 H, cage protons), 1.8 and 1.4 unsymmetrical doublets (CH_2) (1 H each, J = 11 Hz)
19	8.8 (d, 1 H, H_a), 6.7 (d, 1 H, H_b), 5.8 (broad singlet, 2 H, H_c), 3.9 (b, 2 H, H_d), 3.0–3.4 (broad doublet, H_e, H_f), 1.9 (s, 2 H, H_h, H_i) Fluorosulfonated ion ^{19}F shift −37.8
15	3.0–3.9 (broad peak, 8 H, cage protons), 2.1 (broad singlet, 2 H, CH_2)

[a] Proton shifts in parts per million from external capillary Me_4Si; ^{19}F shifts in parts per million from external capillary CCl_3F.

Table II. ^{13}C NMR Parameters of Ions[a]

20	C_3 263.1, C_5 224.7, C_4 150.9, C_9 131.3 (J_{CH} = 169.3 Hz), C_8 129.6 (J_{CH} = 174.1 Hz), C_2 69.2, C_6 66.0, C_{10} 57.1, C_1 51.1, C_7 47.1, CH_3 27.7
22	C_3 228.7, C_5 208.1, C_4 146.4, C_p 142.3, C_o 138.0, 136.4, C_i 133.5, C_m 132.2, 131.8, C_9 131.2 (J_{CH} = 163.1 Hz), C_8 129.8 (J_{CH} = 164.2 Hz), C_2 62.6, C_6 60.0, C_{10} 55.0, C_1 54.3, C_7 45.3
21	C_3 227.2, C_5 202.6, C_4 148.5, C_p 143.0, C_o 139.7, 138.5, C_i 133.5, C_m 132.3, 131.7, C_8 or C_9 93.0, C_2 57.7, C_6 56.8, C_1 45.2, C_{10} 37.8, C_8 or C_9 27.6
18	C_3 227.8, C_5 197.8, C_4 134.8, C_8 or C_9 91.9, C_2 54.0, C_6 50.5, C_1 41.7, C_7 38.7, C_{10} 36.9, C_8 or C_9 27.5
19	C_3 228.6, C_5 197.6, C_4 134.7, C_9 132.8, C_8 130.2, C_2 54.8, C_6 54.1, C_1 53.2, C_{10} 47.4, C_7 44.2
15	C=OH^+ 254.4, 51.1, 48.3, 44.7, 44.4, 43.4, 43.2, 41.7, CH_2 40.2, 31.4
23	$CHOH_2^+$ 95.5, 49.9, 43.9, 41.5, 41.2, 40.5, 40.1, 39.5, 38.9, 36.4

[a] Shifts in parts per million from external capillary Me_4Si.

Table III. ^{13}C NMR Parameters of Precursors[a]

10	C_4 140.8, C_5 136.4, C_8, C_9 134.2 (J_{CH} = 162.1 Hz), C_3 82.1, C_1 55.2, C_7 54.7, C_{10} 53.6, C_6 47.9, C_2 45.3, CH_3 32.0
14	C_i 150.2, C_p 139.8, C_o 136.1, 135.9, C_4 134.9, C_8, C_9 129.3 (J_{CH} = 159.5 Hz), C_5 127.6, C_m 125.9, C_3 85.9, C_1 58.1, C_7 55.3, C_{10} 53.7, C_6 47.8, C_2 46.6
9	C=O 220.2, 50.2, 44.3, 43.5, 42.7, 42.1, 41.1, CH_2 40.4, 39.0, 32.4
6	CHOH 81.1, 53.6, 45.4, 44.8, 42.8, 42.1, 41.1, 40.8, 40.0, CH_2 38.4
12	C_3 221.4, C_4 166.9, C_5 137.9, C_8 133.5, C_1 53.9, C_7 51.3, C_{10} 49.4, C_2 46.2, C_6 45.4

[a] Shifts are in parts per million from external capillary Me_4Si in $CDCl_3$ at 37 °C.

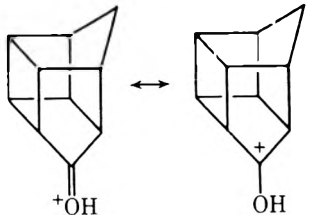
cursor **6** in $CDCl_3$, except for 1.1-ppm deshielding of the proton shift for carbinol carbon. The ^{13}C NMR spectrum of this solution at −70 °C showed the species to be a protonated alcohol. The solution was stable up to −10 °C.

All attempts at preparing the secondary pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-6-yl cation **1** or the tertiary analogues **2** and **3** from precursors **6**, **7**, and **8** either in $FSO_3H/SbF_5/SO_2ClF$ or SbF_5/SO_2ClF solutions at low temperatures were unsuccessful. It was also not possible to prepare the secondary *endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dienyl cation from tricyclic precursors **11** and **13**.

The ^{1}H and ^{13}C NMR data of the studied ions are summarized in Tables I and II. ^{13}C NMR data for some of the precursors are given in Table III.

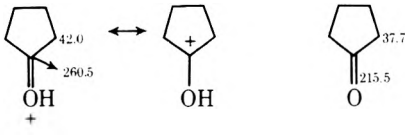
Discussion

Protonated pentacyclodecanone obtained from ketone **9** in FSO_3H/SO_2ClF at −78 °C can be considered as a model 6-hydroxypentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-6-yl (1,3-bishomocubyl) cation **15a**. Comparing its ^{13}C shifts to the shifts of the precursor, the protonated carbonyl carbon is deshielded by 34 ppm, but at the same time there is little deshielding of the cage carbon atoms; the shifts indicate that the contribution from the structure **15** is predominant. Comparing ^{13}C



15 **15a**

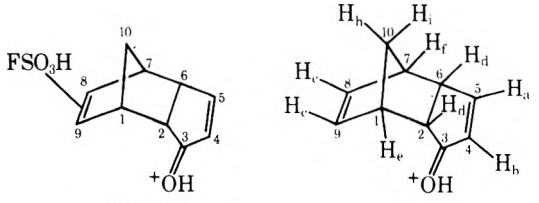
shift differences of **15** and **9** to the differences in ^{13}C shifts of protonated cyclopentanone **16** and cyclopentanone **17**,[4] the former is less by about 11 ppm than the latter indicating the rigidity of the cage system. Contribution from the structure **16a** seems to be more significant in protonated cyclopenta-



16 **16a** **17**

none as the α-carbon shifts are more deshielded than those of other protonated higher alicyclic homologues.[4a] The contribution of structure **15a** is thus more limited, as the cage ring carbons show no significant deshielding. This conclusion may be, however, somewhat ambiguous as the rigid cage structure may not allow sufficient predictions to be made from ^{13}C NMR shifts as to the carbocationic nature of **15a**.

8- or 9-fluorosulfonated protonated ketone **18** was obtained from ketone **12** in FSO_3H/SO_2ClF solution at −78 °C. However, protonated ketone **19** was formed in HF/SO_2ClF solution at −78 °C. It is indicated from the ^{13}C shifts that significant

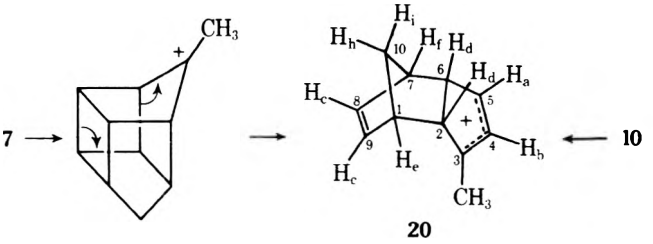


18 **19**

charge has been delocalized into the C_4 and C_5 centers. The ^{13}C data are summarized in Table II.

The ^1H NMR spectrum of the ion generated from the alcohol **7** (both the syn and anti isomers) was tentatively assigned the structure **20** by Dilling and co-workers,[3] as their ^1H NMR data were consistent with this ion. We have now confirmed the structure of the ion by ionizing tricyclic alcohol **10** in FSO_3H/SO_2ClF at −90 °C which gave the same allylic ion. The ^{13}C NMR spectra also clearly indicate the formation of the allylic ion **20**.[4b] The formation of ion **20** from **7** can be visualized to take place through the intermediacy of the 1,3-bishomocubyl cation **3** as shown in Scheme I. ^{13}C NMR chemical shifts are in good agreement with those of reported substituted cyclopentenyl cations.[5] The assignments were made by the customary methods discussed previously.[6] The ^{13}C shifts and their assignments are summarized in Table II. We were unable to observe the parent ion **3** even when the

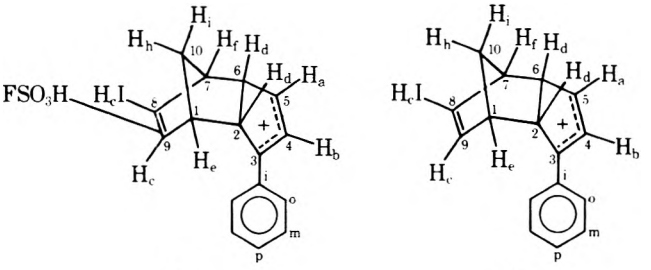
Scheme I



20

ionization was carried out at −120 °C. Ionization in even stronger superacids leads to unidentifiable species. Our studies thus confirm the tentative assignment made by Dilling and co-workers[3] for the ion generated from the alcohol **7**.

A phenyl group adjacent to a carbocationic center is known to delocalize positive charge very efficiently.[7] Hence, we felt that the tertiary phenyl substituted precursor **8** would give rise to the corresponding phenyl substituted 1,3-bishomocubyl cation **2**. Ionization of alcohol **8** in FSO_3H/SO_2ClF at −78 °C gave a species which displayed a complicated ^1H NMR spectrum. The low field signals were attributable to an allylic cation. The ^{13}C NMR spectrum revealed the presence of a mixture of closely related allylic ions, with one ion predominating. Ionization of alcohol **14** under similar conditions gave rise to the same mixture of ions whose ^1H and ^{13}C NMR spectra were identical. The ^{13}C signal at $\delta_{C^{13}}$ 93 (doublet) clearly indicated the fluorosulfonation at C_8 or C_9 site of the isolated double bond of **22**. The ion was assigned the structure **21**. Further evidence for fluorosulfonation came from the ^{19}F



21 **22**

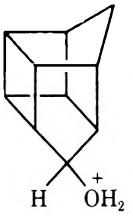
NMR spectrum (Table I). It was, however, not possible to decide whether the fluorosulfonation site is C_8 or C_9. ^{13}C NMR shifts of the major fluorosulfonated species are given in Table II. Ionization of **8** in HF/SO_2ClF solution at −90 °C resulted in ring-opened 3-phenyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-yl cation **22** whose ^1H and ^{13}C NMR spectra are shown in Figure 2. The ion **22** was also obtained by the ionization of **14** under similar conditions. The parent ion **2** was never observed from **8** either in $FSO_3H/SbF_5/SO_2ClF$ or SbF_5/SO_2ClF solutions even at very low temperatures.

Our failure to obtain 1,3-bishomocubyl ions **2** and **3** can be attributed to the instability of these species under long life superacidic conditions. Indeed there is evidence for these ions in solvolytic reactions[3,4c] where the lifetimes are shorter. The obvious driving force for the ring opening is the relief of strain of the pentacyclic ring systems (roughly 16.4 kcal/mol) as indicated by Cookson and co-workers.[8] Thus, this explains the reason for the limited contribution from **15a** to ion **15**.

It is interesting to note that alcohols **7** and **10** gave allylic cation **20** in FSO_3H/SO_2ClF solution, whereas alcohols **8** and **14** lead to a mixture of fluorosulfonated allylic ions **21**. This may be due to differences in the solvation of the ionic species and also to the different degree of participation of the isolated C_8=C_9 double bond with the allylic center. In the ion **22** (in HF/SO_2ClF) most of the charge is delocalized into the phenyl ring whereas no such participating group exists in ion **20** as indicated by ^{13}C chemical shifts and also by the C–H coupling is at C_8 and C_9 positions of ions **20** and **22** as compared to their

precursors (Tables II and III). Ion **20** shows increased coupling (δ_{C_8-H} 7.2 Hz, δ_{C_9-H} 12 Hz) as compared to the ion **22** (δ_{C_8-H} 3.6 Hz, δ_{C_9-H} 4.7 Hz). This is probably due to the greater degree of participation of the isolated double bond with the allylic center in ion **20** as compared to the ion **22**. Hence, ready fluorosulfonation occurring on the isolated double bond of the incipient ion **22** is indicated during the ionization of precursors **8** and **14** in FSO_3H/SO_2ClF solutions. However, we were able to obtain ion **22** in HF solutions because under the experimental conditions at low temprature it does not easily attack isolated double bonds.

The secondary alcohol **6** when dissolved in FSO_3H/SO_2ClF at −78 °C gave only protonated alcohol **23** which was stable up to −10 °C. The carbinol carbon showed ^{13}C NMR deshielding of 14 ppm (Tables II and III). Dilling[3] observed ^{1}H NMR deshielding of 1.1 ppm of the carbinyl methine proton.



23

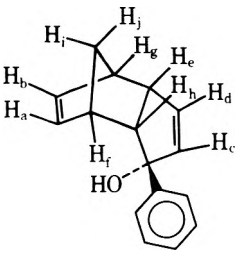
24

The stability of protonated alcohol **23** up to −10 °C demonstrates the instability of the parent ion **1**. The lack of any rearrangement of **23** into **24** is further attributable to the relative instability of ion **24**. Alcohol **6** in stronger superacids such as FSO_3H/SbF_5 or SbF_5 solutions gave only polymeric material. We were also unable to obtain the secondary allylic tricyclic ion **24** either from precursors **11** or **13** using superacids under varied conditions.

Experimental Section

Materials. Precursors **6**–**13** were prepared by known methods[2a,b,c,e,3] starting from dicyclopentadiene.

3-Phenyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ol. To freshly prepared phenyllithium (prepared from 0.35 g of lithium metal in dry ether under nitrogen with 8.25 g of bromobenzene in ether) was slowly added 7.3 g of dienone **12** in 25 ml of dry ether over a period of 15 min. The resulting mixture was refluxed for 3 h. Then the reaction mixture was worked up in the usual manner. The product obtained was recrystallized from hexane twice to obtain 8.2 g of **13** (65%): mp 67–68 °C (lit.[9] mp 65–66 °C); ^{1}H NMR δ 7.64 (s, 5 H, aromatic), an unsymmetrical doublet of doublets centered at 6.64 (1 H, H_a or H_b, J_{ab} = 4, J_{af} or J_{bj} = 2 Hz), 6.24 (1 H, J_{ab} = 4, J_{af} or J_{bj} = 2.6 Hz, H_a or H_b), 5.94 (m, 2 H, H_c and H_d), unresolved multiplet around 3.8 and 3.3 (4 H, H_h, H_e, H_f, and H_g), singlet at 2.3 (1 H, OH), overlapping two unsymmetrical doublets of triplets centered at 1.9 (H_i or H_j, J_{ij} = 7, J_{fj} = 2 Hz) and 1.7 (J_{fi} = 3 Hz).



Preparation of Ions. Twice distilled FSO_3H was dissolved in a twofold amount of SO_2ClF at dry ice/acetone temperature (ca. −78 °C). To this solution was slowly added with vigorous stirring a cold solution of appropriate precursor dissolved in SO_2ClF, to give approximately 15–20% solution of the ion. Solutions of ions in HF/SO_2ClF were similarly prepared using quartz equipment. An ethanol/liquid N_2 bath was used to obtain temperatures below −78 °C.

^{19}F and ^{1}H NMR spectra were obtained on a Varian Model A56/60A spectrometer equipped with variable temperature probes and external Me_4Si and CCl_3F capillaries were used as references.

^{13}C NMR spectra were obtained using a Varian Model XL-100 NMR spectrometer equipped with FT accessory with variable temperature probe as previously described.[10]

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

Registry No.—**6**, 15443-36-4; **9**, 15584-52-8; **10**, 52916-88-8; **12**, 5530-96-1; **13**, 51965-70-9; **14**, 59231-05-9; **15**, 59231-06-0; **18**, 59230-92-1; **19**, 59231-07-1; **20**, 59230-93-2; **21**, 59230-95-4; **22**, 59230-94-3; **23**, 59231-08-2.

References and Notes

(1) Stable Carbocations. 200. Part 199: G. A. Olah and H. Mayr, *J. Am. Chem. Soc.*, in press.
(2) (a) W. L. Dilling and J. A. Alford, *J. Am. Chem. Soc.*, **96**, 3615 (1974); (b) W. L. Dilling and C. E. Reinke, *Tetrahedron Lett.*, 2547 (1967); (c) W. L. Dilling, C. E. Reinke, and R. A. Plepys, *J. Org. Chem.*, **34**, 2605 (1969); **37**, 3753 (1972); (d) W. L. Dilling, R. A. Plepys, and R. D. Kroening, *J. Am. Chem. Soc.*, **91**, 3404 (1969); **92**, 3522 (1970); (e) *ibid.*, **94**, 8133 (1972).
(3) W. L. Dilling, R. A. Plepys, and J. A. Alford, *J. Org. Chem.*, **39**, 2856 (1974).
(4) (a) G. Liang, Ph.D. Thesis, Case Western Reserve University, 1973. (b) All our attempts to trap the ion **20** were unsuccessful. However, experience indicate that trapping of allylic cations is generally difficult. (c) Our work on these caged compounds in superacidic media cannot be directly connected to the problem of σ bridging in solvolytic reactions of these systems, as rightly pointed out by one of the referee, although knowledge of stable intermediates are of obvious significance in any mechanistic studies.
(5) G. A. Olah, P. R. Clifford, Y. Halpern, and R. G. Johanson, *J. Am. Chem. Soc.*, **93**, 4219 (1971).
(6) (a) D. N. Grant and E. G. Paul, *J. Am. Chem. Soc.*, **86**, 2984 (1964); (b) D. K. Dalling and D. N. Grant, *ibid.*, **89**, 6612 (1967).
(7) G. A. Olah, P. W. Westerman, and J. Nishimura, *J. Am. Chem. Soc.*, **96**, 3548 (1974).
(8) R. C. Cookson, E. Crundwell, R. R. Hill, and J. Hudec, *J. Chem. Soc.*, 3062 (1964).
(9) M. Rosenblum, *J. Am. Chem. Soc.*, **79**, 3179 (1957).
(10) G. A. Olah and G. Liang, *J. Am. Chem. Soc.*, **96**, 189 (1974).

Nucleophilic Substitution at the Pyrrole Ring. Comparison with Furan, Thiophene, and Benzene Rings in Piperidinodenitration[1]

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The reactivity of the pyrrole ring in nucleophilic aromatic substitution has been evaluated for the first time by rate measurements for the piperidinodenitration of 1-methyl-2,5-dinitropyrrole (1) at varying temperatures. Relative rates (k_{rel}) have been established at 25 ° C and show that 1 is markedly less reactive than 2,5-dinitrofuran and 2,5-dinitrothiophene, the k_{rel} values being 1, 2.4×10^6, and 4.4×10^3, respectively. A less significant difference is found with the rate of 1,4-dinitrobenzene ($k_{rel} = 9.6$). The factors affecting the observed reactivities and activation parameters are discussed.

Nucleophilic aromatic substitution at the pyrrole ring has been little studied. Thus, monographs dealing with the pyrrole chemistry either ignore the subject or sometimes present[2-5] a few instances of this reaction as rather exceptional reactions.[5] One of the reasons for this state of affairs is no doubt the fact that pyrrole derivatives with substituents suitable for nucleophilic displacement, such as halogenonitropyrroles, are not easily available. For example, halogenopyrroles undergo a rapid, spontaneous decomposition[6] and cannot be nitrated. Furthermore, in view of the fact that halogenopyrroles may suffer from the loss of the halogen atom as a positive entity under acidic conditions, some doubt has been cast[7] upon the nature of one of the few known substitutions with nucleophilic reagents at the pyrrole ring, i.e., the conversion of 2,3,4,5-tetrachloro- and 2,3,4,5-tetrabromopyrrole to 2,3,4,5-tetraiodopyrrole with potassium iodide.[8] Moreover, the reactivity of pyrrole derivatives bearing a hydrogen atom bound to nitrogen toward nucleophilic reagents is expected to be depressed by the proton-abstracting action of the electron donor and the resulting formation of an unreactive conjugate base of the starting substrate.

Prior to our report[9] on the easy replacement of a nitro group in 1-methyl-2,5-dinitropyrrole (1) by several nucleophilic reagents, the only well-characterized case of nucleophilic aromatic substitution on the pyrrole ring was the formation of 5-acyl-2,3-dihydropyrrole[2,1-*b*]oxazoles from 2-acyl-1-(2-hydroxyethyl)-5-nitropyrroles, in the presence of bases.[10] Both 1 and the substrates of the latter reaction are characterized by the presence of good leaving groups, electron-withdrawing substituents, and a blocking group at position 1. These structural features are obviously among the factors responsible for the reactivity of these compounds toward the nucleophilic reagents.

In this paper we report on a kinetic investigation of the piperidinodenitration of 1 in acetonitrile and of the related 2,5-dinitrofuran (2) and 2,5-dinitrothiophene (3). These data provide the first evaluation of the reactivity of the pyrrole ring in nucleophilic substitution and of its comparison with the other main five-membered heteroaromatic rings. We have also found of interest to include in this study 1,4-dinitrobenzene (4) as a link to benzenoid reactivity.

Experimental Section

Melting points are uncorrected. Elemental microanalyses were performed at the Microanalysis Laboratory of the University of Trieste. Uv and visible spectra data were obtained on either a Beckman DB-GT instrument, matched by a Kontron W+W 1100 recorder, or a Hitachi Perkin-Elmer 46 BCD instrument. NMR spectra were recorded on a JEOL C-60HL instrument by using $(CH_3)_4Si$ as internal reference. Mass spectra were recorded on an AEI MS 12 spectrometer.

1-Methyl-2,5-dinitropyrrole (1). 1-Methyl-2-nitropyrrole was nitrated in acetic anhydride according to a described procedure.[11] From the mixture containing the 2,4- and 2,5-dinitro isomers, 1 was isolated by chromatography on Al_2O_3, with benzene as eluent, and recrystallized from hexane (mp 98–99 °C, lit.[11] 99 °C).

2,5-Dinitrofuran (2) was prepared from 5-nitrofuran-2-carboxylic acid[12] and recrystallized from hexane (mp 100–100.5 °C, lit.[12] 101 °C).

2,5-Dinitrothiophene (3). A mixture of 2- and 3-nitrothiophene, as obtained from nitration of thiophene, was further nitrated according to a known procedure.[13] The crude nitration product was subjected to chromatography on HCl-washed silica gel, with a mixture of petroleum ether (bp 30–50 °C) and benzene (4:1–3:1) as eluent. The first fractions yielded a 20% crop (based upon the crude) of 3, which was recrystallized from hexane (mp 79.5–80 °C, lit.[14] 80–82 °C). The absence of 2,4-dinitrothiophene was checked by NMR.

1,4-Dinitrobenzene (4). A commercial sample (Merck) was sublimated under reduced pressure (mp 173–174 °C, lit.[15] 174 °C).

1-Methyl-2-nitro-5-piperidinopyrrole. Piperidine (0.22 ml, 2.3×10^{-3} mol) was added to a solution of 0.1 g of 1 (5.85×10^{-4} mol) in 5 ml of dimethyl sulfoxide. The mixture was kept for three days at room temperature, poured into an excess of water, and repeatedly extracted with small portions (5 ml) of hexane. The combined hexane extract was washed with water. Upon evaporation from the dried solution, an orange-colored residue was obtained (90 mg), that was sublimed under reduced pressure and recrystallized from hexane: mp 80.5–81.5 °C; λ_{max} (CH_3CN) 399 nm (ϵ_{399} 1.634×10^4 l. mol^{-1} cm^{-1}); τ (in CCl_4) 3.12 (d, 1 H, J = 4 Hz), 4.51 (d, 1 H, J = 4 Hz), 6.32 (s, 3 H), 7.0–7.25 (m, 4 H), 8.37 (m, 6 H); M^+ at *m/e* 209.

Anal. Calcd: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.3; H, 7.1; N, 20.1.

2-Nitro-5-piperidinofuran was obtained from 2 according to the method reported by Severin:[16] mp 94–94.5 °C (lit.[16] 99 °C); λ_{max} (CH_3CN) 436 nm (ϵ_{436} 2.98×10^4 l. mol^{-1} cm^{-1}). The same procedure was followed for the preparation of **2-nitro-5-piperidinothiophene** from 3: mp 122–124 °C (lit.[17] 126 °C); λ_{max} (CH_3CN) 450 nm (ϵ_{450} 3.11 $\times 10^4$ l. mol^{-1} cm^{-1}).

1-Nitro-4-piperidinobenzene was obtained by adding 0.47 g of piperidine (5.4×10^{-3} mol) to a solution of 0.11 g of 4 (6.5×10^{-4} mol) in 25 ml of acetonitrile, and by refluxing for 60 h. Evaporation of the solvent left an oily residue, which was extracted with ether. After evaporation of the ether solution, the residue was crystallized from hexane: mp 102 °C (lit.[18] 105.5 °C); λ_{max} (CH_3CN) 397 nm (ϵ_{397} 2.02 $\times 10^4$ l. mol^{-1} cm^{-1}).

Piperidine was kept over Na until evolution of hydrogen ceased, and was refluxed for 4 h over Na and distilled from K.

Acetonitrile was refluxed upon P_4O_{10} and distilled therefrom.

The kinetics were followed spectrophotometrically at wavelengths corresponding to the absorption maxima of the reaction products, under pseudo-first-order conditions (excess of nucleophile). The substitutions on 2 and 3 were followed in the thermostated compartment of a Beckman DB-GT or a Hitachi Perkin-Elmer 46 BCD spectrophotometer; owing to the high reactivity of the furan derivative, we used a two-compartment cell (optical length 0.875 cm) where the solutions of the reagents were thermostated separately before mixing. The kinetics of 1 and 4 were run in ampules. The range of concentration of the substrates was nearly 10^{-5} M (2 and 3) or 10^{-4} (1 and 4). The concentration of piperidine was chosen according to the reactivity of the substrates. In any case, no evidence was found for the presence of terms other than first order in piperidine in the kinetic expression.

Table I. Kinetic Data for the Piperidinodenitration of Compounds 1–4 in Acetonitrile at Different Temperatures

Compd	k,[a] l. mol^{-1} sec^{-1} (temp, °C)			
1	3.42×10^{-6} (59.5)	5.80×10^{-6} (67.4)	8.96×10^{-6} (74.7)	14.7×10^{-6} (81.7)
2	0.455 (19.9)	0.624 (26.5)	0.834 (34.0)	1.068 (40.0)
3	1.06×10^{-3} (25.0)	1.84×10^{-3} (34.9)	2.94×10^{-3} (44.3)	
4	1.42×10^{-5} (54.4)	2.07×10^{-5} (61.1)	3.13×10^{-5} (68.4)	4.43×10^{-5} (75.9)

[a] Corrected for statistical factors.

Table II. Activation Parameters and Relative Rates for the Piperidinodenitration of Compounds 1–4 in Acetonitrile at 25 °C

Compd	$\Delta H^{\ddagger}$, kcal mol^{-1}	$-\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}	k,[a] l. mol^{-1} s^{-1}	k_{rel} (25 °C)
1	14.5 (± 1)	40 (± 2)	$2.4 (\pm 0.7) \times 10^{-7}$	1
2	7.0 (± 0.3)	36 (± 1)	0.57 (± 0.01)	2.4×10^{6}
3	9.3 (± 0.3)	41 (± 1.5)	$1.06 (\pm 0.01) \times 10^{-3}$	4.4×10^{3}
4	11.5 (± 0.6)	46 (± 2)	$2.3 (\pm 0.3) \times 10^{-6}$	9.6

[a] Corrected for the statistical factor.

The second-order rate constants, as derived from experimental pseudo-first-order rate constants, were corrected for the thermal expansion of the solvent and for the statistical factor (two alike leaving groups).

Results and Discussion

Compounds 1–4 undergo the piperidinodenitration reaction in acetonitrile solution. Under kinetic conditions, only the expected nitropiperidino products were observed (TLC and infinity absorbance values) for the reactions of 2, 3, and 4; minor amounts of a side product, which became detectable when the reaction had progressed by no less than 20%, were revealed by TLC for the reaction of 1. For preparative purposes, 1-methyl-2-nitro-5-piperidinopyrrole was conveniently obtained from 1 in dimethyl sulfoxide, which is a faster solvent than acetonitrile in nucleophilic aromatic substitution,[19] with no interference of side products.

Good pseudo-first-order linear plots were obtained for the reactions of 2 and 3. However, deviations from linearity were observed for compounds 1 and 4 beyond 15% reaction. In the latter cases the first-order rate constants were evaluated from initial rate determinations. It is worth noting that in the piperidinodebromination of 2-bromo-5-nitrofuran (5) in methanol solution,[20] which leads to the same product as the reaction of 2, a pseudo-first-order kinetics law is obeyed only in the initial stages of the reaction (up to nearly 10%), because the reaction product decomposes at a rate comparable with that of its formation. This complication is not observed in the reaction of 2 because in the latter case the rate is 400 times as high as for compound 5. Solvent[19] as well as leaving group effects are held responsible for this difference in rate.

Rate data have been obtained for the piperidinodenitration reactions at varying temperatures (Table I). Activation parameters and relative rates at 25 °C are reported in Table II.

The observed order of reactivity is

$$2 > 3 > 4 > 1 \qquad (1)$$

For the first three compounds it is in agreement with that found for the piperidinodebromination reaction.[17,20] As expected, the reactivity of the pyrrole ring is markedly lower than that of the other, similarly activated, heteroaromatic substrates; surprisingly, it is just one order of magnitude lower than that of the benzene derivative.

Owing to the geometry of the five-membered ring, the steric effect of the *N*-methyl group is not expected to play a significant role;[21] in particular, repulsive interactions between adjacent groups appear to be smaller than in the benzenoid ring. Presumably the moderate electron-releasing effect of that group can be transmitted through nitrogen to depress the reactivity of the ring to some extent. In any case, the overall rate-depressing influence of the *N*-methyl group should be small and the observed rate constant for the reaction of 1, though a lower limit for the expected reactivity of un-ionized 2,5-dinitropyrrole, should be a fair measure of the latter.

The differences in reactivity between the heteroaromatic substrates are mainly caused by changes in enthalpy of activation, the entropy of activation varying within rather narrow limits. Although the benzene ring system (4) is not strictly comparable with the heteroaromatic substrates (1–3), its place in the reactivity order of compounds 1–4 is still controlled by the enthalpy of activation. The entropy of activation of 4 is somewhat lower than that for the other compounds but is more than offset by the enthalpy of activation. As a result, 4 is only moderately more reactive than the pyrrole substrate. The entropy data indicate that the reactions of the heteroaromatic substrates require essentially similar reorganization of the solvent in going from substrate to transition state.

The observed relative reactivity of the five-membered ring systems, as shown by sequence 1, is worth some comments in terms of stabilization of the transition state (rate enhancement) and of the ground state (rate depression) by electronic effects. In connection with the former point the heteroatom is expected to contribute to accommodate the negative charge in the ring system by its electronegativity and, in the case of thiophene, by the use of sulfur d orbitals. The pyrrole system (1) is less favored by this rate-enhancing effect than the other two systems (2 and 3).

Rate-depressing effects may derive from the conjugative interaction of the ring heteroatom with the leaving group (NO_2) in the ground state and the aromaticity of the ring system. The low reactivity of the pyrrole system, 1, in nucleophilic substitution may thus be mainly interpreted in terms of the stability of the ground state, since a significant conjugative interaction between the electron-releasing ring nitrogen and the nitro group, as occurring in the starting substrate, must be lost in the transition state. Such an interaction is expected to be stronger than that of the ring oxygen of sulfur, in view of the stronger tendency of nitrogen to share its electrons,[22] and may well be responsible for the position of 1 in the rate sequence 1.

The low aromatic character of the furan system may be a major factor for the higher reactivity of 2 relative to that of 3 in nucleophilic substitution as well as for the higher tendency of furan derivatives, with respect to similarly activated thiophene derivatives, to form Meisenheimer-type adducts.[23] The importance of this effect also stems out of the fact that it does not depend on the charge type of substitution. Accordingly, in the electrophilic substitution of admittedly not strictly comparable substrates, the furan ring is also more reactive than the thiophene ring, in spite of the very large inversion of the pyrrole reactivity (i.e., pyrrole > furan > thiophene) relative to nucleophilic substitution.

As to the position of 1,4-dinitrobenzene (4) in the observed sequence, although the rate-depressing effect deriving from the conjugative effect is absent here, the low reactivity may derive from a substantially large resonance energy of the benzenoid ring of this compound.

The influence of the leaving group and other structural effects will be the object of further investigations.

Acknowledgment. The authors are grateful to Dr. Roberto Mosca (University of Trieste) for the elemental analyses.

Registry No.—1, 56350-95-9; 2, 826-03-9; 3, 59434-05-8; 4, 100-25-4; 5-nitrofuran-2-carboxylic acid, 645-12-5; 1-methyl-2-nitro-5-piperidinopyrrole, 56350-96-0; piperidine, 110-89-4; 2-nitro-5-piperidinofuran, 4818-49-9; 2-nitro-5-piperidinothiophene, 19991-84-5; 1-nitro-4-piperidinobenzene, 6574-15-8.

References and Notes

(1) Presented at the Fifth International Congress of Heterocyclic Chemistry, Ljubljana, July 13–18, 1975.
(2) A. Albert, "Heterocyclic Chemistry", 2d ed, Athlone Press, London, 1968, pp 190, 223.
(3) K. Schofield, "Heteroaromatic Nitrogen Compounds", Butterworths, London, 1967, p 100.
(4) R. Livingston in "Rodd's Chemistry of Organic Compounds", Vol. 4a, 2d ed, S. Coffey, Ed., Elsevier, Amsterdam, 1973, p 346.
(5) A. Gossauer, "Die Chemie der Pyrrole", Springer-Verlag, West Berlin, 1974, p 323.
(6) G. A. Cordell, *J. Org. Chem.*, **40**, 3161 (1975).
(7) Reference 3, pp 101–102.
(8) Kalle and Co., D. R. P. Patent 38 423; *Chem. Zentralbl.*, 423 (1887).
(9) G. Doddi, P. Mencarelli, and F. Stegel, *J. Chem. Soc., Chem. Commun.*, 273 (1975).
(10) V. Vecchietti, E. Dradi, and F. Lauria, *J. Chem. Soc. C*, 2554 (1971).
(11) P. Fournari and J. Tirouflet, *Bull. Soc. Chim. Fr.*, **484** (1963).
(12) R. Marquis, *Ann. Chim. Phys.*, **4**, 196 (1905).
(13) A. H. Blatt, S. Bach, and L. W. Kresch, *J. Org. Chem.*, **22**, 1693 (1957).
(14) W. Steinkopf and T. Höppner, *Justus Liebigs Ann. Chem.*, **501**, 174 (1933).
(15) O. Wyler, *Helv. Chim. Acta*, **15**, 23 (1932).
(16) T. Severin and H. Kullmer, *Chem. Ber.*, **106**, 1688 (1973).
(17) D. Spinelli, C. Dell'Erba, and A. Salvemini, *Ann. Chim. (Rome)*, **52**, 1156 (1962).
(18) E. Lellman and W. Geller. *Ber.*, **21**, 2282 (1888).
(19) G. Illuminati in "Solutions and Solubilities", Part 2, M. R. J. Dack, Ed., Wiley, New York, N.Y., in press.
(20) D. Spinelli, G. Guanti, and C. Dell'Erba, *Boll. Sci. Fac. Chim. Ind. Bologna*, **25**, 71 (1967).
(21) D. Spinelli, G. Consiglio, R. Noto, and A. Corrao, *J. Chem. Soc., Perkin Trans. 2*, 1632 (1975).
(22) G. Marino, *Adv. Heterocycl. Chem.*, **13**, 241 (1971).
(23) G. Doddi, A. Poretti, and F. Stegel, *J. Heterocycl. Chem.*, **11**, 97 (1974), and unpublished results.

Pyrrole Chemistry. The Cyanovinyl Aldehyde Protecting Groups†

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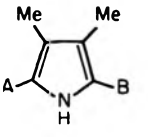
Protection of pyrrolic aldehyde groups with either methyl or ethyl cyanoacetate or malononitrile gives the corresponding cyanovinyl derivatives which are stable toward a variety of acids, oxidants, and reductants. Removal of the protecting groups with aqueous base regenerates the parent aldehyde.

The aldehyde function is one of great importance in the chemistry of pyrroles.[2] Alone, its electron-withdrawing properties can confer considerable stability on an otherwise sensitive system. 2-Formylpyrroles condense readily with 2-unsubstituted pyrroles in the presence of acid to form the very stable and synthetically useful 2,2′-dipyrromethene salts.[3] This reaction forms the basis for several well-known routes to porphyrins,[4] including the regiospecific synthesis of Johnson et al.[5] It is often convenient, given the nature of the readily available pyrrollic starting materials (usually 5-methylpyrrole-2-carboxylate esters), to introduce the formyl group several steps before it is required in the dipyrromethene synthesis. Although 2-formylpyrroles are resistant to autoxidation or Cannizzaro disproportionation, they are very susceptible to decomposition under acidic conditions and in the presence of many of the reagents commonly used in pyrrole syntheses (bromine, sulfuryl chloride, lead tetraacetate).

We report here further applications of the cyanovinyl protecting groups which were first employed by Fisher[6] in, for example, the synthesis of 2,5-diformyl-3,4-dimethylpyrrole (**1a**), and later by Woodward[7] in the synthesis of chlorophyll. Similar use of these protecting groups has been made by Davies,[8] and by Badger[9] in an unsuccessful assault on porphyrin a.

Cyanovinyl derivatives are prepared from the Knoevenagel reaction of 2-formylpyrroles with malononitrile or esters of



1

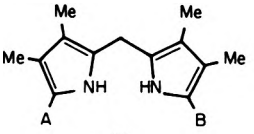
	A	B
a	OHC	CHO
b	H	$CH=C(CN)CO_2Me$
c	H	CHO
d	Me	$CH=C(CN)CO_2Me$
e	ClH_2C	$CH=C(CN)CO_2Me$
f	BrH_2C	$CH=C(CN)CO_2Me$
g	$MeCO_2CH_2$	$CH=C(CN)CO_2Me$
h	$MeOH_2C$	$CH=C(CN)CO_2Me$
i	Me	CO_2Et
j	Me	CHO
k	H	$CH=C(CN)_2$
l	Me	H
m	Me	$CH=\overset{+}{N}Me_2Cl^-$
n	Me	$CH=C(CN)_2$
o	ClH_2C	$CH=C(CN)_2$

† Dedicated to Professor H. H. Inhoffen on the anniversary of his 70th birthday.

cyanoacetic acid, in the presence of a basic catalyst, usually a primary or secondary amine. The reaction conditions required to generate the protected aldehyde vary with the substitution pattern of the pyrrole. Thus 2-formyl-5-pyrrole carboxylate esters tend to give quantitative yields in a few seconds, while trialkylpyrrole aldehydes and 2-formylpyrrole-3,5-dicarboxylate esters[10] require prolonged treatment especially when cyanoacetates rather than malononitrile are used. These compounds generally crystallize well and fluoresce in the solid state, under ultraviolet light, with yellow, orange, or greenish-yellow emission. They are usually higher melting and less soluble than the aldehydes from which they are derived. Indeed the choice as to which protecting group to use is in part dictated by solubility considerations: malononitrile gives the least soluble derivatives, and its use should be avoided in systems of inherently low solubility, such as derivatives of 3,4-dimethylpyrrole. In addition to conferring solubility the cyanoacrylates are also less deactivated toward electrophilic substitution than are the dicyanovinylpyrroles; for example, Fischer[6] was able to Gattermann-formylate 1b while **1k** under the same conditions gave only unchanged starting material.

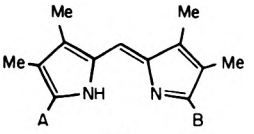
Cis–trans isomerization was observed with the cyanoacrylates, and while one configuration usually predominated the ratio of isomers varied as a series of transformations was effected. Regeneration of the aldehyde function was achieved by heating with strong aqueous caustic alkali; this limits the usefulness of these protecting groups to pyrroles bearing substituents which are base inert or else are reparable such as esters. Further possible limitations, as yet unexplored, would be that certain 2,2′-dipyrrylmethane-3-carboxylate esters, and their polypyrrolic homologues, are known to cyclize to dipyrrolopyridones[11] in alkali. In addition, acetic ester substituents might decarboxylate, under the strongly basic conditions, especially when adjacent to the protecting group.

Our interest in these protecting groups arose while seeking a satisfactory synthesis of the difficultly soluble 5,5′-diformyl-3,3′,4,4′-tetramethyl-2,2′-dipyrromethane (**2e**). Johnson et al.[12] had started with the readily available dipyrrylmethane diester **2a** and converted it via the unstable diacid



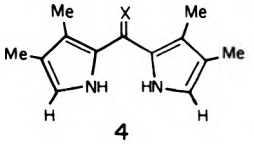
2

a A = B = CO_2Et
b A = B = CO_2H
c A = B = H
d A = B = $CH=\overset{+}{N}Me_2Cl^-$
e A = B = CHO
f A = B = $CH(OMe)_2$
g A = B = $CH=C(CN)CO_2Me$
h A = $CH=C(CN)_2$; B = $CH=C(CN)CO_2Me$



3

a A = B = Me (HBr)
b A = B = $CHBr_2$ (HBr)
c A = B = $CH(OMe)_2$



4

a X = S
b X = O

2b to the even less stable 5,5′-unsubstituted pyrromethane **2c**. Vilsmeier formylation with phosphorus oxychloride in dimethylformamide followed by incomplete hydrolysis gave a very unsatisfactory preparation of **2e**. An adaptation of MacDonald's[13] procedure, involving a tetrabromination of **3a** to give **3b**, followed by **2e** via **3c** and **2f**, proved unsatisfactory owing to incomplete bromination at the beginning. Clezy's[14] preparation, involving formylation with benzoyl chloride in dimethylformamide, on pure **2c** derived from dipyrryl ketone **4b** and dipyrrylthione **4a**, was not known to us at the time our work was in progress.

Our aim was to find a direct synthesis of the dipyrromethane dialdehyde **2e**, protected as the biscyanovinyl derivative **2g**, from monopyrrolic precursors. The protected intermediate **1d** was synthesized by traditional means, and reacted cleanly with 1 equiv of sulfuryl chloride, bromine, or lead tetraacetate to give the corresponding monosubstituted compounds **1e**, **1f**, and **1g** in good yield. The two halomethyl derivatives proved to be indefinitely stable to the atmosphere in the solid state, unlike their monoester pyrrole analogues, which rapidly deliquesced and decomposed under similar conditions. This stability was one of the many evidences of the strong deactivation engendered by the cyanovinyl substituent.

Solvolysis of any of the compounds **1e–g**, in aqueous acidic methanol, conditions which usually convert alkoxycarbonylpyrrolylmethyl carbonium ion sources to the symmetrical pyrromethane, gave in this case mostly the methoxymethyl derivative **1h**, with only traces of the dipyrromethane. This observation was consistent with the strongly electron-withdrawing cyanovinyl group increasing both the activation energy for carbonium ion formation, as well as for electrophilic attack on the pyrrolic nucleus, with the result that most of the pyrrylmethyl carbonium ion was trapped by solvent. The equivalent reaction of the 2-unsubstituted compound **1b** with formaldehyde gave back mostly unreacted starting material, with only traces of the dipyrromethane. Prolonged reaction times led to extensive decomposition.

It was then decided to attempt the synthesis in a nonnucleophilic solvent, to prevent the trapping of the intermediate carbonium ion and its diversion to compounds such as **1h**, and also to allow the use of more vigorous conditions by employing a soluble Lewis acid (Friedel–Crafts) catalyst.

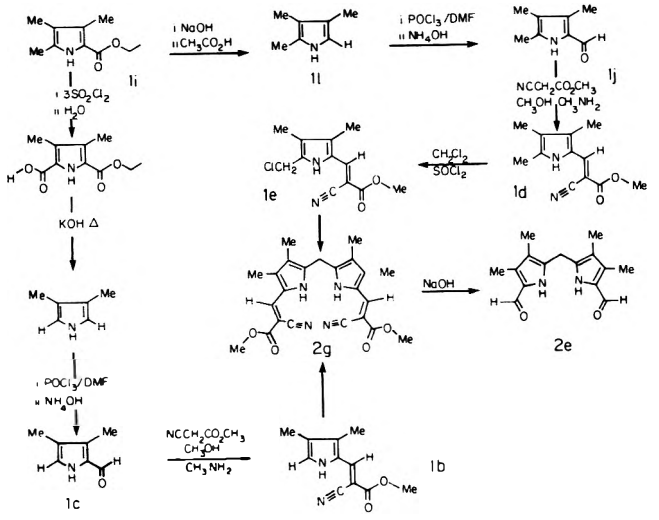
Chloromethylpyrrole **1e** and the 2-unsubstituted pyrrole 1b were dissolved in dry methylene chloride; no reaction ensued, even though under these conditions, pyrrole monoesters react spontaneously with evolution of hydrogen chloride. However, as soon as some anhydrous stannic chloride was added to the above solution (this being our first choice of catalyst; we have never needed to try anything else since), a deep green color set in accompanied by evolution of hydrogen chloride. Workup followed by crystallization gave a yield of greater than 90% of the desired product **2g**.

When dipyrromethane **2g** was subjected to alkaline hydrolysis, the solution, unlike that of monopyrrolic analogues, initially turned a deep green, due, we assume, to the abstraction of a proton from the methane bridge which would generate a fully conjugated delocalized anion. The color soon faded, as the desired dialdehyde **2e** precipitated out of solution in nearly pure form. The overall synthesis of **2e** is outlined in Scheme I.

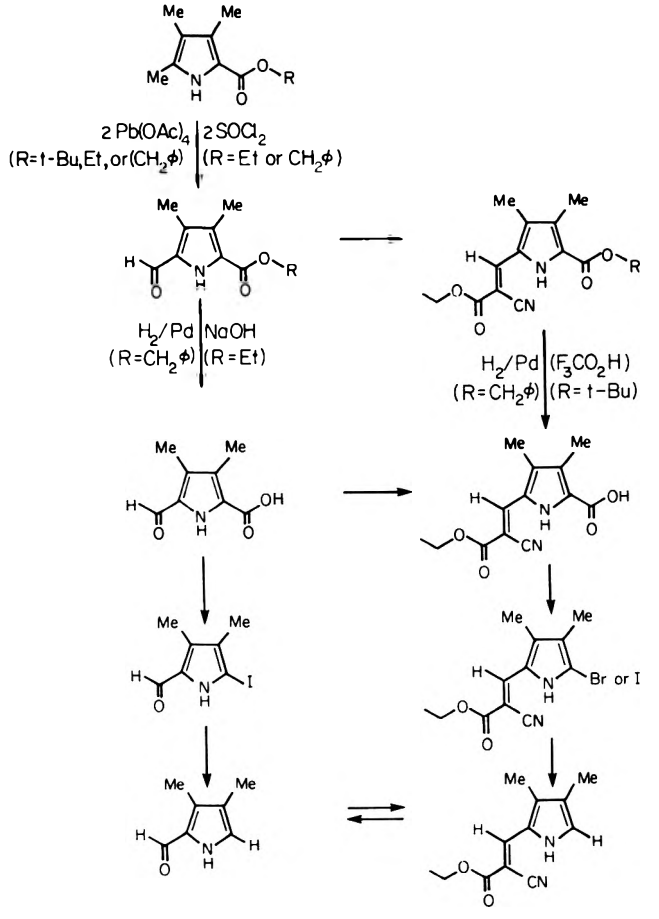
In the above synthesis the 2-unsubstituted pyrrole was prepared from 3,4-dimethylpyrrole. The sequence was both long and wasteful in that both α substituents of the starting material, 2-ethoxycarbonyl-3,4,5-trimethylpyrrole (**1i**), were removed, only to replace one of them at a later stage. In addition if this sequence were to be carried out on a pyrrole containing two different β substituents then an elaborate separation of isomers would be required.[15] A reaction sequence overcoming these limitations is outlined in Scheme II. This route required an ester function which could be removed under nonbasic conditions. Benzyl esters,[16] removable by catalytic hydrogenation, and *tert*-butyl esters,[17,18] removable with acid, have both found considerable use in pyrrole chemistry, and we can now add further testimony to their versatility.

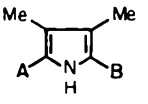
Benzyl esters of pyrrylcarboxylic acids are readily available, in high yield, from the base-catalyzed transesterification of

Scheme I



Scheme II





	A	B
a	Me	$CO_2CH_2\phi$
b	OHC	$CO_2CH_2\phi$
c	MeOCO(CN)C=CH	$CO_2CH_2\phi$
d	EtOCO(CN)C=CH	$CO_2CH_2\phi$
e	$(NC)_2C=CH$	$CO_2CH_2\phi$
f	Me	CO_2t-Bu
g	OHC	CO_2t-Bu
h	EtOCO(CN)C=CH	CO_2t-Bu
i	$(NC)_2C=CH$	CO_2t-Bu
j	EtOCO(CN)C=CH	CO_2H
k	EtOCO(CN)C=CH	Br
l	EtOCO(CN)C=CH	I
m	EtOCO(CN)C=CH	H
n	Me	CO_2CH_2–C$_6$H$_4$–OMe
o	OCH	CO_2CH_2–C$_6$H$_4$–OMe
p	$(NC)_2C=CH$	CO_2CH_2–C$_6$H$_4$–OMe
q	Me	$CO_2CH\phi_2$
r	OHC	$CO_2CH\phi_2$
s	$(NC)_2C=CH$	$CO_2CH\phi_2$
t	$(NC)_2C=CH$	CO_2H

the ethyl esters, whenever a direct Knorr synthesis of the benzyl esters is not available. Reaction of the pyrrole aldehyde **5b** with either the methyl or ethyl ester (it is important to use the same alcohol as the ester alkoxy group; otherwise partial transesterification, presumably via the intermediacy of cyanoketene, will occur under the reaction conditions) of cyanoacetic acid or with malononitrile gave products (**5c, d,** or **e**) so insoluble in the alcohols used as solvent for their preparation that the products were isolated in greater than 95% yield after a reaction time of only a few minutes. In fact, it proved convenient to scavenge mother liquors of the aldehyde with these nitriles to maximize yields in the preparation of the aldehyde. The benzyl esters thus obtained which are so poorly soluble in alcohols dissolve readily in tetrahydrofuran, and catalytic hydrogenation over palladized charcoal produced the required carboxylic acid. The protecting group resisted hydrogenation during the hydrogenolysis and only slowly reduced during prolonged periods of time. Attempted decarboxylative iodination of these acids in aqueous solution proceeded poorly as Badger[8] had already found. However, bromination in warm acetic acid afforded the corresponding α-bromopyrrole **5k** in good yield.

It then became apparent that the use of the corresponding *tert*-butyl esters might avoid some of the problems associated with the benzyl esters, namely the possible overreduction by hydrogen, and the insolubility of the product carboxylic acid. The required 5-formyl-2-*tert*-butoxycarbonylpyrroles had not been reported, but proved readily available via lead tetraacetate oxidation of the 5-methyl derivative. After protection in the usual manner the cyanovinyl derivatives were found to be rather more soluble that their benzyl analogues. It was hoped that a thermal route would be found to generate the α-free pyrrole directly from the *tert*-butyl esters, but all such attempts lead to dark tars. Neat trifluoroacetic acid dissolved the *tert*-butyl esters readily, and the carboxylic acid precipitated out on warming, but their thermal decarboxylations also failed. However, the reaction of an excess of bromine on the *tert*-butyl esters, in hot acetic acid, gave the bromopyrrole directly. Iodine chloride[19] under the same conditions gave only the carboxylic acids.

Since the by-product, isobutylene, interfered with the halogenation, a stepwise procedure was investigated. The *tert*-butyl ester (**5h** or **i**) was dissolved in a hot chlorocarbon followed by the addition of trifluoroacetic acid. Heating was continued until no further solid appeared, at which time the product was collected, by filtration, in greater than 90% yield.

The resulting carboxylic acids (**5j,t**) were lemon yellow crystalline solids, which were stable in air over prolonged periods. Further evidence of the deactivating nature of the cyanovinyl group was indicated by extreme reluctance of the carboxylic acids to undergo thermal decarboxylation; indeed a strong parent ion appeared in the mass spectrum.

The bromination of the free carboxylic acids proceeded in better overall yield than the direct reaction of the *tert*-butyl esters. Similarly iodine chloride, in the absence of isobutylene, reacted in hot acetic acid to give the iodopyrrole, but even in the presence of excess reagent the conversion was incomplete. It was found that the solubility of carboxylic acids, in acetic acid, was markedly improved by the addition of an excess of sodium acetate and acetic anhydride, when the addition of iodine chloride gave the iodopyrrole (**5l**) in high yield.

Hydrogenation over palladized carbon converted both the bromo- and iodopyrroles **5k** and **l** to the 2-unsubstituted pyrroles (**5m**) in high yield. Deprotection at this stage leads to 5-unsubstituted 2-formylpyrroles, of use in pyrromethene synthesis. Unfortunately, the reactions with *tert*-butyl esters are limited to those pyrroles which are readily available from *tert*-butyl acetoacetate. Otherwise one must use the benzyl esters, which are available directly from the Knorr reaction or transesterification, since *tert*-butyl esters are not available by direct transesterification.

An ester group was sought which would be available via a transesterification, and which could be removed with trifluoroacetic acid. Transesterifications were carried out with 2-ethoxycarbonyl-3,4,5-trimethylpyrrole (**1i**) using both *p*-anisyl and benzhydryl alcohols. The resulting esters (**5n,q**) were both oxidized cleanly to the aldehydes (**5o,r**), but their dicyanovinyl derivatives (**5p,s**) were unreactive toward trifluoroacetic acid.

A complete dipyrromethane dialdehyde synthesis was then carried out with the more soluble 3,4-diethylpyrroles, using the most deactivating dicyanovinyl protecting groups as outlined in Scheme III. The resulting tetraethylpyrromethane dialdehyde (**7f**) was also prepared via Clezy's method, and found to be identical in every respect. Only conversion of the benzyl ester (**6i**) to the bromopyrrole (**6k**) via the free acid (**6j**) proceeded in less than excellent yields almost certainly owing to overhydrogenation of the benzyl ester, and the routes outlined in Schemes I and II provide a convenient route, with obvious modifications, to both symmetrically and unsymmetrically substituted 5,5′-diformyldipyrromethanes.

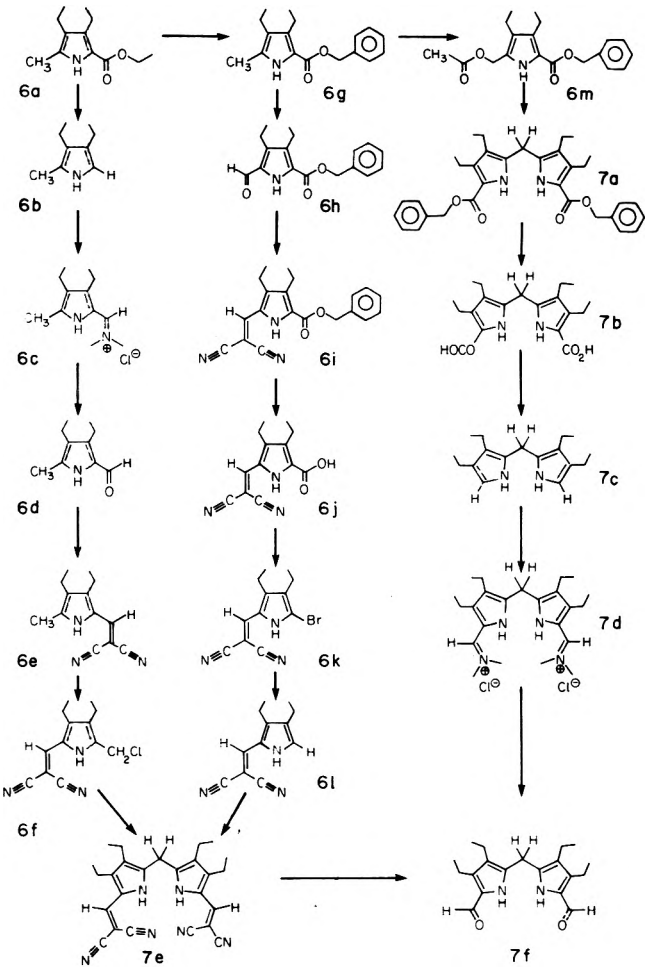
To show that an unsymmetrical pyrromethane was available from our reaction, and in order to assess the susceptibility of pyrromethane "rearrangement" under the reaction conditions, a pyrromethane bearing identical β substituents (methyl) but differing protecting groups was synthesized.

2-Formyl-3,4-5-trimethylpyrrole (**1j**) was protected with malononitrile, and the resulting Knoevenagel adduct (**1n**) chlorinated with sulfuryl chloride. The chloromethylpyrrole (**1o**) reacted with the same α-free dimethylpyrrolecyanoacrylate **1b** as above to give a high yield of the unsymmetrical pyrromethane **2h**. Finally it should be noted that the dicyanovinyl derivatives of 3,4-dimethylpyrrole-2-carboxylic esters can pose technical problems owing to their low solubility. This was particularly true of the free carboxylic acid (**5t**) which proved to be difficult to halogenate as it formed an insoluble adduct with its bromo- or iodopyrrole derivative which precipitated from the reaction mixture before halogenative decarboxylation could proceed to completion. Such problems did not arise when the more soluble 3-methyl-4-ethyl- or 3,4-diethylpyrrole analogues were used.

Experimental Section[20]

2-Formyl-3,4,5-trimethylpyrrole (1j).[21,22] **Method A.** 2-Ethoxycarbonyl-3,4,5-trimethylpyrrole (**1i**) was heated to boiling in a minimal volume of 95% ethanol on the steam bath, and a concentrated aqueous solution of sodium hydroxide (2 equiv) was added. The heating was continued until the mixture became completely water soluble (approximately 2 h), and then the alcohol was evaporated in vacuo. The residue was dissolved in water, neutralized with 1.95 equiv of acetic acid, and steam distilled until no more oily 2,3,4-trimethylpyrrole (**1l**) appeared in the condensate. The distillate was collected in ice water to minimize volatilization, and sodium bicarbonate was added as a preservative.

Scheme III



The 2,3,4-trimethylpyrrole (**1l**), a compound of characteristic benzene odor, solidified on cooling, with entrainment of water; it was dried, in methylene chloride solution, over anhydrous potassium carbonate. The solvent was removed, and the pyrrole was diluted with several volumes of dry *N,N*-dimethylformamide (DMF).

Phosphorus oxychloride (1 ml/g of the theoretical is a convenient excess) was added dropwise to three volumes of ice-cooled DMF. To this, with continued ice cooling, was slowly added the pyrrole solution. The mixture warmed up, became dark red, and eventually became viscous.

After several hours, the mixture was cautiously poured onto crushed ice and water (2 l./mol). Anhydrous sodium carbonate was added slowly until the solution remained only slightly acid (pH 5–6). The solution was then filtered through Celite to remove the dark tars, and the filtrates were made alkaline with aqueous ammonia and heated on the steam bath until the product had recrystallized in coarse form.

The crystals were washed with water and allowed to dry. Their color varied from orange to dark chocolate brown, but the material was suitable for subsequent reactions without further purification. The overall yield was variable; a 1-mol reaction gave 56%.

A purer sample was prepared by several crystallizations from aqueous methanol, to give light tan, elongated plates: mp 146.5–147.5 °C (lit.[21] 147 °C); ^{1}H NMR 1.90 (s, 3 H), 2.23 (s, 6 H), 9.47 (s, 1 H), 10.83 ppm (bs, 1 H); ir 3200 (NH), 1620 cm^{-1} (C=O).

Method B. 2-*tert*-Butoxycarbonyl-3,4,5-trimethylpyrrole[23] (**5f**, 41.8 g, 0.2 mol) was heated to boiling in *N,N*-dimethylformamide (100 ml). Benzoyl chloride (43 ml, 1.5 ml/g of theory, 80% excess) in DMF

(100 ml) was added over a 2-min period, and the heating was continued for 10 min. The mixture evolved gas, and became very dark.

The imine salt (**1m**) crystallized out when the mixture was allowed to cool for 2 h. The filtered solids were rinsed with DMF, and then diethyl ether, which caused further product, also recovered, to crystallize from the filtrates. Yield of crude salts: first crop, 32.5 g; second crop, 8.3 g.

The crude salts were dissolved in water (300 ml), and filtered through Celite. Aqueous ammonia (30 ml, concentrated) was added to the dark orange-brown filtrates, and the mixture was heated until the product (17.5 g, 64%) recrystallized in granular form.

2-(2-Cyano-2-methoxycarbonylvinyl)-3,4,5-trimethylpyrrole (1d). 2-Formyl-3,4,5-trimethylpyrrole (**1j**, 27.4 g, 0.2 mol), methyl cyanoacetate (40 g, 0.404 mol), methanol (200 ml), and diethylamine (2 ml) were taken down to dryness on the steam bath. Benzene (200 ml) and more diethylamine (2 ml) were added to the residue, and the heating was continued until no more water was observed to be azeotroping with the benzene. On cooling, spectacular orange-red crystals were deposited. The mother liquors were evaporated down to an oil, from which additional solids were recovered by washing with hexane, and then 50% (v/v) aqueous methanol.

The combined solids were dissolved in methylene chloride, filtered, and crystallized from methanol. The yield of beautiful, large chunky crystals was 38.1 g (87.5%); an additional 8.5% could be recovered from the mother liquors. The compound readily entrains minor amounts of colored by-products, so that the color varies from yellow, when pure, to orange-red, with a blue reflex. An analytical sample was recrystallized from methylene chloride–methanol: mp 156.0–157.5 °C; ^{1}H NMR 1.93 (s, 3 H), 2.13 (s, 3 H), 2.29 (s, 3 H), 3.83 (s, 3 H), 7.87 (s, 1 H), 9.54 ppm (bs, 1 H); ir 3300 (NH), 2200 (C≡N), 1710 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H. 6.47; N, 12.84. Found: C, 65.87; H, 6.42; N, 12.93.

5-Chloromethyl-2-(2-cyano-2-methoxycarbonylvinyl)-3,4-dimethylpyrrole (1e). 2-(2-Cyano-2-methoxycarbonylvinyl)-3,4,5-trimethylpyrrole (**1d**, 6.54 g, 0.03 mol), dissolved and filtered in methylene chloride (60 ml), was stirred on a magnetic stirrer/hot plate in an Erlenmeyer flask, and treated dropwise with a solution of sulfuryl chloride (4.25 g, 0.031 mol) in methylene chloride (6 ml), over a 3-min period, at room temperature. Little color change occurred during the addition. The solvent was carefully boiled away and replaced near the end with diethyl ether, as the product crystallized. The yield of lemon-yellow needles was 6.1 g (80.8%). An analytical sample was recrystallized from methylene chloride–diethyl ether: mp 165–168 °C dec; ^{1}H NMR 2.03 (s, 3 H), 2.18 (s, 3 H), 3.87 (s, 3 H), 4.62 (s, 2 H), 7.98 (s, 1 H), 9.73 ppm (bs, 1 H); ir 3270 (NH), 2210 (C≡N), 1710 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{13}ClN_2O_2$: C, 57.04; H, 5.19; Cl, 14.03; N, 11.09. Found: C, 56.97; H, 5.14; Cl, 14.29; N, 11.15.

5-Bromomethyl-2-(2-cyano-2-methoxycarbonylvinyl)-3,4-dimethylpyrrole (1f). 2-(2-Cyano-2-methoxycarbonylvinyl)-3,4,5-trimethylpyrrole (**1d**, 4.36 g, 0.02 mol) was dissolved in methylene chloride (50 ml) and anhydrous diethyl ether (200 ml) was added, followed by rapid dropwise addition of a solution of bromine (3.4 g, 0.021 mol) in methylene chloride (20 ml). The color darkened from yellow to brown. Left standing overnight, protected from moisture, the solution deposited greenish-yellow flakes of product, which were filtered off and washed with ether and then ligroin, yield 3.72 g (62.6%). An analytical sample was recrystallized from methylene chloride, filtered, and washed with hexane. The sample darkened progressively above 150 °C and melted at 175–179 °C dec: ^{1}H NMR 2.04 (s, 3 H), 2.17 (s, 3 H), 3.88 (s, 3 H), 4.50 (s, 2 H), 7.99 (s, 1 H), 9.62 ppm (bs, 1 H); ir 3280 (NH), 2210 (C≡N), 1720 (C=O), 1590 cm^{-1} (C=C).

Anal. Calcd for $C_{12}H_{13}BrN_2O_2$: C, 48.50; H, 4.41; Br, 26.89; N, 9.43. Found: C, 48.51; H, 4.43; Br, 27.09; N, 9.37.

5,5′-Bis(2-cyano-2-methoxycarbonylvinyl)-3,3′,4,4′-tetramethyl-2,2′-dipyrromethane (2g). 2-(2-Cyano-2-methoxycarbonylvinyl)-3,4-dimethylpyrrole[6] (**1b**, 2.04 g, 0.01 mol) and 5-chloromethyl-2-(2-cyano-2-methoxycarbonylvinyl)-3,4-dimethylpyrrole (**1e**, 2.52 g, 0.01 mol) were dissolved in dry methylene chloride (50 ml). Anhydrous stannic chloride (3 g) in methylene chloride (10 ml) was then added, causing an immediate color change from light orange to dark green. After 1 h at room temperature the catalyst was quenched by addition of concentrated hydrochloric acid, followed by water. The organic phase was rinsed with water, then dried over anhydrous potassium carbonate. The resulting solution was filtered and taken down to small volume on the steam bath. The hot solution was diluted all at once with hexane (50 ml), causing the product to precipitate out after a brief induction period. Most of the dark by-products remained in solution. The solids were collected and washed with hexane, crude yield 3.78 g (90%). The solids were redissolved in methylene chloride and reprecipitated as before, to give 3.48 g (82.9%) of clean, lemon-yellow, fluffy, microcrystalline product. A repetition of the synthesis gave a yield of 3.65 g (86.9%) after recrystallization. An analytical sample was prepared by recrystallization first from methanol and then methylene chloride–methanol: mp 214–221 °C dec; ^{1}H NMR 2.01 (s, 6 H), 2.16 (s, 6 H), 3.83 (s, 6 H, a shoulder appeared on this singlet due presumably to cis–trans isomerization), 4.04 (s, 2 H), 7.93 (s, 2 H), 9.48 ppm (bs, 2 H); ir 3400 (NH), 2200 (C≡N), 1710 (C=O), 1590, 1540 cm^{-1} (C=C); mass spectrum M$^+$ *m/e* 420 (calcd = obsd).

Anal. Calcd for $C_{23}H_{24}N_4O_4$: C, 65.70; H, 5.75; N, 13.33. Found: C, 65.73; H, 5.77; N, 13.61.

5,5′-Diformyl-3,3′,4,4′-tetramethyl-2,2′-dipyrromethane[12,14] (2e). 5,5′-Bis(2-cyano-2-methoxycarbonylvinyl)-3,3′,4,4′-tetramethyl-2,2′-dipyrromethane (**2g**, 1.01 g, 0.0024 mol) was suspended in boiling methanol (100 ml). Potassium hydroxide (10.1 g) in water (20 ml) was added; the solid dissolved with the formation of a dark green color. The green color soon faded, and the methanol was boiled off. The heating was continued on the steam bath for several hours, and a light tan sludge eventually appeared. The extremely insoluble product was periodically filtered off, and the filtrates reheated. The yield of crude, crystalline, light tan material was 403 mg (65%): mp 295–298 °C dec (lit.[14] 293–297 °C); mass spectrum M$^+$ *m/e* 258 (calcd = obsd).

2-Benzyloxycarbonyl-3,4,5-trimethylpyrrole[25] (5a). Method A. Sodium metal (~6 g) was dissolved, under argon, in anhydrous benzyl alcohol (500 ml). 2-Ethoxycarbonyl-3,4,5-trimethylpyrrole (**1i**, 200 g, 1.105 mol) was then added, and the mixture was heated in an oil bath held at 150 °C, under aspirator vacuum, for at least 3 h. On cooling to room temperature overnight, the product crystallized out of the exceedingly viscous solution as a mass of interlocking needles. The mixture was mashed up and slurried with 50% (v/v) aqueous methanol containing enough acetic acid to neutralize the sodium. The product could then be filtered readily, to give nearly colorless, shiny needles, which were rinsed with aqueous methanol.

In order to remove the water the moist filter cake was dissolved in methylene chloride and the organic phase was filtered and boiled down, as hot hexane was added. The product crystallized from the hot solution as snow-white needles, with yields in the range of 200–230 g (74.5–85.5%), mp 117–117.5 °C (lit.[24] 118 °C).

Method B.[25] 2-Benzyloxycarbonyl-3,4,5-trimethylpyrrole (5a) (Direct Knorr Synthesis). Benzyl acetoacetate (1536 g, 8 mol) in acetic acid (1500 ml) was nitrosated with a solution of sodium nitrite (552 g, 8 mol) in water (650 ml). The resulting solution of benzyl oximinoacetoacetate was added, along with a slurry of zinc dust (1600 g, 24.2 mol) in water, to a vigorously stirred solution of 3-methyl-2,4-pentanedione[25] (912 g, 8 mol) in acetic acid (2000 ml), in a 12-l. flask over a 2-h period. More acetic acid (1650 ml) was added as the reaction progressed.

The solution was decanted from the residual zinc and diluted slowly with water to precipitate the product in easily filtered form. After filtration and washing with water, the solids were dissolved in methylene chloride. The organic phase was gravity filtered to remove any remaining zinc, and the methylene chloride was displaced with hexane, from which the product readily crystallized. The pyrrole was collected as several crops, all of which were recrystallized from methylene chloride–(hexane or methanol), to give 866 g (44.5%): mp 116.5–117.5 °C; ^{1}H NMR 1.86 (s, 3 H), 2.08 (s, 3 H), 2.25 (s, 3 H), 5.26 (s, 2 H), 7.29 (s, 5 H), 9.43 ppm (bs, 1 H); ir 3280 (NH), 1650 cm^{-1} (C=O).

2-Benzyloxycarbonyl-5-formyl-3,4-dimethylpyrrole[26] (5b). 2-Benzyloxycarbonyl-3,4,5-trimethylpyrrole (**5a**, 121.5 g, 0.5 mol) was dissolved in acetic acid (500 ml, glacial), and lead tetraacetate (480 g of moist commercial product, 1 mol = 443 g) was added, over a 0.5-h period, as a slurry in acetic acid (300 ml). The first half of the reagent reacted with considerable exotherm, the remainder more sluggishly, and the temperature rose to 78 °C. The mixture was then heated on the steam bath for 1 h, after which the Pb(IV) test, with water, was negative.

Water (500 ml) was added slowly to the hot solution to hydrolyze the diacetate, and the mixture was seeded. After crystallization had set in, the suspension was further diluted with water (2500 ml). The filtered and water-washed solids were dissolved in methylene chloride, and the solution was filtered before being boiled down to a volume of 300 ml and diluted with hexane (500 ml). After a recrystallization from the same solvents, the light tan granular first crop weighed 68.87 g (53.6%). Subsequent crops amounted to 26.34 g (20.5%) for a total yield of 74.1%: mp 119.0–119.5 °C (lit.[26] 119–120 °C); ^{1}H NMR 2.25 (s, 6 H), 5.30 (s, 2 H), 7.34 (s, 5 H), 9.70 (s, 1 H), 9.90 ppm (bs, 1 H); ir 3290 (NH), 1680, 1655 cm^{-1} (C=O).

2-Benzyloxycarbonyl-5-(2-cyano-2-methoxycarbonylvin-

yl)-3,4-dimethylpyrrole (5c). 2-Benzyloxycarbonyl-5-formyl-3,4-dimethylpyrrole (**5b**, 1.35 g, 5.25 mmol) and methyl cyanoacetate (1.0 g, an excess) were heated to boiling in methanol (25 ml). Acetic acid (1 drop) and alcoholic methylamine (several drops) were then added. The product soon crystallized out, and the mixture was allowed to cool before filtration. The brilliant lemon-yellow, fluffy solids were rinsed with methanol, then hexane. The yield was 1.65 g (93%). An analytical sample was recrystallized from methylene chloride–methanol: mp 143.0–145.5 °C, and on remelting 144.0–145.0 °C; ^{1}H NMR 2.13 (s, 3 H), 2.27 (s, 3 H), 3.87 (s, 3 H), 5.35 (s, 2 H), 7.37 (s, 5 H), 7.98 (s, 1 H), 10.15 ppm (bs, 1 H); ir 3400 (NH), 2210 (C≡N), 1730, 1715 (C=O), 1600 cm^{-1} (C=C).

Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.35; H, 5.36; N, 8.27.

2-Benzyloxycarbonyl-5-(2-cyano-2-ethoxycarbonylvinyl)-3,4-dimethylpyrrole (5d) (with R. A. Sawka). 2-Benzyloxycarbonyl-5-formyl-3,4-dimethylpyrrole (**5b**, 1.35 g, 5.25 mmol) was dissolved in hot absolute ethanol (25 ml). Ethyl cyanoacetate (1.0 g, an excess) was added, followed by 1 drop of acetic acid and 5 drops of methylamine in ethanol. After a few seconds a sulfur-yellow flocculent precipitate began to separate and then the mixture became very thick. After cooling to room temperature the product was collected by filtration, washed with a little anhydrous ethanol and then hexane, and air dried to give 1.80 g (97%). An analytical sample was recrystallized from methylene chloride–ethanol: mp 167.5–168 °C; ^{1}H NMR 1.36 (t, 3 H, J = 7 Hz), 2.16 (s, 3 H), 2.28 (s, 3 H), 4.34 (q, 2 H, J = 7 Hz), 5.36 (2 H, s), 7.37 (5 H, m), 8.00 (1 H, s), 10.20 ppm 1 H, bs); ir 3430 (NH), 2205 (C≡N), 1709 cm^{-1} (b, C=O).

Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.23; H, 5.79; N, 8.11.

2-Carboxy-5-(2-cyano-2-ethoxycarbonylvinyl)-3,4-dimethylpyrrole (5j). Method A. 2-*tert*-Butoxycarbonyl-5-(2-cyano-2-ethoxycarbonylvinyl)-3,4-dimethylpyrrole (**5h**, 29.4 g, 0.0927 mol) was heated to boiling in 1,2-dichloroethane (100 ml) on a steam bath, and filtered, if needed. Trifluoroacetic acid (10 ml) was added, and the heating was continued for 80 min. After 5 min, crystalline product began to appear, and the mixture eventually became thick, as the color of the solution gradually deepened to a bright permanganate purple. After 45 min, additional TFA (10 ml) was added; more solvent was added as needed.

After cooling, the product was filtered off and rinsed with dichloroethane, then hexane. The yield of brilliant lemon-yellow crystals was 23.2 g (95.5%). An analytical sample was recrystallized from tetrahydrofuran—absolute ethanol to give clusters of chunky, transparent, yellow blades: mp 212–213 °C dec; ir 3400 (NH), 3150–2400 (CO_2H), 2215 (C≡N), 1730, 1670 (C=O), 1590 cm^{-1} N (C=C).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.38; H, 5.43; N, 10.68.

Method B. 2-Benzyloxycarbonyl-5-(2-cyano-2-ethoxycarbonylvinyl)pyrrole (**5d**, 3.40 g, 0.01 mol) and 10% palladium on charcoal (0.24 g) was added to tetrahydrofuran (100 ml) and reduced under 1 atm with hydrogen. The solution was filtered through Celite, and the filtrate taken down to dryness to give 2.5 g (95%) of product, mp 211–212 °C dec.

2-*tert*-Butoxycarbonyl-3,4,5-trimethylpyrrole[23] (5f). To a solution of *tert*-butyl acetoacetate (632 g, 4 mol) in acetic acid (1000 ml), stirred magnetically and immersed in an ice-filled polyethylene bucket, was added a solution of sodium nitrite (276 g, 4 mol) in water (350 ml), dropwise, so as to maintain a reaction temperature below 40 °C.

The resulting solution of *tert*-butyl oximinoacetoacetate was added slowly to a rapidly stirred solution of 3-methyl-2,4-pentanedione (457 g, 4 mol) in acetic acid (1000 ml), concurrently with a slurry of zinc dust (800 g, 12.3 mol) in a minimal volume of water. The addition of reactants required approximately 135 min, and the temperature reached 104 °C.

The resulting solution was decanted from the unreacted zinc and diluted with an equal volume of water. The product was filtered from the still-warm solution and rinsed with much water. The filter cake was slurried with dilute aqueous ammonia (50 ml of concentrated NH_4OH in 2500 ml of slurry), which served as a preservative from atmospheric oxidation or discoloration until the workup could be resumed.

The product was refiltered, and the filter cake dissolved in methylene chloride and filtered. The organic phase was isolated, refiltered, and reduced in volume as the solvent was replaced by methanol.

The product formed transparent, colorless prisms: first crop, 359.2 g (43%); second crop, 38.05 g (4.6%). Recrystallization of the combined crops gave crops of 332.2 (39.74%) and 52.7 g (6.31%), for a total bottled yield of 46.05%, mp 138.5 °C (lit.[23] 137–138 °C). The ability of this compound to form colorless crystals from the blackest of solutions is quite remarkable; ^{1}H NMR 1.55 (s, 9 H), 1.88 (s, 3 H), 2.17 (s, 3 H), 2.22 (s, 3 H), 9.57 ppm (bs, 1 H); ir 3300 (NH), 1660 cm^{-1} (C=O).

2-*tert*-Butoxycarbonyl-5-formyl-3,4-dimethylpyrrole (5g). 2-*tert*-Butoxycarbonyl-3,4,5-trimethylpyrrole (**5f**, 104.5 g, 0.5 mol) in glacial acetic acid (500 ml) was treated, in several portions, with lead tetraacetate (497 g of commercial material, 1.1 mol). The mixture was swirled after each addition of oxidant; the first equivalent reacted especially exothermically and the temperature reached approximately 60 °C. The addition of the lead tetraacetate required only 20 min; some acetic acid (100 ml) was used to rinse it in. The mixture was then heated on the steam bath for 20–30 min, until the temperature reached 80 °C. Ethylene glycol (~10 ml) was added to destroy any lead dioxide present (dark-colored lead tetraacetate was often used with eminently satisfactory results, provided that the appearance—crystallinity, etc.—was otherwise normal).

The mixture was then slowly diluted with water (3000 ml) and seeded. The resulting solids wgre filtered off, washed with water, and dissolved in methylene chloride. The organic phase was gravity filtered, and the solvent was displaced with hexane on the steam bath. When the volume had been reduced to 250 ml, the solution was allowed to cool and seeded. The coarse, tan crystals were rinsed with hexane, yield 71.5 g (64.1%).

The mother liquors were scavenged with malononitrile, to give a 16.8% yield of the dicyanovinylpyrrole, increasing the total isolable conversion to aldehyde to 80.9%. An analytical sample was crystallized from methylene chloride–hexane: mp 99.8–100.9 °C; ^{1}H NMR 1.59 (s, 9 H), 2.22 (s, 3 H), 2.25 (s, 3 H), 9.75 (s, 1 H), 10.10 ppm (bs, 1 H); ir 3300 (NH), 1680, 1660 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{17}NO_3$:C, 64.55; H, 7.68; N, 6.27. Found: C, 64.66; H, 7.73; N, 6.27.

2-*tert*-Butoxycarbonyl-5-(2-cyano-2-ethoxycarbonylvinyl)-3,4-dimethylpyrrole (5h). 2-*tert*-Butoxycarbonyl-5-formyl-3,4-dimethylpyrrole (**5g**, 44.6 g, 0.2 mol) and ethyl cyanoacetate (30 g, 32.5% excess) were warmed on the steam bath in ethanol (100 ml, absolute), and methylamine catalyst (2 ml) was added to the hot solution. After a few minutes of heating, the product crystallized out peacefully, and the mixture became thick with solid. After chilling on ice, the product was filtered and rinsed with cold ethanol (60 ml, absolute), then hexane. The first crop weighed 55.8 g (87.8%). An additional 2.86 g (4.5%) was isolated from the mother liquors, for a total yield of 92.3%. An analytical sample was recrystallized from methylene chloride–95% ethanol: mp 172.0–174.0 °C; ^{1}H NMR 1.38 (t, 3 H, J = 7 Hz), 1.61 (s, 9 H), 2.16 (s, 3 H), 2.25 (s, 3 H), 4.33 (q, 2 H, J = 7 Hz), 7.97 (s, 1 H), 10.14 ppm (bs, 1 H); ir 3400 (NH), 2210 (C≡N), 1710 (C=O), 1600 cm^{-1} (C=C).

Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.21; H, 6.94; N, 8.75.

5-Bromo-2-(2-cyano-2-ethoxycarbonyl)-3,4-dimethylpyrrole (5k). 5-Carboxy-2-(2-cyano-2-ethoxycarbonylvinyl)-3,4-dimethylpyrrole (**5j**, 5.26 g, 0.02 mol) and anhydrous sodium acetate (5.0 g) were warmed to 70 °C in glacial acetic acid (50 ml). A solution of bromine (3.86 g, 0.024 mol) in acetic acid (10 ml) was added dropwise over a 5-min period. The bromine color was discharged as rapidly as it entered the reaction mixture (including the excess bromine which presumably reacted with the sodium acetate). The solution remained a clean brilliant lemon-yellow throughout the reaction, which is not the case if the sodium acetate be absent.

The solution was diluted slowly with water (400 ml), causing precipitation of product, which was filtered off and washed with water. The filter cake was then washed with dilute aqueous ammonia (1:4), which was probably a mistake, as the yellow solids temporarily turned green, and the washings became yellow. The washings remained yellow as long as the ammonia was used to rinse the solids, so that it is likely that the product was being attacked, rather than purified by removal of starting material. What was left of the filter cake was dissolved in methylene chloride, and crystallized from methanol (no transesterification was noted) after removal of any aqueous phase, and filtration, yield 3.51 g (59.1%). An analytical sample was recrystallized from methylene chloride–absolute ethanol to give transparent, brilliant orange-yellow crystals: mp 139.5–141.5 °C; ^{1}H NMR 1.37 (t, 3 H, J = 7.5 Hz), 1.98 (s, 3 H), 2.18 (s, 3 H), 4.32 (q, 2 H, J = 7.5 Hz), 7.85 (s, 1 H), 9.59 ppm (bs, 1 H); ir 3250 (NH), 2210 (C≡N), 1710 (C=O), 1580 cm^{-1} (C=C).

Anal. Calcd for $C_{12}H_{13}BrN_2O_2$: C, 48.50; H, 4.41; Br, 26.89; N, 9.43. Found: C, 48.35; H, 4.46; Br, 26.97; N, 9.36.

2-(2-Cyano-2-ethoxycarbonylvinyl)-5-iodo-3,4-dimethylpyrrole (5l). 5-Carboxy-2-(2-cyano-2-ethoxycarbonylvinyl)-3,4-dimethylpyrrole (**5j**, 13.1 g, 0.05 mol), anhydrous sodium acetate (14 g, 0.17 mol), acetic anhydride (10 ml), and acetic acid (100 ml) were heated on a stirrer–hot plate until the solution became homogeneous (near 105 °C). Addition of a solution of iodine chloride (16.25 g, 0.10

mol) in glacial acid (50 ml) was then started immediately, and completed within 6 min, haste being necessary as the pyrrole solution is unstable at elevated temperatures. The solution was boiled for 5 min, until the purple vapors of free iodine had gone. Water (700 ml) was then slowly added, causing oiling and then crystallization of product.

The solids were filtered off, washed extensively with water, and then dissolved in methylene chloride. The organic phase was filtered, and the solvent displaced with methanol (no transesterification occurred) on the stirrer-hot plate. The solution was concentrated until it became thick with solids at the boiling point. The product was filtered off, after cooling, and washed with a minimum volume of methanol, then hexane. The yield of olive-green, fluffy granules was 13.68 g (79.5%). An analytical sample was recrystallized from methylene chloride charcoal, and then from 95% ethanol: mp 125.0–151 °C (a small amount of solid remained until 151 °C); ^{1}H NMR 1.38 (t, 3 H, J = 7.5 Hz), 1.98 (s, 3 H), 2.19 (s, 3 H), 4.33 (q, 2 H, J = 7.5 Hz), 7.80 (s, 1 H), 9.60 ppm (bs. 1 H); ir 3400 (NH), 2200 (C≡N), 1720, 1675 sh (C=O), 1580 cm^{-1} (C=C).

Anal. Calcd for $C_{12}H_{13}IN_2O_2$: C, 41.88; H, 3.81; I, 36.87; N, 8.14. Found: C, 41.92; H, 3.93; I, 36.89; N, 8.00.

2-(2-Cyano-2-ethoxycarbonylvinyl)-3,4-dimethylpyrrole[6] **(5m).** 2-(2-Cyano-2-ethoxycarbonylvinyl)-5-iodo-3,4-dimethylpyrrole (**5l**, 3.5 g, 0.1 mol), anhydrous sodium acetate (3 g), and 10% palladium on charcoal (0.4 g) were hydrogenated overnight in tetrahydrofuran (100 ml) at room temperature and pressure. The mixture was filtered through Celite and the filtrate taken down to dryness. The residue was crystallized from methanol to give 2.0 g (92%) of bright yellow needles, mp 194–195 °C (lit.[6] 190–191 °C).

2-Benzyloxycarbonyl-3,4-diethyl-5-methylpyrrole (6g). 2-Ethoxycarbonyl-3,4-diethyl-5-methylpyrrole[27] (**6a**, 86.5 g, 0.414 mol) and benzyl alcohol (160 ml) were heated to boiling on a hot plate in an Erlenmeyer flask to drive off any water present. Several milliliters of a stock solution of sodium (8 g) in benzyl alcohol (200 ml) were then added, causing immediate vigorous evolution of ethanol vapors and a considerable temperature drop. A little more catalyst was added when the reaction had subsided, and the heating was resumed until the boiling point of benzyl alcohol, 209 °C, was again reached. The hot reaction mixture was then *immediately* quenched in a solution of acetic acid (10 ml) in methanol (500 ml). The color of the reaction mixture had remained light throughout, and only about 15 min had elapsed from initial addition of the catalyst until the quenching.

Aqueous methanol (1000 ml, 50% v/v) was then added, followed by water (500 ml). The product oiled out at first, but soon crystallized, the benzyl alcohol remaining in solution. On standing, the initially tan solids typically acquired a reddish tinge. The solids were rinsed with 40% methanol–water, then with water, before being dissolved in methanol, filtered, and recrystallized from a volume of 500 ml. A first crop of 77 g and a second crop of 13.1 g or 90.1 g total (80.3%) were recovered. An analytical sample was recrystallized from methanol: mp 72.0–73.0 °C; ^{1}H NMR 1.03 (t, 3 H, J = 7.5 Hz), 1.09 (t, 3 H, J = 7.5 Hz), 2.12 (s, 3 H), 2.34 (q, 2 H, J = 7.5 Hz), 2.52 (q, 2 H, J = 7.5 Hz), 5.24 (s, 2 H), 7.23 (s, 5 H), 10.00 (bs, 1 H).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.11; H, 7.74; N, 5.18.

2-*p*-Methoxybenzyloxycarbonyl-3,4,5-trimethylpyrrole (5n). 2-Ethoxycarbonyl-3,4,5-trimethylpyrrole (**1i**, 45.1 g, 0.25 mol) and *p*-anisyl alcohol (40.1 g, 0.29 mol) were heated together on a hot plate in an Erlenmeyer flask. Sodium metal (0.62 g) was warmed in *p*-anisyl alcohol (10 ml), under nitrogen; only part dissolved.

When the temperature of the pyrrole solution had reached 216 °C the sodium alkoxide solution was added, causing considerable evolution of gas (ethanol). The temperature fell to 205 °C, but was raised to 232 °C before the reaction mixture was quenched in a mixture of methanol (300 ml), water (200 ml), and acetic acid (10 ml).

The resulting oily droplets soon solidified. The product was filtered off and rinsed with 60% aqueous methanol (90 ml, v/v). The washed solids were then dissolved in boiling methanol (150 ml), filtered hot, and allowed to crystallize, forming a thick mass of fluffy balls, in a dark red solution. These solids were recrystallized from methanol, giving light cream-colored flakes, 18.2 g (27%). An analytical sample was recrystallized from methanol: mp 106.5–108.0 °C; ^{1}H NMR 1.87 (s, 3 H), 2.11 (s, 3 H), 2.25 (s, 3 H), 3.68 (s, 3 H), 5.22 (s, 2 H), 6.82 and 7.30 (AB q, 4 H, J = 9 Hz), 9.57 ppm (bs, 1 H); ir 3300 (NH), 1650 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.09; H, 7.12; N, 5.09.

2-Diphenylmethoxycarbonyl-3,4,5-trimethylpyrrole (5q). Benzhydrol (30 g, 0.163 mol) was melted under argon, and sodium metal (0.75 g, 0.0326 g-atom) was added, dissolving rapidly above 140 °C. When the sodium had dissolved, 2-ethoxycarbonyl-3,4,5-trimethylpyrrole (**1i**, 18.1 g, 0.1 mol) was added, and the mixture was heated until the temperature reached 190 °C, care being taken to avoid foaming, as the ethanol was evolved, particularly above 150 °C. The reaction mixture was quenched immediately from 190 °C by pouring it into a mixture of methanol (200 ml), water (40 ml), and acetic acid (10 ml). The product soon crystallized, and after standing for 30 min, it was filtered off and washed with 80% (v/v) aqueous methanol. The solids were dissolved in methylene chloride, filtered, and recrystallized from methanol. The yield, as fluffy needles, was 12.28 g (38.5%). An analytical sample was recrystallized from methanol: mp 155.5–156.3 °C; ^{1}H NMR 1.87 (s, 3 H), 2.00 (s, 3 H), 2.34 (s, 3 H), 7.1–7.45 (m, 11 H), 9.33 ppm (bs, 1 H).

Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.71; H, 6.65; N, 4.34.

5-Formyl-2-*p*-methoxybenzyloxycarbonyl-3,4-dimethylpyrrole (5o). 2-*p*-Methoxybenzyloxycarbonyl-3,4,5-trimethylpyrrole (**5n**, 5.51 g, 0.02 mol) in glacial acetic acid (20 ml) was treated with one portion of lead tetraacetate (19.6 g, 0.044 mol). The mixture warmed up, and then set solid due to the formation of monoacetoxymethylpyrrole. The mixture was then heated on the steam bath until the solids had redissolved, and the Pb(IV) test had become negative. Water was added to the hot solution until it became just opalescent. The solution was then chilled on ice and seeded, being further diluted with water (100 ml in toto) after crystallization had started.

The solids were filtered, washed with water, and recrystallized wet from methanol. The product was redissolved in methanol, filtered, and recrystallized, to give light tan flakes, 3.28 g (57.1%). An analytical sample was recrystallized from methanol: mp 110.0–110.5 °C; ^{1}H NMR 2.23 (s, 6 H), 3.77 (s, 3 H), 5.23 (s, 2 H), 6.86 and 7.32 (AB q, 4 H, J = 8.7 Hz), 9.70 (s, 1 H), 9.98 ppm (bs, 1 H); ir 3280 (NH), 1690, 1650 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.64; H, 5.97; N, 4.88.

2-Diphenylmethoxycarbonyl-5-formyl-3,4-dimethylpyrrole (5r). 2-Diphenylmethoxycarbonyl-3,4,5-trimethylpyrrole (**5q**, 6.38 g, 0.02 mol) in glacial acetic acid (50 ml) was treated with one portion of lead tetraacetate (19.6 g, 0.044 mol). After the initial reaction had subsided, the mixture was warmed on the steam bath until Pb(IV) was no longer present. The final solution was a clear light orange.

Water (150 ml) was added slowly to the hot solution, causing crystallization of product. The filtered and washed (water) solids were dissolved in methylene chloride, and the solution was filtered and boiled down as methanol was added. This, one of the less soluble pyrrole aldehydes, crystallized from boiling methanol to give 4.22 g (63.3%) after cooling, filtering, and rinsing with methanol. Only a negligible amount remained in the mother liquors to be scavenged with malononitrile. An analytical sample was recrystallized from methylene chloride–methanol: mp 196.0–198.0 °C; ^{1}H NMR 2.27 (s, 3 H), 2.31 (s, 3 H). 7.11, 7.33, and 7.43 (11 H), 9.73 ppm (s, 1 H); ir 3290 (NH), 1680, 1650 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74; N, 4.20. Found: C, 75.47; H, 5.73; N, 4.17.

5-(2,2-Dicyanovinyl)-2-*p*-methoxybenzyloxycarbonyl-3,4-dimethylpyrrole (5p). 5-Formyl-2-*p*-methoxybenzyloxycarbonyl-3,4-dimethylpyrrole (**5o**, 1.43 g, 5.0 mmol) and malononitrile (0.80 g, 0.33 g = 1 equiv) were boiled in methanol with a few drops of methylamine catalyst (saturated ethanolic methylamine). The solution was boiled down until the product crystallized, forming orange, granular chunks, 1.14 g (68%). An analytical sample was recrystallized from methylene chloride–methanol: mp 135.5–136.5 °C; ^{1}H NMR 2.13 (s, 3 H), 2.26 (s, 3 H), 3.79 (s, 3 H), 5.29 (s, 2 H), 6.89 and 7.36 (AB q, 4 H, J = 8.5 Hz), 7.53 (s, 1 H), 10.00 ppm (bs, 1 H); ir 3400 (NH), 2220 (C≡N), 1690 (C=O), 1580 cm^{-1} (C=C).

Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.99; H, 5.20; N. 12.38.

5-(2,2-Dicyanovinyl)-2-diphenylmethoxycarbonyl-3,4-dimethylpyrrole (5s). 2-Diphenylmethoxycarbonyl-5-formyl-3,4-dimethylpyrrole (**5r**, 1.67 g, 5.0 mmol) and malononitrile (0.81 g, 2.5 equiv) were dissolved in methylene chloride (20 ml). Methanol (25 ml) and methylamine catalyst (several drops) were added and the solution was boiled down until the product crystallized. After cooling, the yellow flat needles were filtered off and rinsed with methanol, to give a yield of 1.75 g (91.8%). An analytical sample was recrystallized from methylene chloride–methanol: mp 204.5–205.0 °C; ^{1}H NMR 2.13 (s, 3 H), 2.32 (s, 3 H), 7.08 (s, 1 H), 7.36 (m, 10 H), 7.53 (s, 1 H), 10.18 ppm (bs, 1 H); ir 3370 (NH), 2210 (C≡N), 1680 (C=O), 1575 cm^{-1} (C=C).

Anal. Calcd for $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02. Found: C, 75.39; H, 5.05; N, 10.96.

2-Benzyloxycarbonyl-3,4-diethyl-5-formylpyrrole (6h). 2-Benzyloxycarbonyl-3,4-diethyl-5-methylpyrrole (**6g**, 27.1 g, 0.1 mol)

in glacial acetic acid (150 ml) was treated with lead tetraacetate (100 g, moist commercial material, 0.23 mol), in several portions over a 10-min period, acetic acid (50 ml) being used to facilitate the addition. The first equivalent of oxidant reacted readily, with noticeable exotherm. The remainder dissolved more slowly, and the mixture had to be warmed to 85–90 °C to complete the reaction.

When the Pb(IV) test was negative, water was slowly added to the clear, light orange solution, until permanent opalescence appeared. The mixture was then chilled on ice and seeded. The addition of water was resumed only after crystals of product had become well established; the mixture was then diluted to at least 1 l. When the oils had thoroughly solidified, the solids were filtered off and washed with water. The product was recrystallized from methanol (150 ml), with seeding, to give a first crop of 18.5 g (64.9%). When scavenged with malononitrile, the mother liquors afforded 7.14 g (21.4%) of the dicyanovinyl derivative, for a total isolable conversion to aldehyde of 86.3%. An analytical sample was recrystallized from methanol: mp 78.5–79.5 °C; ^{1}H NMR 1.12 (t, 3 H, J = 7.5 Hz), 1.18 (t, 3 H, J = 7.5 Hz), 2.70 (q, 2 H, J = 7.5 Hz), 2.73 (q, 2 H, J = 7.5 Hz), 5.31 (s, 2 H), 7.30 (s, 5 H), 9.69 (s, 1 H), 10.21 ppm (bs, 1 H); ir 3260 (NH), 1685, 1655 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.40; H, 6.70; N, 4.89.

2-Benzyloxycarbonyl-5-(2,2-dicyanovinyl)-3,4-diethylpyrrole (6i). The crude water-washed filter cake of 2-benzyloxycarbonyl-3,4-diethyl-5-formylpyrrole (**6h**) prepared from 2-benzyloxycarbonyl-3,4-diethyl-5-methylpyrrole (**6g**, 13.55 g, 0.05 mol), acetic acid (80 ml), and the lead tetraacetate (50 g, moist, 0.11 mol), dissolved and filtered in methylene chloride, then evaporated to dryness, was dissolved in methanol (50 ml) and malononitrile (5.5 g, 0.083 mol) was added. The mixture was heated to boiling on the steam bath, and then treated with methylamine catalyst. The mixture turned orange, and soon went solid with lemon-yellow product. More methanol was added to facilitate the filtration, which was carried out on the chilled solution. The product was rinsed with methanol, and then hexane; yield 10.8 g (64.7%). An analytical sample was recrystallized from methylene chloride–methanol: mp 130.7–131.0 °C; ^{1}H NMR 1.13 (t, 6 H, J = 7.5 Hz), 2.58 (q, 2 H, J = 7.5 Hz), 2.75 (q, 2 H, J = 7.5 Hz), 5.34 (s, 2 H), 7.35 (s, 5 H), 7.52 (s, 1 H), 10.03 (bs, 1 H); ir 3400 (NH), 2220 (C≡N), 1720 (C=O), 1575 cm^{-1} (C=C).

Anal. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.61. Found: C, 71.90; H, 5.68; N, 12.61.

5-Bromo-2-(2,2-dicyanovinyl)-3,4-diethylpyrrole (6k). 5-Benzyloxycarbonyl-2-(2,2-dicyanovinyl)-3,4-diethylpyrrole (**6i**), 6.66 g, 0.02 mol) in tetrahydrofuran (150 ml) with 10% palladized charcoal (0.5 g) was stirred overnight at room temperature under 1 atm of hydrogen. (The volume of hydrogen taken up seemed to suggest that some of the dicyanovinyl groups had reduced as well.)

The catalyst was filtered off, and the filtrate evaporated to dryness under vacuum. The resulting solid was dissolved in warm acetic acid (60 ml) and treated with a solution of bromine (6.4 g, 0.04 mol) in acetic acid (10 ml).

Water was added to precipitate the product, and when the oils had solidified, they were filtered off, dissolved in methylene chloride, refiltered, and crystallized from methanol. The yield was 1.76 g (31.6%) of brownish, chunky crystals. An analytical sample was recrystallized from methylene chloride–methanol: mp 142.0–143.0 °C; ^{1}H NMR 1.12 (t, 3 H, J = 7.5 Hz), 1.17 (t, 3 H, J = 7.5 Hz), 2.47 (q, 2 H, J = 7.5 Hz), 2.61 (q, 2 H, J = 7.5 Hz), 7.36 (s, 1 H), 9.54 ppm (bs, 1 H); ir 3250 (NH), 2210 (C≡N), 1580 cm^{-1} (C=C).

Anal. Calcd for $C_{21}H_{12}BrN_3$: C, 51.82; H, 4.35; Br, 28.73; N, 15.11. Found: C, 51.44; H, 4.65; Br, 28.97; N, 15.12.

2-(2,2-Dicyanovinyl)-3,4-diethylpyrrole (6l). 5-Bromo-2-(2,2-dicyanovinyl)-3,4-diethylpyrrole (**6k**, 565.6 mg, 2.03 mmol), anhydrous sodium acetate (2 g), and 10% Pd/C (0.29 g) were hydrogenated overnight in tetrahydrofuran (50 ml) at room temperature and pressure. The solution was filtered to remove catalyst and sodium salts, and evaporated to dryness. The solids were dissolved in methylene chloride, refiltered, and recrystallized from methanol. The product, 164.2 mg (41%), was collected as bright yellow-orange, chunky crystals. An analytical sample was recrystallized from methylene chloride–methanol: mp 146.0–147.5 °C; ^{1}H NMR 1.15 (t, 3 H, J = 7.5 Hz), 1.22 (t, 3 H, J = 7.5 Hz), 2.48 (q, 2 H, J = 7.5 Hz), 2.60 (q, 2 H, J = 7.5 Hz), 7.10 (d, 2 H, J = 4 Hz), 7.44 (s, 1 H), 9.62 ppm (bs, 1 H); ir 3350 (NH), 2210 (C≡N), 1580 cm^{-1} (C=C).

Anal. Calcd for $C_{12}H_{13}N_3$: C, 72.33; H, 6.57; N, 21.09. Found: C, 71.44; H, 6.62; N, 20.85.

3,4-Diethyl-2-formyl-5-methylpyrrole[28] (6d). 2-Ethoxycarbonyl-3,4-diethyl-5-methylpyrrole (**6a**, 62.76 g, 0.3 mol) was dissolved in hot methanol (300 ml) and sodium hydroxide (20 g, 0.5 mol) in water (100 ml) was added. After heating for 3 h on the steam bath, the remaining solvent was evaporated in vacuo.

The sodium salts were dissolved in water, neutralized with a slight deficiency of acetic acid (30 ml), and steam distilled until no further oily 3,4-diethyl-2-methylpyrrole (**6b**) condensed. Sodium carbonate was added to the distillate as a preservative. The oily product was extracted into methylene chloride and dried over anhydrous potassium carbonate. The filtered solution was evaporated under reduced pressure, and the product was diluted with dry *N,N*-dimethylformamide (50 ml).

An excess of phosphorus oxychloride (50 ml) was added to dry, ice-cooled DMF (100 ml) over a 10-min period, followed, over a 15-min period, by the pyrrole solution.

After standing overnight, protected from moisture, the solution was poured onto crushed ice. Solid sodium carbonate was cautiously added, until the solution was almost neutral. After a filtration through Celite to remove minor dark tars, the solution was basified (sodium carbonate or ammonia) and warmed to complete the hydrolysis of the iminium salt (**6c**). The aldehyde product floated to the surface as a dark brown oil, which eventually solidifed. To obtain a light-colored compound, the crude solids were three times recrystallized from aqueous methanol, to give 17.8 g (35.9%) of light tan granules: mp 77.0 –77.5 °C (lit.[28] 74 °C); ^{1}H NMR 1.07 (t, 3 H, J = 7.5 Hz), 1.20 (t, 3 H, J = 7.5 Hz), 2.27 (s, 3 H), 2.38 (q, 2 H, J = 7.5 Hz), 2.69 (q, 2 H, J = 7.5 Hz), 9.42 (s, 1 H), 10.92 ppm (bs, 1 H); ir 3200 (NH), 1610 cm^{-1} (C=O).

Scavenging the mother liquors with malononitrile and methylamine afforded 16.4 g (25.6%) of the dicyanovinylpyrrole, for a total recovered yield of 61.5% of useful products.

2-(2,2-Dicyanovinyl)-3,4-diethyl-5-methylpyrrole (6e). Because of the high solubility of the aldehyde precursor to this compound, it was advantageous in maximizing yields to use the crude aldehyde without purification, or else the mother liquors from the purification of the aldehyde.

3,4-Diethyl-2-formyl-5-methylpyrrole (**6d**) was dissolved in benzene, and an excess of malononitrile was added, followed by methylamine or diethylamine catalyst. The mixture was boiled to drive off the water formed in the reaction, and the boiling was continued until the mixture became thick with crystals. The product was recrystallized from methylene chloride–methanol, giving orange to golden-yellow chunks. An analytical sample was recrystallized from methylene chloride–methanol: mp 160.5–161.4 °C; ^{1}H NMR 1.09 (t, 3 H, J = 7.5 hz), 1.14 (t, 3 H, J = 7.5 Hz), 2.34 (s, 3 H), 2.43 (q, 2 H, J = 7.5 Hz), 2.56 (q, 2 H, J = 7.5 Hz), 7.28 (s, 1 H), 9.38 ppm (bs, 1 H); ir 3300 (NH), 2215 (C≡N), 1590 cm^{-1} (C=C).

Anal. Calcd for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 73.11; H, 7.05; N, 19.94.

2-Chloromethyl-5-(2,2-dicyanovinyl)-3,4-diethylpyrrole (6f). 2-(2,2-Dicyanovinyl)-3,4-diethyl-5-methylpyrrole (**6e**, 2.13 g, 0.01 mol) was dissolved in warm methylene chloride (20 ml). Diethyl ether (10 ml was added, followed at once by the rapid dropwise addition of a solution of sulfuryl chloride (1.4 g, 0.01 mol) in methylene chloride (5 ml) to the magnetically stirred solution, before the starting material could recrystallize. The stirred solution was carefully boiled down, as diethyl ether was slowly added, eventually causing crystallization of the pure product, in a yield of 2.1 g (84.8%). An analytical sample was recrystallized from methylene chloride–ether as shiny yellow needles: mp 138–140.5 °C dec; ^{1}H NMR 1.13 (t, 6 H, J = 7.0 Hz), 2.49 (q, 2 H, J = 7.0 Hz), 2.58 (q, 2 H, J = 7.0 Hz), 4.63 (s, 2 H), 7.44 (s, 1 H), 9.59 ppm (bs, 1 H); ir 3300 (NH), 2210 (C≡N), 1580 cm^{-1} (C=C).

Anal. Calcd for $C_{13}H_{14}ClN_3$: C, 63.03; H, 5.70; Cl, 14.31; N, 16.96. Found: C, 63.13; H, 5.73; Cl, 14.20; N, 16.81.

5,5′-Bis(2,2-dicyanovinyl)-3,3′,4,4′-tetraethyl-2,2′-dipyrromethane (7e). 2-Chloromethyl-5-(2,2-dicyanovinyl)-3,4-diethylpyrrole (**6f**, 136.1 mg, 5.5 mmol) and 2-(2,2-dicyanovinyl)-3,4-diethylpyrrole (**6l**, 100.1 mg, 5.03 mmol) were dissolved in methylene chloride (10 ml). Several drops of anhydrous stannic chloride were added, causing a deepening of the color to brown. After a brief warming on the steam bath, the solution was quenched with concentrated HCl (10 ml), followed by water. The organic phase was washed with water, dried over K_2CO_3, and filtered. The solvent was boiled off and replaced with methanol, from which the product, 152.7 mg (74.5%), crystallized. An analytical sample was recrystallized from methylene chloride–methanol: mp 203–209 °C dec; ^{1}H NMR 1.09 (t, 6 H, J = 7.5 Hz), 1.17 (t, 6 H, J = 7.5 Hz), 2.48 (q, 4 H, J = 7.5 Hz), 2.60 (q, 4 H, J = 7.5 Hz), 4.13 (s, 2 H), 7.38 (s, 2 H), 9.38 ppm (s, 2 H); ir 3350 (NH), 2200 (C≡N), 1580 cm^{-1} (C=C); mass spectrum M$^+$ m/e 410 (calcd = obsd).

Anal. Calcd for $C_{25}H_{26}N_6$: C, 73.14; H, 6.38; N, 20.47. Found: C, 73.14; H, 6.41; N, 20.48.

5-Acetoxymethyl-2-benzyloxycarbonyl-3,4-diethylpyrrole (6m). 2-Benzyloxycarbonyl-3,4-diethyl-5-methylpyrrole (**6g**, 27.1 g, 0.1 mol) was dissolved in acetic acid (100 ml) containing a little acetic anhydride, and lead tetraacetate (48 g, 0.108 mol) was added in one portion. The mixture was swirled manually, and after a brief induction period, the reagent dissolved, reacting exothermically. The mixture was warmed briefly to 60 °C and then ethylene glycol (5–10 ml) was added to reduce any remaining Pb(IV). Water (400 ml) was next slowly added to precipitate the product in an easily filtered form. The thoroughly washed, filtered solids were dissolved in methylene chloride, separated from the water, refiltered, and crystallized from hexane by displacement of the methylene chloride. The compound crystallized as fine, white needles, 17.6 g (53.4%).

The mother liquors were evaporated, and the residues were dissolved in ethanol (100 ml) and boiled on the steam bath, after addition of concentrated HCl (1 ml), for 1 h. On cooling, the symmetrical dipyrromethane (**7a**), 6.40 g (24.3%), crystallized out, giving an overall yield of useful products of 77.7%. An analytical sample was recrystallized from methylene chloride–hexane: mp 113.5–115.0 °C; ^{1}H NMR 1.10 (t, 3 H, J = 7.5 Hz), 1.13 (t, 3 H, J = 7.5 Hz), 2.00 (s, 3 H), 2.45 (q, 2 H, J = 7.5 Hz), 2.73 (q, 2 H, J = 7.5 Hz), 5.02 (s, 2 H), 5.28 (s, 2 H), 7.32 (s, 5 H), 9.55 ppm (bs, 1 H); ir 3280 (NH), 1730, 1665 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.14; H, 7.00; N, 4.25.

5,5′-Bis(benzyloxycarbonyl)-3,3′,4,4′-tetraethyl-2,2′-dipyrromethane (7a). 5-Acetoxymethyl-2-benzyloxycarbonyl-3,4-diethylpyrrole (**6m**, 13.18 g, 0.04 mol) was heated to boiling (steam bath) in 95% ethanol (100 ml). Concentrated hydrochloric acid (1 ml) was added, and the heating was continued for 1 h. The solution was then seeded and allowed to cool. Large masses of colorless, chunky blades crystallized out, first crop 7.05 g (67%). The mother liquors were evaporated to dryness, and the resulting solids recrystallized from methylene chloride–methanol, giving an additional 2.60 g (24.7%) of product. An analytical sample was recrystallized from methylene chloride–methanol: mp 119.5–120.5 °C; ^{1}H NMR 1.05 (t, 6 H, J = 7.5 Hz), 1.12 (t, 6 H, J = 7.5 Hz), 2.44 (q, 4 H, J = 7.5 Hz), 2.72 (q, 4 H, J = 7.5 Hz), 3.77 (s, 2 H), 5.18 (s, 4 H), 7.18 (m, 10 H), 9.89 ppm (bs, 2 H); ir 3320 (NH), 1685, 1650 cm^{-1} (C=C).

Anal. Calcd for $C_{33}H_{38}N_2O_4$: C, 75.25; H, 7.27; N, 5.32. Found: C, 75.22; H, 7.27; N, 5.34.

3,3′,4,4′-Tetraethyl-5,5′-diformyl-2,2′-dipyrromethane (7f). Method A. 5,5′-Bis(benzyloxycarbonyl)-3,3′,4,4′-tetraethyl-2,2′-dipyrromethane (**7a**, 5.26 g, 0.01 mol) in tetrahydrofuran (150 ml) was stirred under hydrogen at atmospheric pressure and room temperature for 3.5 h in the presence of 10% Pd/C (0.42 g) and triethylamine (2 drops). After the catalyst had been filtered off and rinsed with hot THF, the filtrates were evaporated to dryness at reduced pressure, giving greenish-white crystalline crusts of the dicarboxylic acid (**7b**).

The solids were dissolved in *N,N*-dimethylformamide (20 ml) and the resulting solution was heated to boiling under argon. An air-cooled condenser was used to allow the argon stream to carry off the vapors of residual tetrahydrofuran and toluene. The mixture was boiled for 25 min, during which the original greenish color had become a medium brown. The solution was then chilled on ice, and an excess of benzoyl chloride (6.0 g, 5.2 ml, 42.7 mmol) was added dropwise over a 2-min period, causing the color to become an orange-red. Overnight at room temperature, the iminium salt (**7d**) crystallized out. This was filtered off, rinsed with DMF and diethyl ether, and dissolved in water. The aqueous solution was filtered, then warmed on the steam bath and basified with potassium carbonate. A brown oil separated at once, and this soon solidified. The aqueous solution became colorless, and the odor of dimethylamine could be detected. The solids were recovered and recrystallized from 95% ethanol. The yield of this nicely soluble dialdehyde was 1.70 g (54.1%), as light tan, chunky needles. An analytical sample was recrystallized from ethanol containing a trace of triethylamine: mp 179.5–180.5 °C; ^{1}H NMR 1.08 (t, 6 H, J = 7.5 Hz), 1.23 (t, 6 H, J = 7.5 Hz), 2.48 (q, 4 H, J = 7.5 Hz), 2.72 (q, 4 H, J = 7.5 Hz), 3.99 (s, 2 H), 9.53 (s, 2 H), 11.15 ppm (bs, 2 H); ir 3200 (NH), 1610 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.34; N, 8.91. Found: C, 72.47; H, 8.28; N, 8.97.

Method B. 5,5′-Bis(2,2-dicyanovinyl)-3,3′,4,4′-tetraethyl-2,2′-dipyrromethane (**7e**, 0.41 g, 1 mmol) in ethanol (50 ml) was treated with potassium hydroxide (5.0 g) in water (10 ml). The mixture was heated on the steam bath for 3 h and the residue treated with water (150 ml). The product was collected by filtration and crystallized from ethanol to give 0.28 g (89%), mp 178–179.5 °C.

2-Benzyloxycarbonyl-5-(2,2-dicyanovinyl)-3,4-dimethylpyrrole (5e). 2-Benzyloxycarbonyl-5-formyl-3,4-dimethylpyrrole (**5b**, 25.7 g, 0.1 mol) and malononitrile (8 g, 0.1 mol = 6.6 g) were heated to reflux on a steam bath in methanol (250 ml). The solution was removed from the heat source and treated with methylamine stock solution (1 ml, methylamine-saturated ethanol). An orange color formed at once, and the reaction quickly went thick with product. After cooling in an ice bath, the product was recovered by filtration and washed with methanol, then hexane, yield 29 g (95%).

An analytical sample was recrystallized from methylene chloride–methanol: mp 156.0–157.0 °C; ^{1}H NMR 2.13 (3 H, s), 2.28 (3 H, s), 5.35 (2 H, s), 7.36 (5 H, bs), 7.52 (H, s), 9.99 ppm (H, bs); ir 3400 (NH), 2215 (C≡N), 1725 (C=O), 1580 cm^{-1} (C=C).

Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.80; H, 4.95; N, 13.76. Found: C, 70.61; H, 4.97; N, 13.72.

2-*tert*-Butoxycarbonyl-5-(2,2-dicyanovinyl)-3,4-dimethylpyrrole (5i). This was prepared in the manner described above for **5e** from 2-*tert*-butoxycarbonyl-5-formyl-3,4-dimethylpyrrole (**5g**) and malononitrile in methanol with methylamine catalysis and recovered in two crops by crystallization.

An analytical sample was recrystallized from methylene chloride–methanol as beautiful, bright lemon-yellow chunks: mp 142.5–144.0 °C; ^{1}H NMR 1.60 (9 H, s), 2.18 (3 H, s), 2.26 (3 H, s), 7.57 (H, s), 9.46 ppm (H, bs); ir 3400 (NH), 2215 (C≡N), 1690 (C=O), 1570 cm^{-1} (C=C).

Anal. Calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.32; H, 6.35; N, 15.40.

2-Carboxy-5-(2,2-dicyanovinyl)-3,4-dimethylpyrrole (5t). 2-*tert*-Butoxycarbonyl-5-(2,2-dicyanovinyl)-3,4-dimethylpyrrole (**5i**, 29.09 g, 0.1073 mol) was heated to gentle reflux on a steam bath in 1,2-dichloroethane (105 ml). The solution was filtered hot and treated hot with trifluoroacetic acid (10 ml). The heating was continued for 75 min. The color began to darken with the addition of the acids; within 5 min product began to crystallize, and the mixture eventually became thick.

The lemon-yellow crystals were filtered from the dark greenish-brown solution and rinsed with dichloroethane, methylene chloride, and finally hexane, yield 19.3 g (83.8%).

An analytical sample was recrystallized from tetrahydrofuran–methanol, forming fluffy, lemon-yellow needles: ir 3300 (NH), 3160 (CO_2H), 2230, 2215 (C≡N), 1710 (C=O), 1590 cm^{-1} (C=C); mass spectrum M$^+$ m/e 215 (calcd = obsd).

Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.30; H, 4.21; N, 19.66.

The compound was too insoluble to make its preparation from the benzyl ester practical.

2-(2,2-Dicyanovinyl)-3,4,5-trimethylpyrrole (1n). 2-Formyl-3,4,5-trimethylpyrrole (1j, 13.7 g, 0.1 mol) and malononitrile (10 g, 0.15 mol) were heated to reflux in methanol (50 ml) on the steam bath. Diethylamine (1 ml) was then added, causing an immediate deepening of color and exothermic boiling. Crystallization began within 2 min. Most of the solvent was allowed to boil away, and displaced with benzene (30 ml). After cooling, the product was recovered by filtration, and rinsed with methanol, then hexane, yield 18.5 g (essentially quantitative) of coarse orange granules.

An analytical sample was recrystallized from methylene chloride–methanol: mp 175.5–177.0 °C; ^{1}H NMR 1.95 (3 H, s), 2.12 (3 H, s), 2.32 (3 H, s), 7.30 (H, s), 9.25 ppm (H, bs); ir 3310 (NH), 2210 cm^{-1} (C≡N).

Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.29; H, 5.99; N, 22.59.

5-Chloromethyl-2-(2,2-Dicyanovinyl)-3,4-dimethylpyrrole (1o). 2-(2,2-Dicyanovinyl)-3,4,5-trimethylpyrrole (**1n**, 3.70 g, 0.02 mol) was dissolved in boiling methylene chloride (45 ml). Dry diethyl ether (40 ml) was added, followed at once, before recrystallization could occur, by the rapid dropwise addition of a solution of sulfuryl chloride (2.80 g, 0.02 mol = 2.70 g) in methylene chloride (7 ml) to the gently swirled solution. The reaction proceeded without any marked change in color, and the product soon crystallized out as bright orange granules. After filtration and ethereal rinse, 2.63 g (59.9%) of product was obtained.

Note: This procedure was only executed once; later experience on analogous compounds suggests that the diethyl ether be omitted until the product is to be isolated.

An analytical sample was recrystallized from methylene chloride–diethyl ether, as yellow needles, material decomposed upon heating: ^{1}H NMR 2.03 (3 H, s), 2.14 (3 H, s), 4.58 (2 H, s), 7.42 (H, s), ca. 9.5 ppm (H, bs); ir 3300 (NH), 2220 (C≡N), 1600 cm^{-1} (C=C).

Anal. Calcd for $C_{11}H_{10}ClN_3$: C, 60.14; H, 4.59; N, 19.13; Cl, 16.14. Found: C, 60.53; H, 4.62; N, 19.00; Cl, 15.87.

5-(2-Cyano-2-methoxycarbonylvinyl)-5′-(2,2-dicyanovin-

yl)-3,3′,4,4′-tetramethyl-2,2′-dipyrromethane (2h). 2-Chloromethyl-5-(2,2-dicyanovinyl)-3,4-dimethylpyrrole (**1o**, 1.103 g, 0.005 mol = 1.0975 g) and 2-(2-cyano-2-methoxycarbonylvinyl)-3,4-dimethylpyrrole (**1b**, 1.022 g, 0.005 mol) were dissolved in dry methylene chloride (50 ml) with the exclusion of moisture. Anhydrous stannic chloride (1.3 g) was added, causing an immediate deepening of color to dark brown. After brief warming on the steam bath, the reaction mixture was quenched with concentrated hydrochloric acid, then water. The K_2CO_3-dried, filtered organic phase was boiled down and diluted with methanol, from which the product readily crystallized as yellow flakes, 1.37 g (70.8%).

An analytical sample was recrystallized from methylene chloride–methanol: mp 215–218 °C dec; ^{1}H NMR 2.01 (6 H, s), 2.14, 2.16 (6 H, two overlapping s), 3.82 (3 H, s), 4.03 (2 H, s), 7.33 (H, s), 7.91 (H, s), 9.45 ppm (2 H, bs); ir 3400 (NH), 2220 (C≡N), 1720 (C=O), 1590, 1535 cm^{-1} (C=C).

Anal. Calcd for $C_{22}H_{21}N_5O_2$: C, 68.20; H, 5.46; N, 18.08. Found: C, 67.68; H, 5.37; N, 18.33.

Acknowledgments. We wish to thank the National Institutes of Health (GM 04229 and AM 17989) and the Canadian National Research Council for financial assistance.

Registry No.—**1b**, 59434-99-0; **1d**, 59435-00-6; **1e**, 59435-01-7; **1f**, 59435-02-8; **1i**, 2199-46-4; **1j**, 27226-50-2; **1l**, 3855-78-5; **1m**, 59435-03-9; **1n**, 59435-04-0; **1o**, 59435-05-1; **2e**, 21211-62-1; **2g**, 59435-06-2; **2h**, 59435-07-3; **5a**, 4424-76-4; **5b**, 59435-08-4; **5c**, 59435-09-5; **5d**, 59435-10-8; **5e**, 59435-11-9; **5f**, 50634-31-6; **5g**, 59435-12-0; **5h**, 59435-13-1; **5i**, 59435-14-2; **5j**, 59435-15-3; **5k**, 34463-41-7; **5l**, 59435-16-4; **5n**, 59435-17-5; **5o**, 59435-18-6; **5p**, 59435-19-7; **5q**, 59435-20-0; **5r**, 59435-21-1; **5s**, 59435-22-2; **5t**, 59435-23-3; **6a**, 16200-50-3; **6b**, 34874-30-1; **6c**, 59435-24-4; **6d**, 41728-28-3; **6e**, 59435-25-5; **6f**, 59435-26-6; **6g**, 59435-27-7; **6h**, 59435-28-8; **6i**, 59435-29-9; **6k**, 59435-30-2 **6l**, 59435-31-3; **6m**, 59435-32-4; **7a**, 59435-33-5; **7b**, 59435-34-6; **7d**, 59435-35-7; **7e**, 59448-45-2; **7f**, 59435-36-8; methyl cyanoacetate, 105-34-0; benzyl oximinoacetoacetate, 27331-98-2; 3-methyl-2,4-pentanedione, 815-57-6; ethyl cyanoacetate, 105-56-6; *tert*-butyl acetoacetate, 540-88-5; *tert*-butyl oximinoacetoacetate, 14352-65-9; benzyl alcohol, 100-51-6; *p*-anisyl alcohol, 105-13-5; benzhydrol, 91-01-1; malononitrile, 109-77-3.

References and Notes

(1) National Science Foundation Predoctoral Fellow, 1968–1972.
(2) H. Fischer and H. Orth, "Die Chemie des Pyrrols", Johnson Reprint Co., New York, N.Y., 1968.
(3) R. L. N. Harris, A. W. Johnson, and I. T. Kay, *Q. Rev., Chem. Soc.*, **20**, 211 (1966).
(4) K. M. Smith, *Q. Rev., Chem. Soc.*, **25**, 31 (1971).
(5) R. L. N. Harris, A. W. Johnson, and I. T. Kay, *J. Chem. Soc. C*, 22 (1966).
(6) H. Fischer and H. Höfelmann, *Justus Liebigs Ann. Chem.*, **533**, 216 (1938).
(7) R. B. Woodward, *Angew. Chem.*, **72**, 651 (1960).
(8) J. L. Davies, *J. Chem. Soc. C*, 1392 (1968).
(9) G. M. Badger, R. L. N. Harris, and R. A. Jones, *Aust. J. Chem.*, **17**, 987, 1002, 1022 (1964).
(10) T. T. Howarth, A. H. Jackson, J. Judge, G. W. Kenner, and D. J. Newman, *J. Chem. Soc., Perkin Trans. 1*, 490 (1974).
(11) A. H. Corwin and S. R. Buc, *J. Am. Chem. Soc.*, **66**, 1151 (1944); A. H. Corwin and R. C. Ellingson, ibid., **66**, 1146 (1944).
(12) E. Bullock, R. Grigg, A. W. Johnson, and J. W. F. Wasley, *J. Chem. Soc.*, 2326 (1963).
(13) A. Markovac and S. F. MacDonald, *Can. J. Chem.*, **43**, 3364 (1965).
(14) R. Chong, P. S. Clezy, A. J. Liepa, and A. W. Nichol, *Aust. J. Chem.*, **22**, 229 (1969).
(15) R. Grigg, A. W. Johnson, and G. Shelton, *Justus Liebigs Ann. Chem.* **746**, 32 (1971).
(16) S. F. MacDonald, *J. Chem. Soc.*, 4176 (1952).
(17) F. K. Signaigo and H. Adkins, *J. Am. Chem. Soc.*, **58**, 709 (1936).
(18) A. Treibs and K. Hintermeier, *Ber.*, **87**, 1167 (1954).
(19) A. Treibs and H. G. Kolm, *Justus Liebigs Ann. Chem.*, **614**, 176 (1958).
(20) Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ir spectra (KBr) were determined on a Perkin-Elmer 137 spectrophotometer and the ^{1}H NMR spectra on a Varian Associates A-60 spectrometer using saturated solutions in deuteriochloroform containing internal Me_4Si. Combustion analyses were carried out by Scandinavian Microanalytical Laboratories, Herlev, Denmark.
(21) H. Fischer and B. Walach, *Justus Liebigs Ann. Chem.*, **450**, 115 (1926).
(22) A. Treibs and R. Zinsmeister, *Ber.*, **90**, 91 (1957).
(23) E. Bullock, A. W. Johnson, E. Markham, and K. B. Shaw, *J. Chem. Soc.*, 1438 (1958).
(24) J. Ellis, A. H. Jackson, A. C. Jain, and G. W. Kenner, *J. Chem. Soc.*, 4225 (1958).
(25) A. W. Johnson, E. Markham, R. Price, and M. B. Shaw, *J. Chem. Soc.*, 4254 (1958).
(26) G. M. Badger and A. D. Ward, *Aust. J. Chem.*, **17**, 655 (1964).
(27) H. W. Whitlock and R. Hanauer, *J. Org. Chem.*, **33**, 2169 (1968).
(28) D. Dolphin, R. L. N. Harris, J. L. Huppatz, A. W. Johnson, and I. T. Kay, *J. Chem. Soc.*, 35 (1966).

Chemistry of 2-(Chloromethyl)furans. Reaction of 2-(Chloromethyl)furans with Aqueous Potassium Cyanide and Other Nucleophiles[1]

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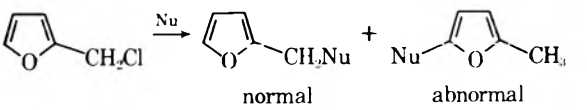
The reaction of 2-(chloromethyl)furan with aqueous cyanide solution was investigated. Experimental evidence is provided for the existence of 5-methylene-2,5-dihydro-2-furonitrile as a reaction intermediate. The effect of temperature, concentration, and solvent on the nature of the products was also examined. Analogous studies were carried out with 4-*tert*-butyl-2-(chloromethyl)furan. A number of 2-(chloromethyl)furans with substituents at various positions of the furan nucleus were synthesized and the reactions of these substituted furans with aqueous cyanide were investigated. The substituents were found to have a noticeable effect on the distribution of the isomeric nitriles obtained. The observed changes could be rationalized in terms of the electronic effects of the substituents. The reactions of 4-*tert*-butyl-2-(chloromethyl)furan with selected nucleophiles were also examined. A mechanism for the nucleophilic displacements of 2-(chloromethyl)furans is proposed.

The reactions of 2-(chloromethyl)furan (**1a**) with various nucleophiles in aqueous and nonaqueous media has generated considerable interest[1,3–20] since Kirner[3] reported the first practical synthesis of the compound more than 45 years ago. An intriguing feature of these reactions is that they often yield 2,5-disubstituted (abnormal) rather than 2-substituted furans (normal).



1a **2a** **3a**

As a result of previous studies, several facts have been established: (1) the so-called rearrangement takes place during

the reaction and only occurs in water or in protic solvents;[12-15] (2) the yield of abnormal product is controlled by an equilibrium established in the reaction mixture; (3) several nucleophiles (cyanide, alkoxide, phenoxide, benzenesulfinate, etc.) give rise to rearranged products[11,16,17] while others afford only the normal displacement products;[17] and (4) the alcoholysis of 2-(chloromethyl)furans is reported to follow first-order kinetics[12,16,19] while the reaction of **1a** with cyanide ion in aprotic solvents is believed to exhibit second-order kinetics.[13,14,15]

A few years ago, we demonstrated the existence of 5-methylene-2,5-dihydro-2-furonitrile (**4a**) as a primary product in the reaction of **1a** with aqueous cyanide,[1] and, more recently, other authors have shown that the rate-determining step in the formation of the abnormal product was proton removal from **4a**.[18] We have since investigated this reaction more thoroughly to establish the actual isomeric composition of the mixture and to examine the influence of conditions on the product distribution. Although the reactions of **1a** with various nucleophiles have been reported,[10,11,16,17,18] nucleophilic displacement reactions involving substituted 2-(chloromethyl)furans had not been investigated. It thus appeared of interest to compare the reactions of **1a** and various substituted 2-(chloromethyl)furans with aqueous potassium cyanide. In addition, a comparative study of the reactions of **1a** and 4-*tert*-butyl-2-(chloromethyl)furan (**1b**) with selected nucleophiles was also undertaken. On the basis of our findings and those of other investigators, a possible mechanism for the reactions of 2-(chloromethyl)furans is proposed.

Results

Although much work had been done by previous investigators, several aspects of the reaction of **1a** with aqueous cyanide still remained unexplored. The relative percentages of the principal products, **2a** and **3a**, had never been measured accurately or directly. Previous reports gave widely different values ranging from 0 to 100% for each of the products.[3,4,6,7,9] Similarly, in reactions involving other nucleophiles, different percentages of normal and abnormal compounds were reported.[10,20] These discrepancies may have arisen because **2a** and **3a** had never been isolated but were converted instead to derivatives whose yield was then established. The presence of possible by-products was never investigated and the optimum conditions for the reaction in an aqueous medium were never established. To clarify this situation, we first examined the composition of the reaction mixture. Unfortunately, early investigators did not describe the conditions under which they carried out their reactions, the first experimental details being given by Reichstein[5] in 1930. We adopted the Reichstein conditions in order to compare our results with those of previous workers although optimum yields are not obtained under this procedure. Mixture of the reagents produced an immediate exothermic reaction. After the exotherm subsided, all organic products were extracted with ether. The solvent was then removed under reduced pressure and the reaction mixture was analyzed by NMR. Both **2a** and **3a** were also prepared by independent routes. Several runs indicated that the yields of **2a** and **3a** were of comparable magnitude, averaging approximately 40 and 60%, respectively. In addition, a small amount of furfuryl alcohol (**5a**) was also formed. In runs at higher temperatures, another substance, a nitrile of unknown structure, was also observed. Although this product was never characterized, it was shown not to be the third possible isomer, 2-methyl-3-furonitrile (**6a**), which we synthesized via an alternative route. During our initial runs, no effort was made to control the temperature of the reaction. Depending upon the initial temperature of the reactants and the rate of stirring, the temperature of the mixture ranged between 60 and 90 °C. We did, however, examine the reaction at ambient temperature and at 0 °C. Analysis of the product mixture obtained from reactions carried out at low temperatures revealed the presence of two additional compounds, starting material and **4a**. The yield of **2a** did not change significantly as a function of temperature; the yield of **3a** was somewhat higher at lower temperatures. Although the observed difference was small (5%), it was real and reproducible in all reactions. A similar trend was also noticed in later investigations with substituted 2-(chloromethyl)furans.

We also investigated the influence of cyanide concentration on the reaction products. Results obtained with 1, 2, and 4 N potassium cyanide solutions were compared with those obtained under our standard reaction conditions (6 N potassium cyanide). Compounds **2a, 3a, 5a,** and the unknown nitrile were each observed. As expected, at decreasing cyanide concentrations, the yield of **5a** increased. This is a result of the increasing probability of the reaction of **1a** with water rather than with cyanide. In more concentrated cyanide solutions the yields of **2a** and **3a** increased, but not equally. In dilute solution, the relative yield of **3a** was higher than that of **2a**.

Moldenhauer and co-workers[9] had attempted to change the relative distribution of **2a** and **3a** in the product mixture by using various metal cyanides. We examined the effect of mercuric, silver, cuprous, ammonium, and benzyltrimethylammonium cyanides on the ratio of **2a** and **3a**. Mercuric cyanide caused a violent reaction and, even at 0 °C afforded only an intractable black tar. Silver cyanide was too insoluble to allow use of our standard isolation procedure and we abandoned this reaction. Cuprous cyanide was also very insoluble, but a mixture of potassium cyanide and cuprous cyanide, which affords a water-soluble complex, was used. This reaction was examined at 0 °C, at ambient temperature, and without temperature control. The best yields were obtained at the lower temperature. Different proportions of potassium cyanide and cuprous cyanide were also employed, but again the standard isolation method could not be used. Ammonium and benzyltrimethylammonium cyanides were both prepared in situ and used in lower concentration than potassium cyanide. None of the various cations present in the reaction mixture changed the ratio of products significantly. Cuprous ions appeared to favor the formation of **2a** while a higher yield of **3a** was obtained with benzyltrimethylammonium cyanide.

Oshiro and co-workers[15] had thoroughly investigated the reaction of **1a** and metal cyanides in aprotic solvents. However, since the effect of mixed solvents had not been examined, we decided to examine the reaction of **1a** in aqueous 1,2-dimethoxyethane solutions of various composition (40, 60, 80, and 99% by volume of 1,2-dimethoxyethane). In 40% 1,2-dimethoxyethane, there was essentially no change in the product distribution. In 60% 1,2-dimethoxyethane, unreacted **1a** was observed. Based on the amount of starting material recovered, the reaction was approximately 10 times slower in 80% 1,2-dimethoxyethane and approximately 100 times slower in 99% 1,2-dimethoxyethane than in the 60% solvent mixture. In the presence of 40% 1,2-dimethoxyethane, the product distribution was the same as under standard conditions, and the relative yields of **2a** and **3a** did not change. The observed rate changes, therefore, appeared to be the result of the decreasing solubility of potassium cyanide in the organic medium as well as the decreasing polarity of the solvent. Oshiro's observation[15] that the reaction rate is directly proportional to the product of the dielectric constant of the solvent and the solubility of the inorganic reagent in that particular solvent is thus applicable to our conditions. Another expected effect of the decrease in water content was the decrease in the yield of **5a**.

The reaction between **1a** and potassium cyanide was also investigated in deuterium oxide at 0 °C. NMR analysis of the

mixture, after 3 h, indicated the presence of **1a, 2a, 3a, 4a,** and **5a.** The percentages of **1a** (10%) and **4a** (17%) were unexpectedly high as compared to the results in the undeuterated medium (1 and 14%, respectively). The relative proportions of **2a** and **3a** indicated that the formation of **2a** was slightly favored. The rate of the reaction was approximately 11% slower in deuterium oxide than in water. The difference may be due to the slower rate of hydrolysis of potassium cyanide in deuterium oxide or the slower ionization of **1a** in this medium. The rate of rearomatization of **4a** in deuterium oxide was also slower than in water. Incorporation of deuterium in the methylene group of **2a** and in the methyl group of **3a** was also observed.

All of the data thus obtained point to a unimolecular mechanism in which the rate is controlled by the heterolysis of **1a.** The product ratio is then determined by competition between the nucleophiles in the succeeding fast steps. In 1,2-dimethoxyethane, the reduced polarity of the medium decreased the rate of the reaction but did not change the product distribution significantly. If **2a** were formed by a bimolecular mechanism, a noticeable change should be seen in the relative ratios of **2a** and **3a.** The small increase of **3a** observed in the presence of cuprous cyanide also supports a unimolecular mechanism although it might be argued that a small amount of **2a** is formed by a competing bimolecular mechanism. The hydrolysis and alcoholysis of **1a** have been reported to be unimolecular processes[10-12] and it may be assumed that an analogous nucleophilic reaction would follow similar kinetics.

Since all experimental evidence seemed to support a unimolecular mechanism, the failure to detect even a small amount of the other possible isomer, **6a,** was disturbing. In order to evaluate qualitatively the distribution of the positive charge in the furfuryl cation, several Hückel type molecular orbital calculations were carried out.[21a,b] All calculations showed considerably less charge density at C_3 than at the methylene carbon or at C_5, thus supporting the observed reactivity at these positions.

Although **4a** had been postulated as an intermediate as early as 1932,[6] this compound had not been detected until recently. Yur'ev and co-workers[22] isolated 5-methylene-2-(chloromethyl)-2,5-dihydro-2-furonitrile from the reaction of 2,5-bis(chloromethyl)furan with potassium cyanide in aqueous benzene. A 2,5-dihydrofuran was also reported in the alcoholysis of **1a** under basic conditions.[10] A few years later, 5-methylene-2-methoxy-2,5-dihydrofuran was isolated by Hill.[16] In the present investigation, the presence of a transient species preceding the formation of **3a** was detected by a set of resonances in the NMR spectrum of the crude product mixture obtained from the reaction of **1a** and aqueous potassium cyanide at 0 °C.[1]

The reaction of 4-*tert*-butyl-2-(chloromethyl)furan (**1b**) with aqueous potassium cyanide was investigated next since, a priori, the bulk of a *tert*-butyl group in the 4 position could hinder the approach of an attacking nucleophile at the 5 position. While the reaction of **1a** with aqueous potassium cyanide went to completion in 0.5 h, at ambient temperature, the reaction of **1b** under the same conditions required over 24 h. The decrease in reactivity observed for **1b** relative to **1a** may partially be attributed to its lesser water solubility.

Several runs at 37.5 ± 0.5 °C afforded yields of normal (**2b**) and abnormal (**3b**) products averaging approximately 25 and 75%, respectively, as compared to 40% (**2a**) and 60% (**3a**) for **1a.** A time–concentration study showed that **3b** formed before **2b.** Intermediate **4b** was not observed during the first 6–7 h of the reaction. It did, however, appear toward the end of the reaction, indicating that the rate of aromatization must, at this stage, be decreasing.

The effect of temperature on the reaction of **1b** with aqueous cyanide was also investigated. The relative percentages of the isomeric products showed only a slight variation with increasing temperature. As in the case of **1a,** the yield of abnormal product appeared to decrease slightly with increasing temperature.

The influence of cyanide concentration on the reaction products was examined. A slight increase in the yield of **3b** was noted as the cyanide concentration was decreased, but again the total effect of this change on the isomer distribution was small.

The rate of the reaction of **1b** with aqueous potassium cyanide was much slower than that of **1a** with the same reagent. The yield of abnormal product was appreciably greater than that obtained from **1a,** indicating that substituents had a definite influence on the final isomeric composition.

Examination of a Courtauld model of **1b** showed considerable hydrogen–hydrogen repulsion between one of the protons on the *tert*-butyl group and the 5 proton of the furan ring, whereas a similar model of the intermediate methylene compound, 3-*tert*-butyl-5-methylene-2,5-dihydro-2-furonitrile (**4b**), showed less hydrogen–hydrogen interference. Relief of steric strain might therefore be invoked to explain the larger percentage of abnormal product. To test this hypothesis, 4-isopropyl-2-(chloromethyl)furan (**1c**) was synthesized (Scheme IV). Treatment of **1c** with aqueous potassium cyanide, however, afforded the highest observed yield of abnormal product (**3c**) among the 2-(chloromethyl)furans examined, 84%, thus eliminating steric strain as a determining factor in the reaction.

Since, in extended allylic systems susceptible to SN2′ mechanisms, a bulky group on the saturated carbon prevents formation of the normal product but does not affect the yield of abnormal product, the analogous furan system, 3-*tert*-butyl-2-(chloromethyl)furan (**1d**), was synthesized (Scheme V). When this halide was treated with aqueous potassium cyanide, at 70 °C, three products were obtained, the two expected isomeric products (**2d** and **3d**) and 4-*tert*-butyl-5-methyl-2(5*H*)-furanone (**7**). Lactone **7** could be eliminated, however, by carrying out the reaction at a lower temperature. The relative percentage of the two isomeric products was very similar (**2d,** 39% and **3d,** 61%) to that obtained for **1a.** Since the formation of the normal product was not suppressed, the operation of a SN2′ mechanism seems unlikely.

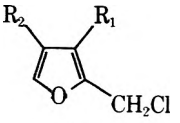
Halogen atoms have been known to act as electron-withdrawing or electron-donating groups depending on whether they primarily exert an inductive or resonance effect. It appeared of interest to examine the effect of a bromine substituent on the aforementioned product distribution. 4-Bromo-2-(chloromethyl)furan (**1e**) was thus synthesized (Scheme VI). Although the reaction of **1e** with aqueous potassium cyanide was slow, a yield of 83% of abnormal product (**3e**) was obtained.

Since bromine appeared to function as an electron-donating group, it was decided to study the effect of an electron-withdrawing substituent, such as a carbethoxy or cyano group, in the 4 position. The reaction of ethyl 2-(chloromethyl)-4-furoate (**1f**) with aqueous potassium cyanide gave 53% of normal product (**2f**) and only 47% of the abnormal product (**3f**). When 5-(chloromethyl)-3-furonitrile (**1g**) was treated with the same reagent, a quantitative yield of the normal product (**2g**) was obtained.

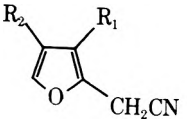
The results of the reactions of the various substituted 2-(chloromethyl)furans with aqueous potassium cyanide are summarized in Table I.

It may be seen from Table I that electron-donating groups favor the formation of the abnormal product and that this effect is most pronounced when the substituent is in the 4 position. Electron-withdrawing groups retard the reaction considerably and may completely inhibit the formation of

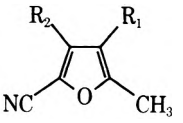
Table I. Relative Percentages of the Isomeric Nitriles Formed from the Reactions of Substituted 2-(Chloromethyl)furans with Aqueous Potassium Cyanide



1a–f



2a–f



3a–f

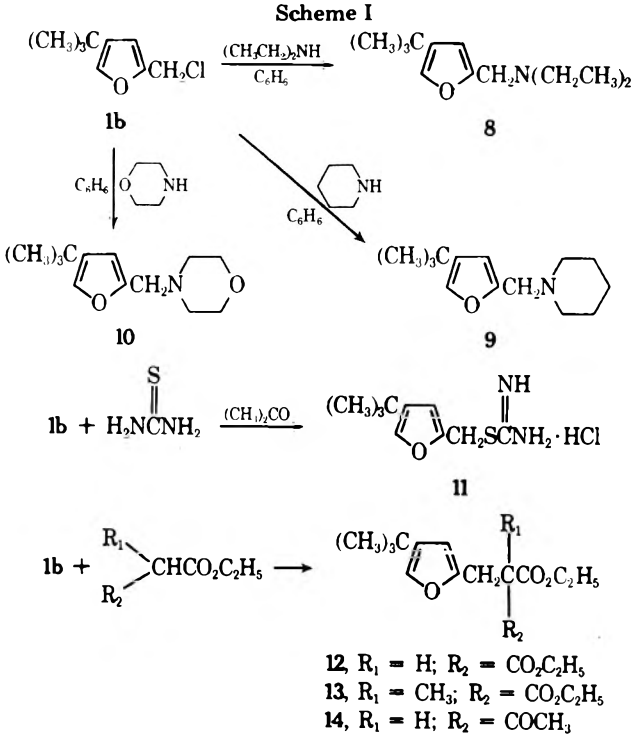
	Substituents		Time, h at	Normal product,	Abnormal product,
	R_1	R_2	37.5 ± 0.5°C	%	%
a	H	H	0.5	40	60
b	H	$C(CH_3)_3$	15	25	75
c	H	$CH(CH_3)_2$	28	16	84
d	$C(CH_3)_3$	H	48	39	61
e	H	Br	96	17	83
f	H	$CO_2C_2H_5$	168	53	47
g	H	CN	168	100	0

abnormal product. The effects of these substituents are consistent with the stabilization of an electron-deficient center and lend support to the postulation of 2-methylenefuryllium ions as the first intermediates formed in the ionization of the corresponding 2-(chloromethyl)furans.

Since nucleophilic displacements with ions other than cyanide had all been performed on 2-(chloromethyl)furan (**1a**), a comparative study of the reactions of **1a** and 4-*tert*-butyl-2-(chloromethyl)furan (**1b**) with selected nucleophiles appeared of interest.

The reactions of **1b** with amines in benzene, with thiourea in acetone, and with esters in sodium ethoxide all yielded normal products (**8**–**14**) (Scheme I).

Scheme I



12, R_1 = H; R_2 = $CO_2C_2H_5$
13, R_1 = CH_3; R_2 = $CO_2C_2H_5$
14, R_1 = H; R_2 = $COCH_3$

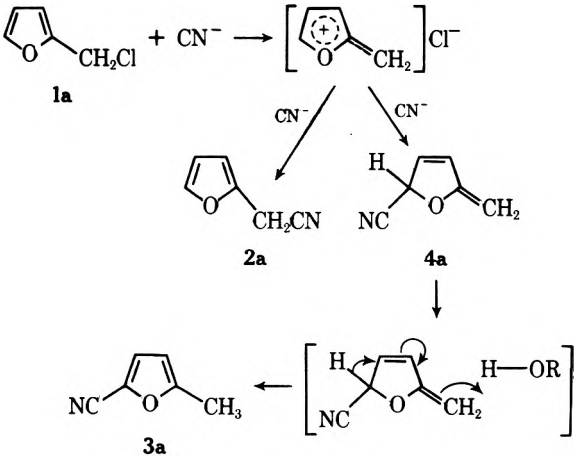
These results confirmed the fact that no rearranged products have ever been observed in nonaqueous media.[12–15]

Although the reaction of **1a** with sodium azide was reported to give only the normal product,[11] NMR analysis of the reaction of **1b** with this nucleophile clearly showed resonances for both a normal and abnormal product. The reaction of **1a** with potassium thiocyanate was previously reported to give the normal thiocyanate.[17] Again the NMR spectrum of the reaction mixture clearly shows resonances for two distinct compounds, a normal and abnormal product. In the case of the normal product, both the isothiocyanate and thiocyanate could be observed. We could not, however, determine whether the abnormal product was a thiocyanate, isothiocyanate, or a mixture of both. Since the cited nucleophiles do not give abnormal products with **1a**, these reactions further illustrate the importance of substituents in the 2-(chloromethyl)furan. Although we did not conduct a rigorous investigation, preliminary NMR studies indicate that the percentage of abnormal product is greater at lower temperatures.

Discussion

On the basis of our findings and those of other investigators,[3–18] a possible mechanism for the reactions of 2-(chloromethyl)furans is proposed in Scheme II.

Scheme II



The reaction is initiated by heterolysis of 2-(chloromethyl)furan to give a furyllium ion as an intimate ion pair with an appropriate anion. After the solvolytic cage of this ion pair collapses, the more nucleophilic ion attacks either at the methylene carbon or at the 5 position. The less nucleophilic hydroxide ion may compete for the cation to a small extent. When hydroxide ion adds to the 5 position, the product is unstable and results in the opening of the furan ring to give products that polymerize. The last step consists of aromatization of 5-methylene-2,5-dihydro-2-furonitrile (**4a**).

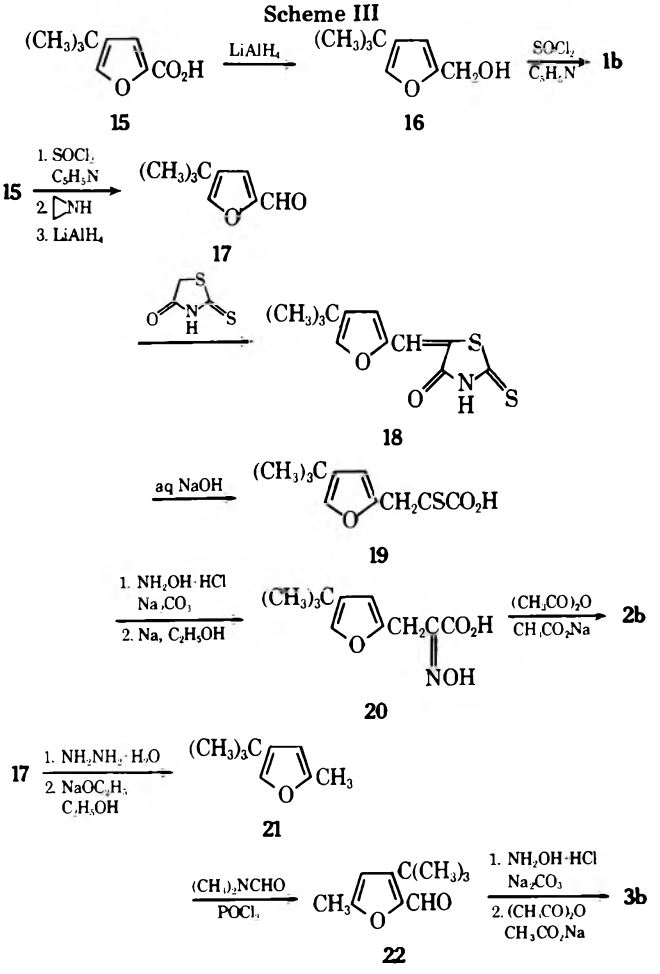
The ease of heterolysis of **1a** is supported by the cleavage products of **1a** in the mass spectrum. Elimination of a chloride ion is the favored process in the decomposition of this compound. The stability of the resulting cation is indicated by the fact that the *m/e* 81 peak is the base peak in the fragmentation of **1a**. Stable furyllium salts have been prepared and are

known to react readily with nucleophiles.[23] Furthermore, the stability of such a cation should be very much dependent on substituents. As we have demonstrated, substituent effects in this system are consistent with stabilization of an electron-deficient center. The effect is most noticeable with substituents in the 4 position, i.e., the position closest to the most electron-deficient site in the ion, the 5 position. Destabilization of the furyllium ion by an electron-withdrawing substituent such as a cyano group results in the exclusive formation of the normal product. The importance of this stabilization is also evident in the reactions of **1a** and **1b** with azide and thiocyanate ions; abnormal product formed only from **1b**, which gives rise to the better stabilized furyllium ion. Therefore, it appears likely that attack at the methylene group and at the 5 position could be competitive processes with many nucleophiles if a sufficiently stabilized furyllium ion is involved in the intimate ion pair. It is well to remember, however, that certain nucleophiles such as hydroxide ion can lead to ring opening when introduced at the 5 position. The large amount of polymeric material observed in these reactions is no doubt the result of such a sequence.

The aromatization process is first order in 5-methylene-2,5-dihydro-2-furonitrile. However, cyanide is essential in this process since the presence of **4a** could only be observed when the cyanide concentration was decreased. Finally, the role of the solvent is all important. A polar solvent is needed for heterolysis of the halide and stabilization of the furyllium ion formed. Furthermore, the solvent must also be protic; the formation of abnormal product has only been observed in water or alcohol. Solvent is apparently needed as a proton source at the methylene carbon in order for aromatization of **4a** to occur.

Synthetic Schemes. The synthetic routes leading to **1b**, **2b**, and **3b** are shown in Scheme III.

Scheme III

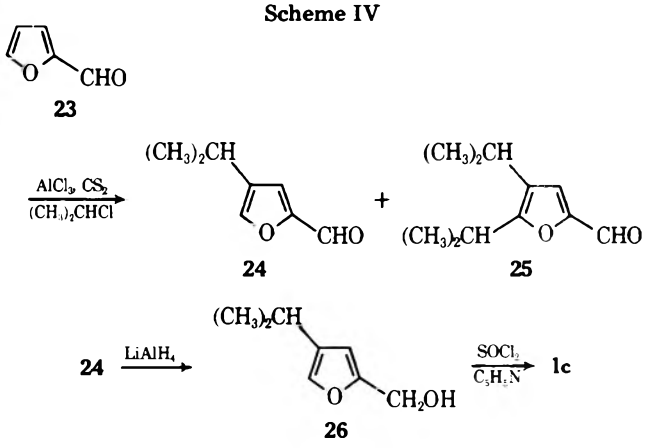


4-*tert*-Butyl-2-(chloromethyl)furan (**1b**) was prepared via the reaction of 4-*tert*-butylfurfuryl alcohol (**16**) with thionyl chloride in pyridine. The alcohol, in turn was obtained by the reduction of 4-*tert*-butyl-2-furoic acid (**15**) with lithium aluminum hydride.

4-*tert*-Butyl-2-furanacetonitrile (**2b**) was synthesized by the rhodanine method[24a,b] from 4-*tert*-butyl-2-furaldehyde (**17**). The aldehyde in turn was obtained by treating the corresponding acid halide with aziridine and reducing the intermediate acyl aziridine with lithium aluminum hydride.[25] The rhodanine derivative of **17** (**18**) was cleaved with aqueous sodium hydroxide to give 4-*tert*-butyl-α-thio-2-furanpyruvic acid (**19**) which was then converted to 4-*tert*-butyl-2-furanpyruvic acid oxime (**20**) with hydroxylamine hydrochloride and sodium ethoxide. Decarboxylation and dehydration of the oximino acid using sodium acetate and acetic anhydride gave **2b**.

4-*tert*-Butyl-5-methyl-2-furonitrile (**3b**) was synthesized in four steps from 4-*tert*-butyl-2-furaldehyde hydrazone. Reduction of the hydrazone with sodium ethoxide in absolute ethanol[26] afforded 4-*tert*-butyl-2-methylfuran (**21**) which, in turn, was formylated with *N,N*-dimethylformamide and phosphorus oxychloride[27] at low temperature to give 3-*tert*-butyl-5-methyl-2-furaldehyde (**22**). Treatment of the aldehyde with hydroxylamine and dehydration of the resulting oxime with acetic anhydride produced **3b**. 4-Isopropyl-2-(chloromethyl)furan (**1c**) was synthesized as shown in Scheme IV.

Scheme IV

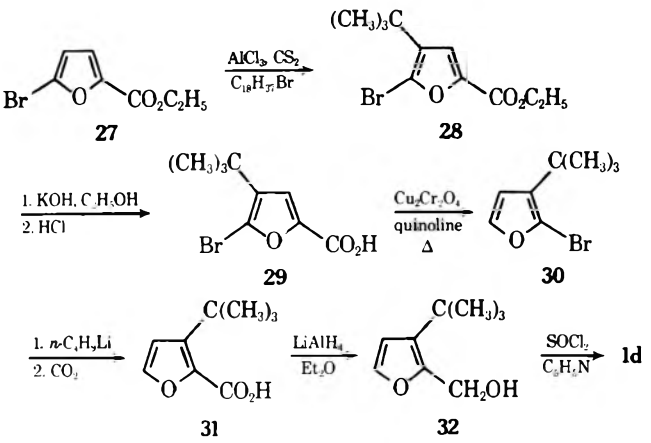


Furaldehyde (**23**) was alkylated with isopropyl chloride and aluminum chloride, in carbon disulfide, to afford 4-isopropyl-2-furaldehyde (**24**). Compound **24** was reduced with lithium aluminum hydride in ether to the corresponding alcohol (**26**) which, in turn, was converted to **1c** on treatment with thionyl chloride in ether–pyridine solution.

The alkylation of **23** with isopropyl chloride was previously described by Gilman[28a,b] and reported to give only 4-isopropyl-2-furaldehyde (**24**). We, however, isolated two products, the desired aldehyde, **24**, and 4,5-diisopropyl-2-furaldehyde (**25**). Furans substituted with electron-withdrawing groups at the 2 position normally undergo electrophilic substitution at the 5 position.[29] Under the conditions of this reaction (excess aluminum chloride), however, **23** undoubtedly complexes with the Lewis acid with resulting reduction of electron density within the furan ring. This effect would be manifested at the 3 and 5 positions, but not at the 4 position. The approximate charge distributions at the 4 and 5 positions of some 2-furyl ketones have been calculated as 0.4 and 0.5, respectively.[30] These values are relatively similar and it is conceivable that deactivation of the 5 position by complexation sufficiently perturbs the electron densities at the 4 and 5 positions to account for the observed substituent orientation in **24** and **25**.

3-*tert*-Butyl-2-(chloromethyl)furan (**1d**) was prepared as illustrated in Scheme V.

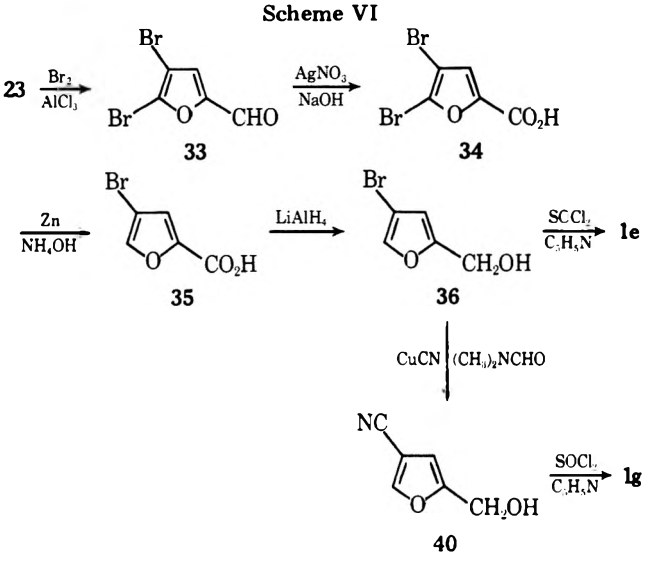
Scheme V



Esterification of 5-bromo-2-furoic acid with ethanol and sulfuric acid,[31] followed by alkylation of the resultant ester (**27**) with *n*-octadecyl bromide and aluminum chloride,[32] afforded ethyl 5-bromo-4-*tert*-butyl-2-furoate (**28**). Hydrolysis of compound **28** with alcoholic potassium hydroxide and decarboxylation of the intermediate acid (**29**) with copper chromite and quinoline[33] then gave 2-bromo-3-*tert*-butylfuran (**30**). Treatment of **30** with *n*-butyllithium and dry ice afforded 3-*tert*-butyl-2-furoic acid (**31**) which, in turn, was converted to **1d** via the corresponding alcohol (**32**).

4-Bromo-2-(chloromethyl)furan (**1e**) was prepared as shown in Scheme VI.

Scheme VI

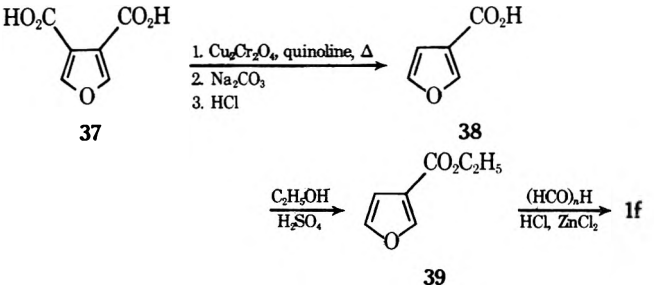


2-Furaldehyde (**23**) was brominated in the presence of excess aluminum chloride[34] to give 4,5-dibromo-2-furaldehyde (**33**) in almost quantitative yield. Oxidation of compound **33** with silver nitrate and sodium hydroxide produced 4,5-dibromofuroic acid[35] (**34**) which was then reduced to 4-bromo-2-furoic acid (**35**) with zinc and ammonium hydroxide.[36] Direct reduction of **35** afforded 4-bromofurfuryl alcohol (**36**). Treatment of compound **36** with thionyl chloride in ether–pyridine solution then gave **1e**.

Ethyl 5-(chloromethyl)-3-furoate (**1f**) was synthesized as shown in Scheme VII.

Decarboxylation of 3,4-furandicarboxylic acid (**37**) was accomplished by heating this compound with copper chromite and quinoline.[37] The resultant acid[37] (**38**) was esterified and its ester (**39**) immediately chloroformylated[38] with paraformaldehyde, hydrogen chloride, and zinc chloride to give **1f**.

Scheme VII



5-(Chloromethyl)-3-furonitrile (**1g**) was prepared via the corresponding alcohol (**40**) which, in turn, was synthesized by heating **36** with cuprous cyanide in *N*,*N*-dimethylformamide[39] as shown in Scheme VI.

Experimental Section

General. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., Alfred Bernhardt Microanalytisches Laboratorium, West Germany; and Microanalysis, Inc., Wilmington, Del. NMR spectra were recorded in carbon tetrachloride solutions (Me_4Si standard) with a Varian A-60A or HA-100D spectrometer. Ir spectra, both neat and in 10% carbon tetrachloride, were obtained on a Perkin-Elmer 521 grating infrared spectrophotometer. Mass spectra were determined on a Consolidated Electrodynamic Corp. CEC-110 double-focusing mass spectrometer. A Nester-Faust NF-190 spinning band column (6 × 450 mm, 23 theoretical plates) was employed for fractional distillations. Analytical gas chromatography was carried out on a F & M 700 chromatograph with a thermal conductivity detector using 12 ft × 0.5 in. o.d. columns packed with 20% silicone oil or 10% Carbowax. Helium was employed as a carrier gas at a flow rate of 60 ml/min. The oven temperature was programmed at 10 °C/min from 80 to 120 °C. For preparative gas chromatography, an Aerograph Autoprep A-700 instrument was employed. Time–concentration studies at 37.5 ± 0.5 °C were carried out in an Elberbach water bath shaker.

2-(Chloromethyl)furan (1a). This compound was synthesized according to the procedure of Kirner[3] using freshly distilled furfuryl alcohol (bp 54–56 °C at 8 mm), thionyl chloride, and pyridine in anhydrous ether. After the removal of pyridinium hydrochloride, the product was obtained as an orange solution in ether and was stored in this form at −20 °C over anhydrous potassium carbonate. Immediately before use, the solvent was removed on a rotary evaporator and the crude product was distilled through a micro-Vigreux column: bp 19–19.5 °C (1.25 mm) [lit.[3] bp 37 °C (15 mm)]; ir (CCl_4) 3150, 3120, 2970, 2920, 1730, 1605, 1496, 1379, 1220, 1150, 1008, 936, 882, 742, and 738 cm^{-1}; NMR (neat) δ 7.30 (m, 1 H, H-5), 6.22 (m, 2 H, H-4 and H-3), and 4.48 (m, 2 H, CH_2); mass spectrum *m/e* (rel intensity) 116 (M^+, 20), 81 ($C_5H_5O^+$, 100), 52 ($C_4H_4^+$, 16), 51 ($C_4H_3^+$, 22), 50 ($C_4H_2^+$, 13), and 39 ($C_3H_3^+$, 7). *Caution: This compound should always be stored in solution because neat samples decompose slowly, even at −20 °C, to give hydrogen chloride which catalyzes polymerization of the furan ring with explosive violence.*

2-Furylacetonitrile (2a). An authentic sample of **2a** was synthesized in 41% yield from 2-furfural according to the procedure of Plucker and Amstutz:[24a] bp 56–58 °C (5 mm) [lit.[23] bp 78–80 °C (20 mm)]; ir (CCl_4) 3158, 3122, 2962, 2920, 2258, 1740, 1600, 1505, 1410, 1218, 1148, 1015, 950, 886, 818, 750, and 740 cm^{-1}; NMR (neat) δ 7.37 (m, 1 H, H-5), 6.28 (m, 2 H, H-4 and H-3), and 3.68 (m, 2 H, CH_2); mass spectrum *m/e* (rel intensity) 107 (M^+, 72), 81 ($C_5H_5O^+$, 7), 79 ($C_5H_5N^+$, 37), 78 ($C_5H_4N^+$, 19), 52 ($C_4H_4^+$ and/or $C_3H_2N^+$, 100), 51 ($C_4H_3^+$, 32), 50 ($C_4H_2^+$, 14), 39 ($C_3H_3^+$, 33). 2-Furylacetonitrile should be stored as a neat liquid at −20 °C because it is heat sensitive and discolors at room temperature within 24 h. Samples refluxed in toluene, xylene, or pyridine for 3 h undergo strong discoloration and, although approximately 60% of **2a** can be recovered, afford intractable tars. The instability of this compound may account for the small amounts of normal product observed by some authors.

To ascertain whether **2a** could rearrange to **3a** under the conditions of our experiment, **2a** was stirred in a saturated potassium cyanide solution at 80 °C for 3 h. Although the solution darkened considerably, only unreacted starting material could be isolated. Other experiments carried out in the presence of potassium chloride or a catalytic amount of furfuryl alcohol were also negative. No trace of an isomeric nitrile could be detected in any of the reaction mixtures.

5-Methyl-2-furonitrile (3a). An authentic sample of **3a** was prepared in 48% yield from 5-methyl-2-furfural via the procedure described by Scott and Johnson:[7] bp 50–51 °C (7 mm) [lit.[7] bp 74–75 °C (27 mm)]; ir (CCl_4) 3180, 3130, 2960, 2928, 2224, 1720, 1595, 1522, 1220, 950, and 796 cm^{-1}; NMR (neat) δ 7.02 (d, 1 H, H-4), 6.17 (m, 1 H, H-3), and 2.34 (m, 3 H, $-CH_3$); mass spectrum *m/e* (rel intensity) 107 (M^+, 100), 106 ($C_6H_4NO^+$, 57), 81 ($C_5H_5O^+$, 3), 79 ($C_5H_5N^+$, 25), 78 ($C_5H_4N^+$, 20), 53 ($C_4H_5^+$, 53), 52 ($C_4H_4^+$ or $C_3H_2N^+$, 67), 51 ($C_4H_3^+$, 32), 50 ($C_4H_2^+$, 22), 43 ($C_2H_3O^+$, 27), and 39 ($C_3H_3^+$, 10).

5-Methyl-2-furonitrile is considerably more stable than the isomeric 2-furylacetonitrile. Attempts to isomerize compound **3a** at 80 °C, in potassium cyanide solution, in the presence of potassium chloride, or with a catalytic amount of furfuryl alcohol, were unsuccessful. Therefore, **3a**, once formed, does not rearrange to **2a** under the conditions of our experiments.

2-Methyl-3-furonitrile (6a). This compound was prepared from ethyl 2-methyl-3-furancarboxylate. The ester was hydrolyzed to the corresponding acid which was then converted to the acid chloride with thionyl chloride and pyridine. Treatment of the acid chloride with ethyleneimine and subsequent reduction of the intermediate acylaziridinium compound with lithium aluminum hydride[25] gave 2-methyl-3-furancarboxaldehyde. This compound reacted with hydroxylamine hydrochloride to yield the corresponding oxime (89.1% yield, mp 74–77 °C) which, in turn, was converted to **6a** without further purification.

2-Methyl-3-furancarboxaldoxime (9.8 g, 0.08 mol) was heated for 10 min in 15 ml of acetic anhydride. The solution was poured into 200 ml of ice-cold water and neutralized with sodium carbonate, whereupon the product was isolated by steam distillation. The distillate was extracted with ether and the organic layer was then separated and dried over anhydrous magnesium sulfate. Solvent was removed on a rotary evaporator, and the residue was distilled, first through a micro-Vigreux column and then through a spinning band column. The yield of pure **6a** was 2.3 g (27%): bp 42–44 °C (2.5 mm); ir (CCl_4) 3160, 2960, 2920, 1680, 1600, 1517, 1240, 950, and 742 cm^{-1}; NMR (neat) δ 7.37 (d, 1 H, H-4), 6.51 (d, 1 H, H-5), and 2.42 (s, 3 H, $-CH_3$); $J_{H_4H_5}$ = ±2.29 Hz. Compound **6a** had approximately the same stability as **3a**.

4-*tert*-Butylfurfuryl Alcohol (16). A solution of 4-*tert*-butyl-2-furoic acid (**15**, 20.0 g, 0.12 mol) in 180 ml of anhydrous ether was added dropwise to a solution of lithium aluminum hydride (6.0 g, 0.16 mol) in 600 ml of anhydrous ether at such a rate as to produce gentle reflux. After the addition was completed, the reaction mixture was refluxed for 2 h longer with continuous stirring. The solution was cooled and water was added dropwise to destroy the excess hydride. The resulting inorganic salts were removed by filtration. The ether filtrate was washed with 5% aqueous sodium carbonate and then dried with anhydrous sodium sulfate. Solvent was removed under reduced pressure and the residue was distilled in vacuo to yield 10.0 g (64.9%) of product: bp 73–74 °C (6 mm); NMR (CCl_4) δ 7.07 (s, 1 H, H-5), 6.21 (s, 1 H, H-3), 4.83 (s, 1 H, –OH), 4.48 (s, 2 H, CH_2), and 1.18 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_9H_{14}O_2$: C, 70.13; H, 9.09. Found: C, 70.32; H, 9.25.

4-*tert*-Butyl-2-(chloromethyl)furan (1b). This compound was synthesized from 4-*tert*-butylfurfuryl alcohol (**16**), thionyl chloride, and pyridine in anhydrous ether, by the procedure described for **1a**. The crude product was distilled in vacuo to yield 7.35 g (42.70%) of **1a**: bp 42–42.5 °C (2.1 mm); NMR (CCl_4) δ 7.13 (s, 1 H, H-5), 6.30 (s, 1 H, H-3), 4.47 (s, 2 H, CH_2), and 1.20 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_9H_{13}ClO$: C, 62.61; H, 7.32; Cl, 20.28. Found: C, 62.38; H, 7.54; Cl, 20.53.

4-*tert*-Butyl-2-furaldehyde (17). This compound was synthesized from 1-(4-*tert*-butyl-2-furoyl)aziridine and lithium aluminum hydride.[25] The yield of aldehyde was 47.9%: bp 55–56 °C (2.5 mm) [lit.[32] bp 93–95 °C (13 mm)]; ir (CCl_4) 3150, 2980, 2850, 2700, 1680, 1580, 1500, 1460, 1365, 1250, 1210, 1145, 943, 760, and 755 cm^{-1}; NMR (CCl_4) δ 9.45 (s, 1 H, –CHO), 7.36 (s, 1 H, H-5), 7.02 (s, 1 H, H-3), and 1.30 [s, 9 H, $-C(CH_3)_3$].

The aziridine derivative was prepared in situ from 4-*tert*-butyl-2-furoyl chloride and ethyleneimine. 4-*tert*-Butyl-2-furoyl chloride was obtained by heating 4-*tert*-butyl-2-furoic acid (12.0 g, 0.072 mol) and thionyl chloride (16.0 g, 0.15 mol) in 30 ml of benzene for 6 h. The excess thionyl chloride and benzene were removed by distillation under reduced pressure. The residue was then distilled in vacuo to give 4-*tert*-butyl-2-furoyl chloride (9.22 g, 69.0% yield): bp 69–71 °C (1.5 mm); ir (CCl_4) 2960, 1750, 1735, 1430, 1150, 1090, 965, and 945 cm^{-1}; NMR (CCl_4) δ 7.46 (s, 1 H, H-5, $J_{3,5}$ = ±1.5 Hz), 7.31 (s, 1 H, H-3, $J_{5,3}$ = +1.5 Hz), and 1.30 [s, 9 H, $-C(CH_3)_3$]. Because of the instability of the halide, an elemental analysis could not be obtained for this compound. The halide was, however, converted to the corresponding anhydride in 57.7% yield to provide additional proof of structure: mp 120–121 °C; ir (CCl_4) 2960, 1795, 1735, 1500, 1460, 1365, 1310, 1245, 1215, 1145, 1095, and 945 cm^{-1}; NMR (CCl_4) δ 7.46 (s, 1 H, H-5), 7.26 (s, 1 H, H-3), and 1.30 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.74; H, 6.83.

5-(4-*tert*-Butylfurfurylidene)rhodanine (18). A solution of 4-*tert*-butyl-2-furaldehyde (3.58 g, 0.024 mol) and rhodanine (3.0 g, 0.023 mol) in 15 ml of glacial acetic acid was heated with anhydrous sodium acetate (5.55 g, 0.068 mol) for 1.5 h and then poured into 100 ml of cold water. The yellow solid that formed was washed with water and recrystallized from 50% aqueous ethanol to yield 5.60 g (89.0%) of product: mp 187–188 °C; ir (CCl_4) 3440, 2980, 1690, 1610, 1565, 1435, 1220, 1190, and 965 cm^{-1}; NMR (CCl_4) δ 7.53 (s, 1 H, =CH), 7.41 (s, 1 H, H-5), 6.83 (s, 1 H, H-3), and 1.20 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_{12}H_{13}O_2NS_2$: C, 53.89; H, 4.87; N, 5.26; S, 23.91. Found: C, 53.74; H, 4.96; N, 5.25; S, 23.93.

4-*tert*-Butyl-α-thio-2-furanpyruvic Acid (19). A suspension of 5-(4-*tert*-butylfurfurylidene)rhodanine (5.60 g, 0.021 mol) in 40 ml of 10% aqueous sodium hydroxide (4.0 g, 0.10 mol) was heated on a steam bath for 0.5 h. The solution was cooled and treated with 40 ml of 10% hydrochloric acid to precipitate the acid. The resulting solid was washed with water and recrystallized from 45% aqueous ethanol to yield 4.15 g (88.0%) of yellow product: mp 96–98 °C; ir (CCl_4) 2960, 2900, 2870, 1700, 1600, 1500, 1410, 1260, and 950 cm^{-1}; NMR (CCl_4) δ 7.80 (s, 1 H, $-CO_2H$), 7.40 (s, 1 H, H-5), 6.90 (s, 1 H, H-3), 4.80 (s, 2 H, CH_2), and 1.40 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_{11}H_{14}O_3S$: C, 58.41; H, 6.19; S, 14.16. Found: C, 58.26; H, 6.20; S, 14.28.

4-*tert*-Butyl-2-furanpyruvic Acid Oxime (20). This compound was synthesized by heating 4-*tert*-butyl-α-thio-2-furanpyruvic acid (4.15 g, 0.019 mol), hydroxylamine hydrochloride (4.15 g, 0.059 mol), and an ethanolic sodium ethoxide solution [prepared from 1.35 g of sodium (0.059 g-atom) and 90 ml of absolute ethanol] for 1.5 h. The ethanol was removed under reduced pressure and the residue was dissolved in 10 ml of 5% aqueous sodium hydroxide. The sulfur that formed was removed by filtration and the filtrate was acidified with 9 ml of 10% hydrochloric acid. Recrystallization of the resulting brown solid from petroleum ether (bp 60–110 °C) gave 2.90 g of product, 71.4% yield: mp 122–123 °C; ir (CCl_4) 3230, 2960, 2900, 2870, 1700, 1600, 1470, 1460, 1420, 1360, 1205, 1180, 1130, 1120, 1095, 1030, 900, and 700 cm^{-1}.

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.67; H, 6.67; N, 6.67. Found: C, 58.59; H, 6.43; N, 6.73.

4-*tert*-Butyl-2-furanacetonitrile (2b). Compound **20** (1.50 g, 0.007 mol) was heated in acetic anhydride (5.50 g, 0.008 mol) for 1.5 h. The mixture was then treated with 125 ml of water and steam distilled. The distillate was extracted with ether, and the ether extracts were then neutralized with a saturated aqueous sodium carbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent and distillation of the residue in vacuo afforded 0.98 g (85.6%) of **2b**: bp 72–72.5 °C (3.5 mm); ir (CCl_4) 2960, 2900, 2870, 2250, 1610, 1540, 1470, 1460, 1420, 1360, 1210, 1120, 1110, 970, 950, and 665 cm^{-1}; NMR (CCl_4) δ 7.08 (s, 1 H, H-5), 6.25 (s, 1 H, H-3), 3.63 (s, 2 H, CH_2), and 1.20 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.62; H, 7.97; N, 8.59. Found: C, 73.50; H, 8.00; N, 8.74.

4-*tert*-Butyl-2-methylfuran (21). This compound was prepared by the reduction of 4-*tert*-butyl-2-furaldehyde hydrazone which, in turn, was synthesized from compound **17** (2.32 g, 0.015 mol) and 99% hydrazine hydrate (3.0 g, 0.06 mol) in 5 ml of ether. The mixture was treated with calcium chloride (1.65 g, 0.015 mol) and stirred for 1.5 h. The ether layer was decanted and dried over magnesium sulfate. Removal of the solvent under reduced pressure afforded 1.87 g (78.2% yield) of crude 4-*tert*-butyl-2-furaldehyde hydrazone. This compound was next added dropwise to a warm ethanolic solution of sodium ethoxide prepared from 0.23 g (0.01 g-atom) of sodium and 6 ml of absolute ethanol. The mixture was heated at reflux for 4 h and the resulting solution was then distilled at atmospheric pressure to yield **21** and ethanol. A saturated aqueous sodium chloride solution was added to the distillate. The oily layer that formed was separated, dried over anhydrous potassium carbonate, and distilled at atmospheric pressure to yield 1.20 g (72.9%) of compound **21** as a clear liquid: bp 151–152 °C; ir (CCl_4) 2960, 2900, 2860, 1610, 1540, 1465, 1455, 1390, 1380, 1360, 1350, 1290, 1220, 1200, 1115, 1110, 960, 920, and 795 cm^{-1}; NMR (CCl_4) δ 7.10 (s, 1 H, H-4), 6.03 (s, 1 H, H-3), 2.23 (s, 3 H, $-CH_3$), and 1.22 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_9H_{14}O$: C, 78.27; H, 10.14. Found: C, 78.09; H, 10.24.

3-*tert*-Butyl-5-methyl-2-furaldehyde (22). To a stirred mixture of *N,N*-dimethylformamide (1.27 g, 0.017 mol) and phosphorus oxychloride (2.66 g, 0.018 mol), prepared at 10 °C, was carefully added freshly distilled **21** (2.40 g, 0.018 mol) at such a rate as to maintain the temperature of the system at 10 °C. The resulting mixture was stirred for 0.5 h at ambient temperature. It was then poured into 20 ml of ice water, and recrystallized from absolute ethanol to yield 1.54 g (51.5%) of 3-*tert*-butyl-5-methyl-2-furaldehyde (22) as pale yellow crystals: mp 40–41 °C; ir (CCl_4) 2965, 2925, 2905, 2870, 1680, 1590, 1505, 1475, 1390, 1370, 1360, 1275, 1235, 1231, and 1060 cm^{-1}; NMR (CCl_4) δ 9.73 (s, 1 H, -CHO), 6.13 (s, 1 H, H-4), 2.35 (s, 3 H, $-CH_3$), and 1.33 [s, 9 H, $-C(CH_3)_3$].

Compound **22** (1.24 g, 0.0075 mol), hydroxylamine hydrochloride (0.84 g, 0.072 mol), and a solution of sodium carbonate (0.64 g, 0.006 mol) in 25 ml of water were heated on a steam bath for 4 h. The resulting solution was allowed to stand overnight, whereupon it was treated with distilled water (10 ml) and then extracted with three 10-ml portions of ether. The ether was removed on a rotary evaporator and the crude oxime (1.09 g, 85.1% yield) used directly in the next step.

3-*tert*-Butyl-5-methyl-2-furonitrile (3b). A solution of crude 3-*tert*-butyl-5-methyl-2-furaldehyde oxime (1.09 g, 0.006 mol) in acetic anhydride (4.40 g, 0.047 mol) was heated at reflux for 0.5 h. The solution was cooled, treated with distilled water (60 ml), and then steam distilled. The distillate was extracted three times with 15-ml portions of ether. After the ether extracts were neutralized with a saturated aqueous sodium carbonate solution and dried over anhydrous magnesium sulfate, the solvent was removed on a rotary evaporator and the residue was distilled in vacuo to give 0.84 g (84.9% yield) of **3b**: bp 50.5–51 °C (1.5 mm); ir (CCl_4) 2980, 2885, 2210, 1670, 1660, 1595, 1530, 1475, 1360, 1235, 1200, 1060, 965, and 810 cm^{-1}; NMR (CCl_4) δ 6.08 (s, 1 H, H-4), 2.30 (s, 3 H, $-CH_3$), and 1.33 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.62; H, 7.97; N, 8.59. Found: C, 73.60; H, 7.76; N, 8.38.

Reaction of 2-(Chloromethyl)furans (1a and 1b) with Potassium Cyanide. This reaction was carried out under the conditions described by Reichstein.[5] To a vigorously stirred solution of potassium cyanide (8.0 g, 0.123 mol) in 15 ml of water was added freshly distilled 2-(chloromethyl)furan (10.0 g, 0.085 mol). The reaction was exothermic. Within 30 min, the exotherm subsided and a heavy precipitate of potassium chloride formed. Stirring was continued for 2 h to assure completion of the reaction. The mixture was extracted with ether and the extracts were then treated with charcoal, dried, and evaporated under reduced pressure. The crude mixture was analyzed directly by NMR or first diluted with carbon tetrachloride and then analyzed. The following product distribution was obtained: furfuryl alcohol, 3%; **2a**, 38%; **3a**, 57%; and a compound of unknown structure, 2%. The relative proportion of **2a** and **3a** observed under these conditions was 40:60, respectively.

Although we utilized Reichstein's conditions[5] in our rate studies, we found that the highest yields of product were obtained when **1a** (10.0 g, 0.085 mol) was treated with a large excess of potassium cyanide (13.0 g, 0.2 mol, 15 ml of water). At lower cyanide levels (6.5 g, 0.1 mol), yields were comparable to those observed with the Reichstein procedure.[5]

The reaction of **1b** with potassium cyanide required 16 h at 37.5 ± 0.5 °C to reach completion. Erlenmeyer flasks containing **1b** (0.30 g, 0.018 mol) and a solution of potassium cyanide (0.18 g, 0.027 mol) in 0.5 ml of water were placed in an Elberbach water bath shaker at the cited temperature. At various time intervals, samples were withdrawn and analyzed as described.

Temperature Studies. Temperature studies were conducted at 0 and 37.5 °C for **1a**, and at 60, 80, 90, and 100 °C for **1b**. The freshly distilled 2-chloromethyl compound (0.018 mol) was added to solutions of potassium cyanide (0.03 mol) in 0.5 ml of water. The resulting mixtures were then stirred in an appropriate constant temperature bath. With compound **1a** at 0 °C, after 3 h, the average product distribution was as follows: furfuryl alcohol, 2%; **1a**, 1%; **2a**, 37%; **3a**, 46%; and **4a**, 14%. At 37.5 °C, the values follow: furfuryl alcohol, 4%; **1a**, trace; **2a**, 37%; and **3a**, 59%.

Concentration Studies. Compound **1a** (10.0 g, 0.085 mol) was treated with 1, 2, and 4 N cyanide solutions prepared from 8.0 g (0.123 mol) of potassium cyanide and appropriate amounts of water. The temperature of the reaction was not controlled and the products were analyzed after 3 h.

Compound **1b** (0.6 g, 0.003 mol) was treated with solutions of potassium cyanide (0.36 g, 0.006 mol) in 0.6, 1, 1.5, and 2 ml of distilled water. The samples were placed in an Elberbach water bath shaker and kept at 37.5 ± 0.5 °C for 96 h. The products were analyzed in the usual manner.

The absolute yields of **2a** and **3a** increased with cyanide concentration. However, when the relative yields of the two nitriles were compared, dilution appeared to favor the formation of **3a**; in more concentrated solutions, larger amounts of **2a** formed. The same trend was observed in the reactions of **1b** with aqueous cyanide.

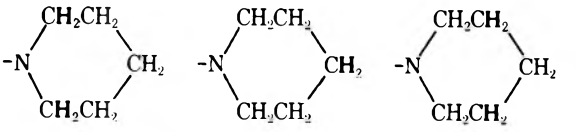
Studies of the Effect of Cations. Various metallic and organic cyanides were used as a source of cyanide ions. Silver cyanide (16.4 g, 0.123 mol) was extremely insoluble in the reaction medium and made it impossible to isolate the products in the usual manner. Mercuric cyanide (31.0 g, 0.123 mol) caused the polymerization of **1a**, even at 0 °C. Cuprous cyanide was used as a complex prepared from 8.3 g (0.128 mol) of potassium cyanide and 1.2 g (0.013 mol) of cuprous cyanide in 15 ml of water. The reactions of this complex with **1a** were performed both with and without temperature control. Ammonium cyanide was prepared in situ by the reaction of 6.5 g (0.122 mol) of ammonium chloride with 8.0 g (0.123 mol) of potassium cyanide in 45 ml of water. Benzyltrimethylammonium cyanide was also generated in situ using 37.2 g (0.123 mol) of benzyltrimethylammonium chloride and 8.0 g (0.123 mol) of potassium cyanide in 67 ml of water. The reactions of ammonium and benzyltrimethylammonium cyanides with **1a** were carried out without temperature control.

Solvent Studies. A gradual change in the polarity of the medium was achieved by the use of mixed solvents; 40, 60, 80, and 99% aqueous 1,2-dimethoxyethane solutions (20 ml), respectively. With the exception of the reaction time, which was increased to 3 h to ensure completion of the reaction, all other conditions remained the same.

Reactions of 1b with Amines, Scheme I. The general procedure used will be described for the preparation of 4-*tert*-butyl-*N,N*-diethylfurfurylamine (8). A solution of diethylamine (2.20 g, 0.03 mol) in 4.5 ml of benzene was added dropwise, with vigorous stirring, to a solution of 4-*tert*-butyl-2-(chloromethyl)furan (2.50 g, 0.015 mol) in 7.5 ml of benzene. The mixture was heated at reflux for 4 h, cooled, and acidified (Congo red) with 10% aqueous hydrochloric acid. The acid layer was separated and the benzene layer was washed with 20 ml of distilled water. The acid layer and aqueous washings were combined and neutralized with saturated aqueous sodium carbonate. Ether and 1 ml of 10% aqueous sodium hydroxide were then added. The ether layer was separated and the aqueous layer was extracted with three 15-ml portions of ether. After the extracts were dried over anhydrous sodium sulfate, the ether was removed under reduced pressure and the residue was distilled in vacuo to give 2.50 g (79.8% yield) of 8 as a clear liquid: bp 57–57.5 °C (1.5 mm); ir (neat) 2960, 2860, 2800, 1380. 1360, 1060, 965, and 925 cm^{-1}; NMR (CCl_4) δ 7.00 (s, 1 H, H-5), 6.04 (s, 1 H, H-3), 3.53 (d, 2 H, CH_2), 2.43 (q, 2 H, $-CH_2CH_3$, J = 7 Hz), 1.20 [s, 9 H, $-C(CH_3)_3$], and 1.02 (t, 6 H, $-CH_2CH_3$, J = 7 Hz).

Anal. Calcd for $C_{13}H_{23}NO$; C, 74.64; H, 11.01; N, 6.70. Found: C, 74,80; H, 11.11; N, 6.88.

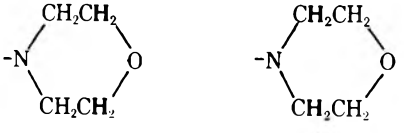
1-(4-*tert*-Butylfurfuryl)piperidine (9), Scheme I. A solution of **1b** (1.50 g, 0.009 mol) in 5 ml of benzene was treated with a solution of piperidine (1.54 g, 0.0018 mol) in 7.5 ml of benzene as described in the preparation of 8. The residual liquid was distilled in vacuo to yield 1.64 g (82.3% yield) of **9** as a clear liquid: bp 72–72.5 °C (1.0 mm); ir (CCl_4) 2960, 2940, 2860, 2875, 2800, 1470, 1440, 1360, 1340, 1300, 1205, 1160, 1150, 1125, 1095, 1100, 1040, 995, 965, 900, and 860 cm^{-1}; NMR



(CCl_4) δ 6.98 (s, 1 H, H-5), 6.02 (s, 1 H, H-3), 3.35 (s, 2 H, CH_2), 2.30 (m, 4 H, see A), 1.66 (s, 2 H, see B), 1.43 (m, 4 H, see C), and 1.20 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_{14}H_{23}NO$: C, 76.02; H, 10.86; N, 6.33. Found: C, 75.95; H, 10.72; N, 6.30.

4-(4-*tert*-Butylfurfuryl)morpholine (10), Scheme I. A solution of **1b** (1.50 g, 0.009 mol) in 5 ml of benzene was treated with a solution of morpholine (1.57 g, 0.018 mol) in 7.5 ml of benzene as described in the preparation of 8. The residue was distilled in vacuo to yield 1.55 g (77%) of **10** as a clear liquid: bp 78–79 °C (0.75 mm); ir (CCl_4) 2960, 2860, 1605, 1470, 1460, 1450, 1360, 1345, 1330, 1240, 1200, 1125, 1110,



1105, 1090, 1070, 1005, 980, 960, 950, 925, 900, and 865 cm^{-1}; NMR (CCl_4) δ 7.03 (s, 1 H, H-5), 6.09 (s, 1 H, H-3), 3.38 (s, 2 H, CH_2), 3.58 (m, 4 H, see D), 2.36 (m, 4 H, see E), and 1.20 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.90; H, 9.41; N, 6.27. Found: C, 69.77; H, 9.33; N, 6.12.

2-(4-*tert*-Butylfurfuryl)-2-thiopseudourea Monohydrochloride (11), Scheme I. A mixture of **1b** (2.00 g, 0.012 mol) and thiourea (10.92 g, 0.012 mol) in 6 ml of acetone was heated at reflux on a steam bath for 5 h. The solid that formed was collected and recrystallized from ethanol–acetone to give 2.33 g (78.3% yield) of **11**: mp 184–185 °C; ir (KBr) 3240, 3050, 2950, 2860, 2770, 2730, 1660, 1645, 1420, 1140, 1120, 1090, 950, 755, and 700 cm^{-1}; NMR (EtOH) δ 6.98 (s, 1 H, H-5), 6.15 (s, 1 H, H-3), 4.98 (s, 2 H, CH_2), and 1.23 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_{10}H_{17}ClN_2OS$: C, 48.30; H, 6.84; S, 13.28; Cl, 14.27; N, 11.27. Found: C, 48.50; H, 6.71; S, 12.98; Cl, 14.42; N, 11.12.

Diethyl (4-*tert*-Butylfurfuryl)malonate (12), Scheme I. Diethyl malonate (4.80 g, 0.031 mol) was stirred for 2 h with an ethanolic solution of sodium ethoxide [prepared from 0.69 g of sodium (0.030 g-atom), and 12 ml of absolute ethanol] and then treated with compound **1b** (2.00 g, 0.012 mol). The mixture was heated at reflux for 4 h. Ethanol was removed under reduced pressure and water was added to the residue. The oily layer that formed was separated and the aqueous layer was extracted with three 10-ml portions of ether. The oily layer and ether extracts were combined, washed with water, and dried over magnesium sulfate. Removal of the ether under reduced pressure and distillation of the residue in vacuo gave 3.0 g (84.8% yield) of **12** as a yellow liquid: bp 112–113 °C (0.9 mm); ir (CCl_4) 2960, 2900, 2860, 1750, 1730, 1470, 1460, 1440, 1365, 1335, 1295, 1145, 1120, 1095, 1030, 960, 925, and 885 cm^{-1}; NMR (CCl_4) δ 7.02 (s, 1 H, H-5), 6.00 (s, 1 H, H-3), 3.61 [t, 1 H, $-CH(CO_2C_2H_5)_2$], 3.13 (d, 2 H, CH_2), 4.14 (q, 4 H, $-CO_2CH_2CH_3$, J = 7 Hz), 1.25 (t, 6 H, $-CO_2CH_2CH_3$, J = 7 Hz), and 1.25 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.86; H, 8.14. Found: C, 64.70; H, 8.02.

Diethyl (4-*tert*-Butylfurfuryl)methyl Malonate (13), Scheme I. Compound **1b** (1.50 g, 0.009 mol) was treated with diethyl methyl malonate (4.30 g, 0.025 mol) and an ethanolic solution of sodium ethoxide [prepared from 0.53 g of sodium (0.023 g-atom) and 9 ml of absolute ethanol] as described for the preparation of **12**. The residue was distilled in vacuo to yield 2.21 g (79.2%) of **13** as a yellow liquid: bp 107–108 °C (2 mm); ir (CCl_4) 2960, 2930, 2900, 2860, 1770, 1730, 1460, 1375, 1360, 1240, 1100, 1020, 980, 925, and 855 cm^{-1}; NMR (CCl_4) 6.96 (d, 1 H, H-5), 5.97 (s, 1 H, H-3), 4.05 (q, 4 H, $-CO_2CH_2CH_3$, J = 7 Hz), 3.08 (s, 2 H, CH_2), and 1.18, 1.20 [m, 18 H, $-CH_3$ and $-C(CH_3)_3$].

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.81; H, 8.39. Found: C, 65.94; H, 8.55.

Ethyl α-Acetyl-4-*tert*-butyl-2-furanpropionate (14), Scheme I. Compound **1b** (1.50 g, 0.009 mol) was treated with ethyl acetoacetate (3.70 g, 0.023 mol) and an ethanolic solution of sodium ethoxide [prepared from 0.53 g of sodium (0.023 g-atom) and 9 ml of absolute ethanol] as described in the preparation of **12**. The residue was distilled in vacuo to yield 2.06 g (81.6%) of **14** as a yellow liquid: bp 110–111 °C (3 mm); ir (CCl_4) 2960, 2860, 1770, 1742, 1740, 1720, 1425, 1360, 1235, 1198, 1120, 1060, 1025, 960, 940, and 860 cm^{-1}; NMR (CCl_4) δ 6.96 (s, 1 H, H-3), 5.93 [m, 1 H, $-CH(CO_2C_2H_5)COCH_3$], 3.05 (d, 2 H, CH_2), 4.18 (q, 2 H, $-CH_2CH_3$, J = 7 Hz), 2.13 (s, 3 H, $-COCH_3$), 1.20 (t, 3 H, $-CH_2CH_3$, J = 7 Hz), and 1.21 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.77; H, 8.28. Found: C, 67.75; H, 8.45.

Reaction of 1b with Sodium Azide. A mixture of compound **1b** (1.80 g, 0.011 mol) and sodium azide (0.98 g, 0.015 mol) in 3.5 ml of water was stirred and heated on a steam bath for 24 h. Ether (10 ml) was added to the cooled mixture. The layers that formed were separated and the aqueous layer was extracted with two 10-ml portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Removal of the ether under reduced pressure and distillation of the residue in vacuo afforded 1.21 g (62.2% yield) of a clear liquid, bp 45–47 °C (1.3 mm), which was diluted with carbon tetrachloride and analyzed by NMR spectroscopy. The following resonances were characteristic of 2-(azidomethyl)-4-*tert*-butylfuran: δ 7.08 (s, 1 H, H-5), 6.23 (s, 1 H, H-3), 4.13 (s, 2 H, CH_2), and 1.21 [s, 9 H, $C(CH_3)_3$]. 2-Azido-4-*tert*-butyl-5-methylfuran was responsible for resonances at δ 6.44 (s, 1 H, H-3), 2.33 (s, 3 H, $-CH_3$), and 1.21 [s, 9 H, $-C(CH_3)_3$]. The ir (CCl_4) spectrum of the mixture exhibited different absorptions for the two azide groups. The following absorptions were noted: 2960, 2920, 2900, 2860, 2055, 2045, 1465, 1455, 1360, 1330, 1260, 1230, 1200, 1125, 1090, 960, 925, 910, 865, 815, and 770 cm^{-1}. When the reaction was performed at 80 °C, the ratio of the isomeric azides was 92% (normal) and 8% (abnormal). At 40 °C, the ratio was 81%:19%.

Reaction of 1b with Potassium Thiocyanate. Compound **1b** (1.50 g, 0.009 mol) was added dropwise to a solution of aqueous potassium thiocyanate (1.20 g, 0.012 mol) and the resulting mixture was heated for 24 h. Runs were carried out at 37, 40, and 80 °C. Ether (15 ml) was added to the cooled mixture and the resulting layers were separated. The aqueous layer was extracted with two 10-ml portions of ether. The combined ether extracts were then dried with anhydrous magnesium sulfate. Removal of the ether under reduced pressure and distillation of the residue in vacuo gave a clear liquid, 1.12 g (65.9%), bp 70–72 °C (0.6 mm), which was diluted with carbon tetrachloride and analyzed by NMR spectroscopy. The following resonances were observed: δ 7.03 (s, 1 H, H-5), 6.18 (s, 1 H, H-3), 4.55 (s, 2 H, CH_2), and 1.17–1.21 [m, 9 H, $-C(CH_3)_3$], 4-*tert*-butylfurfuryl thiocyanate; 7.08 (s, 1 H, H-5), 6.28 (s, 1 H, H-3), 4.41 (s, 2 H, CH_2), and 1.17–1.21 [s, 9 H, $-C(CH_3)_3$], 4-*tert*-butylfurfuryl isothiocyanate; 5.86 (s, 1 H, H-3), 2.48 (s, 3 H, CH_3), and 1.17–1.21 [s, 9 H, $-C(CH_3)_3$], 2-thiocyano- or isothiocyano-4-*tert*-butyl-5-methylfuran. The ir spectrum (CCl_4) of the mixture showed bands at 2960, 2920, 2900, 2860, 2150, 2055, 1788, 1770, 1470, 1460, 1360, 1246, 1232, 1212, 1205, 1128, 1086, 966, and 945 cm^{-1}. The following isomer ratios were observed at 37 °C: normal thiocyanate, 43%; normal isothiocyanate, 43%; abnormal product, 14%.

Anal. Calcd for $C_{10}H_{13}NOS$: C, 61.54; H, 6.66; N, 7.18; S, 16.92. Found: C, 61.41; H, 6.74; N, 7.05; S, 16.65.

Preparation of 4-Isopropyl-2-(chloromethyl)furan (1c), Scheme IV. The alkylation of 2-furaldehyde with isopropyl chloride was carried out according to the procedure of Gilman and Calloway.[28a] 2-Furaldehyde (48.00 g, 0.50 mol) was added dropwise, with stirring, to a suspension of aluminum chloride (80.00 g, 0.60 mol) in 1000 ml of carbon disulfide. A solution of isopropyl chloride (39.30 g, 0.50 mol) in 250 ml of carbon disulfide was then added to this mixture and it was stirred for 24 h at ambient temperature. The mixture was poured onto 100 g of cracked ice and extracted with three 200-ml portions of ether. The extracts were then washed with 200 ml of saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate. Evaporation of the solvent and distillation of the residue in vacuo through a spinning band column afforded three fractions. The first fraction consisted of unreacted 2-furaldehyde (**23**), bp 34–36 °C (4 mm) [lit.[28a] bp 161–162 °C (760 mm)]. The second fraction, 14.5 g (21.0% yield), bp 65–68 °C (2.2 mm) [lit.[28a] bp 101–103 °C (21 mm)], was identified as 4-isopropyl-2-furaldehyde (**24**): ir (CCl_4) 2980, 2930, 2870, 2830, 2740, 1685, 1500, 1460, 1380, 1365, 1250, 1140, 1070, 970, and 940 cm^{-1}; NMR (CCl_4) δ 9.58 (s, 1 H, –CHO), 7.40 (s, 1 H, H-5), 7.06 (s, 1 H, H-3), 2.83 [hep, 1 H, $-CH(CH_3)_2$, J = 7 Hz], and 1.23 [d, 6 H, $-CH(CH_3)_2$, J = 7 Hz]. The third fraction, 2.53 g (2.51%), bp 78–80 °C (0.45 mm), was identified as 4,5-diisopropyl-2-furaldehyde (**25**): ir (CCl_4) 2960, 2930, 2870, 2810, 2800, 2740, 2690, 1685, 1675, 1590, 1520, 1455, 1410, 1380, 1360, 1325, 1245, 1160, 1145, 1135, 1100, 1055, 1040, 980, and 970 cm^{-1}; NMR (CCl_4) δ 9.42 (s, 1 H, –CHO), 6.95 (s, 1 H, H-3), 2.95 [hep, 1 H, $-CH(CH_3)_2$, J = 7 Hz], and 1.16 [m, 12 H, $-CH(CH_3)_2$, J = 7 Hz].

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.88. Found: C, 73.52; H, 8.70.

4-Isopropylfurfuryl Alcohol (26), Scheme IV. A solution of compound **24** (13.00 g, 0.10 mol) in 150 ml of anhydrous ether was reduced with lithium aluminum hydride (4.95 g, 0.13 mol) in 300 ml of anhydrous ether. The ether solution was washed first with a saturated sodium bisulfite solution and then with 10 ml of 5% aqueous sodium carbonate solution. The ether was removed on a rotary evaporator and the residual liquid was distilled in vacuo to yield 2.45 g (17.4%) of **26**: bp 65–66 °C (6 mm); ir (CCl_4) 3610, 3360, 2960, 2910, 2880, 1460, 1380, 1360, 1255, 1165, 1130, 1115, 1080, 1040, 1010, 960, and 910 cm^{-1}; NMR δ 7.06 (s, 1 H, H-5), 6.11 (s, 1 H, H-3), 4.40 (s, 2 H, CH_2), 3.50 (s, 1 H, –OH), 2.75 [hep, 1 H, $-CH(CH_3)_2$, J = 7 Hz], and 1.25 [d, 6 H, $-CH(CH_3)_2$, J = 7 Hz].

Anal. Calcd for $C_8H_{12}O_2$: C, 68.57; H, 8.57. Found: C, 68.46; H, 8.53.

4-Isopropyl-2-(chloromethyl)furan (1c), Scheme IV. A solution of compound **26** (2.45 g, 0.016 mol) in 2.5 ml of anhydrous ether was treated with thionyl chloride (2.14 g, 0.018 mol) and pyridine (1.58 g, 0.019 mol) in 1.5 ml of ether. The reaction mixture was diluted with additional ether and the precipitated solid was then removed by filtration. The ether extracts were neutralized with aqueous potassium hydroxide and dried with anhydrous sodium carbonate. Removal of the solvent under reduced pressure on a rotary evaporator and distillation of the residue in vacuo gave 1.21 g (42.3% yield) of **1c**: bp 55–56 °C (6 mm); ir (CCl_4) 2980, 2920, 2880, 1465, 1425, 1370, 1360, 1290, 1270, 1250, 1170, 1140, 1110, 1070, 960, 950, 875, and 700 cm^{-1}; NMR (CCl_4) δ 7.02 (s, 1 H, H-5), 6.15 (s, 1 H, H-3), 4.38 (s, 2 H, CH_2), 2.70 [hep, 1 H, $-CH(CH_3)_2$, J = 7 Hz], and 1.17 [d, 6 H, $-CH(CH_3)_2$,

J = 7 Hz]; mass spectrum m/e (rel intensity) 158 (M^+, 1.69), 123 ($C_8H_{11}O^+$, 100).

Anal. Calcd for $C_8H_{11}ClO$: C, 60.51; H, 6.94; Cl, 22.10. Found: C, 60.23; H, 6.65; Cl, 21.98.

Preparation of 3-*tert*-Butyl-2-(chloromethyl)furan (1d), Scheme V. 5-Bromo-2-furoic acid (572.91 g, 3.0 mol) was esterified with 1500 ml of absolute ethanol and 30 ml of concentrated sulfuric acid to yield 501.1 g (70%) of **27**: bp 62–63 °C (3 mm) [lit.[31a] bp 134–136 °C (34 mm)]; ir (CCl_4) 2985, 1715, 1580, 1465, 1366, 1351, 1290, 1205, 1142, 1120, 1110, 1010, 950, and 925 cm^{-1}; NMR (CCl_4) δ 7.18 (d, 1 H, H-3), 6.60 (d, 1 H, H-4), 4.39 (q, 2 H, $-CO_2CH_2CH_3$, J = 7 Hz), and 1.40 (t, 3 H, $-CO_2CH_2CH_3$, J = 7 Hz).

Compound **27** (87.6 g, 0.4 mol) was alkylated using *n*-octadecyl bromide (133.2 g, 0.4 mol) and aluminum chloride (106.8 g, 0.8 mol) in 600 ml of carbon disulfide[32] to yield 30.0 g (36.0%) of **28**: bp 110–125 °C (2 mm) [lit.[32] bp 130–142 °C (5 mm)]; ir (CCl_4) 2960, 2925, 2905, 2870, 1730, 1715, 1590, 1490, 1455, 1365, 1345, 1300, 1245, 1215, 1170, 1140, 1095, 1015, 1005, and 960 cm^{-1}; NMR (CCl_4) δ 7.06 (s, 1 H, H-3), 4.29 (q, 2 H, J = 7 Hz), 1.33 (t, 3 H, J = 7 Hz), and 1.33 [s, 9 H, $-C(CH_3)_3$].

Compound **28** (30.0 g, 0.11 mol) was hydrolyzed with ethanolic potassium hydroxide (10.0 g, 0.18 mol) to yield 8.68 g (32.1%) of **29**: mp 164–165 °C (lit.[32] 164–165 °C); ir (CCl_4) 2960, 2865, 1685, 1590, 1490, 1460, 1415, 1360, 1345, 1245, 1215, 1178, 1005, and 960 cm^{-1}; NMR (CCl_4) δ 11.06 (s, 1 H, –OH), 7.26 (s, 1 H, H-3), and 1.36 [s, 9 H, $-C(CH_3)_3$].

2-Bromo-3-*tert*-butylfuran (30), Scheme V. Compound **29** (34.50 g, 0.14 mol), quinoline (53.00 g, 0.75 mol), and copper chromite (6.00 g, 0.026 mol) were heated under nitrogen in a distillation apparatus. The distillate was then redistilled in vacuo to give **30** as a clear liquid: 12.00 g (42.5% yield); bp 63–64 °C (6 mm); ir (CCl_4) 2980, 2905, 2870, 1490, 1475, 1410, 1390, 1365, 1355, 1170, 1150, 1100, 1060, 990, and 890 cm^{-1}; NMR (CCl_4) δ 7.25 (d, 1 H, H-4, J = 2 Hz), 6.26 (d, 1 H, H-5, J = 2 Hz), and 1.30 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_8H_{11}BrO$: C, 49.38; H, 6.41; Br, 37.38. Found: C, 49.72; H, 6.06; Br, 37.24.

3-*tert*-Butyl-2-furoic Acid (31), Scheme V. Compound **30** (11.10 g, 0.055 mol) was added dropwise, under nitrogen, to a solution of 5% *n*-butyllithium (4.74 g, 0.0736 mol) in 20.6 ml of hexane and 80 ml of anhydrous ether. The reaction mixture was cooled, stirred for 4 h, and poured over dry ice. After completion of the reaction, 15 ml of wet ether and then 25 ml of 5% aqueous acetic acid were added to the mixture. Stirring was continued for 1 h. The acid layer was separated and extracted with two 20-ml portions of ether. The combined ether extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the ether under reduced pressure and recrystallization of the residue from aqueous ethanol gave 4.00 g (44% yield) of **31** as a white solid: mp 120–121 °C; ir (CCl_4) 3000, 2980, 2950, 2930, 2880, 1680, 1565, 1485, 1480, 1425, 1310, 1280, 1265, 1085, 1050, and 890 cm^{-1}; NMR (CCl_4) δ 12.33 (s, 1 H, $-CO_2H$), 7.35 (d, 1 H, H-5), 6.51 (s, 1 H, H-4), and 1.36 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_9H_{12}O_3$: C, 64.22; H, 7.14. Found: C, 64.39; H, 7.25.

3-*tert*-Butylfurfuryl Alcohol (32), Scheme V. A solution of compound **31** (4.00 g, 0.024 mol) in 100 ml of anhydrous ether was treated with lithium aluminum hydride (1.11 g, 0.029 mol) in 250 ml of anhydrous ether, as described in the preparation of **26**, to yield 2.50 g (60.0%) of **32**, as a clear liquid: bp 75.5–77 °C (6.5 mm); ir (CCl_4) 3610, 3300, 2980, 2930, 2910, 2870, 1505, 1465, 1390, 1365, 1220, 1170, 1150, 1130, 1080, 915, 895, 885, and 720 cm^{-1}; NMR (CCl_4) δ 7.26 (d, 1 H, H-5, J = 2 Hz), 6.23 (s, 1 H, H-4, J = 2 Hz), 4.50 (s, 2 H, CH_2), 2.66 (s, 1 H, –OH), and 1.25 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_9H_{14}O_2$: C, 70.13; H, 9.09. Found: C, 70.34; H, 9.08.

3-*tert*-Butyl-2-(chloromethyl)furan (1d), Scheme V. A solution of freshly distilled **32** (2.44 g, 0.015 mol) and pyridine (1.45 g, 0.018 mol) in 5 ml of ether was treated with thionyl chloride (1.99 g, 0.17 mol) as described in the preparation of **1a**. Removal of the solvent and distillation of the residue in vacuo gave 1.88 g (65.0% yield) of **1d** as a clear liquid: bp 67.5–68 °C (7.5 mm); ir (CCl_4) 2980, 2900, 2870, 1475, 1460, 1360, 1260, 1220, 1170, 1150, 1070, 1010, 895, and 720 cm^{-1}; NMR (CCl_4) δ 7.20 (d, 1 H, H-5, J = 2 Hz), 6.23 (d, 1 H, J = 2 Hz), 4.65 (s, 2 H, CH_2), and 1.33 [s, 9 H, $-C(CH_3)_3$].

Anal. Calcd for $C_9H_{13}ClO$: C, 62.21; H, 7.54; Cl, 20.53. Found: C, 62.50; H, 7.84; Cl, 20.44.

Preparation of 4-Bromo-2-(chloromethyl)furan (1e), Scheme VI. 2-Furaldehyde (96.0 g, 2.00 mol) was treated with 94 ml of bromine (279.9 g, 3.50 mol) in the presence of aluminum chloride[34] (292 g, 2.20 mol) to yield 105 g (72%) of **33**: mp 36–37 °C (lit.[34] mp 36–37 °C); ir (CCl_4) 3370, 3140, 2830, 2760, 1690, 1570, 1460, 1370, 1325, 1270, 1200, 1175, 1105, 990, 985, 965, 955, and 840 cm^{-1}; NMR (CCl_4) δ 8.10 (s, 1 H, –CHO), and 6.98 (s, 1 H, H-3).

Compound **33** (53.00 g, 0.22 mol) was oxidized with a solution of silver nitrate (79.50 g, 0.47 mol) and sodium hydroxide[35] (58.30 g, 1.45 mol) in 150 ml of water to give 39.00 g (65.7% yield) of **34**: mp 167–168 °C (lit.[10] 168–169 °C); NMR (CCl_4) δ 11.17 (s, 1 H, $-CO_2H$) and 7.23 (s, 1 H, H-3).

A solution of compound **34** (39.00 g, 0.15 mol) in 700 ml of 2:7 aqueous ammonium hydroxide was treated with zinc dust[36] (30.00 g, 0.46 mol) to give 14.00 g (49.3% yield) of **35**, mp 115–127 °C (lit.[36] mp 126–127 °C). The crude product was used in the next reaction without further purification.

4-Bromofurfuryl Alcohol (36), Scheme VI. A solution of crude 4-bromo-2-furoic acid (14.00 g, 0.075 mol) in 100 ml of anhydrous ether was treated with lithium aluminum hydride (4.40 g, 0.12 mol) in 400 ml of the same solvent as described in the preparation of **26**. The residual liquid was distilled in vacuo to give two fractions. The first fraction (bp 42–44 °C, 2.5 mm) was identified as 2-furfuryl alcohol by comparison of its ir and NMR spectra with those of an authentic sample of this compound. The second fraction (bp 63–64 °C, 2.5 mm) afforded 3.31 g of **36** (40% yield): ir (CCl_4) 3620, 3300, 3160, 2925, 2880, 1595, 1515, 1530, 1385, 1360, 1225, 1210, 1150, 1130, 1015, and 910 cm^{-1}; NMR (CCl_4) δ 7.46 (s, 1 H, H-5), 6.23 (s, 1 H, H-3), 4.38 (s, 2 H, CH_2), and 3.80 (s, 1 H, –OH).

Anal. Calcd for $C_5H_5BrO_2$: C, 34.12; H, 2.83; Br, 44.64. Found: C, 34.10; H, 3.07; Br, 44.93.

4-Bromo-2-(chloromethyl)furan (1e), Scheme VI. A solution of freshly distilled 4-bromofurfuryl alcohol (4.80 g, 0.030 mol) and pyridine (2.85 g, 0.036 mol) in 5 ml of ether was treated with thionyl chloride (4.20 g, 0.035 mol) as described in the preparation of **1a**. The residual liquid was distilled in vacuo to give 3.20 g (74.0% yield) of **1e**: bp 31–32 °C (2.5 mm); ir (CCl_4) 3160, 3120, 2960, 1590, 1510, 1430, 1355, 1270, 1235, 1215, 1145, 1125, 1090, 1015, 950, 930, and 880 cm^{-1}; NMR (CCl_4) δ 7.37 (s, 1 H, H-5), 6.37 (s, 1 H, H-3), and 4.45 (s, 2 H, CH_2).

Anal. Calcd for C_5H_4BrClO: C, 30.86; H, 20.58; Br, 40.53; Cl, 18.23. Found: C, 30.72; H, 20.32; Br, 40.36; Cl, 18.01.

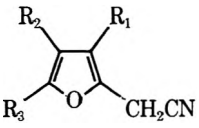
Preparation of Ethyl 5-(Chloromethyl)-3-furoate (1f), Scheme VII. 3,4-Difurandicarboxylic acid (10.00 g, 0.064 mol), copper chromite (1.5 g, 0.0054 mol), and 25 ml of quinoline[37] were heated under nitrogen in a distillation apparatus. The distillate was extracted several times with saturated aqueous sodium carbonate solution. The sodium carbonate extracts were then washed with ether and acidified with 1:1 aqueous hydrochloric acid. Thorough extraction of the acidified solution with ether and evaporation of the ether under reduced pressure gave 1.05 g (12.6% yield) of 3-furoic acid (**38**): mp 120–121 °C (lit.[37] mp 121–122 °C); NMR (CCl_4) δ 12.33 (s, 1 H, CO_2H), 8.17 (s, 1 H, H-2), 7.50 (s, 1 H, H-5), and 6.83 (s, 1 H, H-3).

Compound **38** (0.95 g, 0.0067 mol) was esterified with 5 ml of absolute ethanol and 0.1 ml of concentrated sulfuric acid to yield 0.62 g (65.7%) of **39**: bp 95–95.5 °C (52 mm); ir (CCl_4) 2980, 2960, 2940, 1725, 1590, 1575, 1570, 1500, 1475, 1440, 1400, 1365, 1305, 1160, 1080, 1000, and 875 cm^{-1}; NMR (CCl_4) δ 7.80 (s, 1 H, H-2), 7.37 (s, 1 H, H-5), 6.66 (s, 1 H, H-3), 4.21 (q, 2 H, $-CO_2CH_2CH_3$, J = 7 Hz), and 1.34 (t, 3 H, $-CO_2CH_2CH_3$, J = 7 Hz).

Ethyl 5-(Chloromethyl)-3-furoate (1f), Scheme VII. A mixture of **39** (0.52 g, 0.0026 mol), paraformaldehyde (0.015 g, 0.005 mol), and anhydrous zinc chloride (0.12 g, 0.009 mol) in 2 ml of chloroform was kept at 25 °C while hydrogen chloride was passed into the reaction flask for 2 h. By the end of the reaction, the paraformaldehyde had completely dissolved. The contents of the flask were then poured into 20 ml of cold water. The chloroform layer was separated, washed with three 10-ml portions of water, and dried over calcium chloride. Evaporation of the solvent and distillation of the residue in vacuo afforded 0.38 g (59.0% yield) of **1f**: bp 118–119 °C (3 mm); ir (CCl_4) 2980, 2960, 2930, 2900, 1475, 1460, 1375, 1365, 1305, 1260, 1230, 1200, 1145, 1100, 1075, 970, 965, 945, 840, and 710 cm^{-1}; NMR (CCl_4) δ 7.93 (s, 1 H, H-2), 6.69 (s, 1 H, H-4), 4.52 (s, 2 H, CH_2), 4.25 (q, 2 H, $-CO_2CH_2CH_3$, J = 7 Hz), and 1.31 (t, 3 H, $-CO_2CH_2CH_3$, J = 7 Hz).

Preparation of 5-(Chloromethyl)-3-furonitrile (1g), Scheme VI. 5-Hydroxymethyl-3-furonitrile (40), Scheme VI. A mixture of freshly distilled 4-bromofurfuryl alcohol (**36**, 9.96 g, 0.062 mol), cuprous cyanide (8.40 g, 0.094 mol), and 3 ml of *N,N*-dimethylformamide were heated at reflux for 4 h. The reaction mixture was poured into a solution of sodium cyanide (8.00 g, 0.17 mol) in 24 ml of water and 10 ml of benzene was then added to it. The aqueous layer was extracted three times with 10 ml of benzene. The combined benzene extracts were washed with water and dried over anhydrous sodium sulfate. Removal of the benzene under reduced pressure and distil-

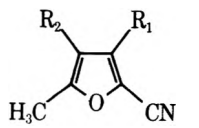
Table II. NMR Spectra of Substituted Furanacetonitriles[a]



Registry no.	Compd	CH_2	R_1	R_2	R_3
2745-25-7	2a	3.68	6.28	6.28	7.37
59413-85-3	2b	3.63	6.25	1.21[b]	7.08
59413-86-4	2c	3.66	6.11	1.23[c]	7.33
				2.91	
59413-87-5	2d	3.78	1.23[b]	6.26	7.25
59413-88-6	2e	3.75	6.40		7.38
59413-89-7	2f	3.78	6.61	1.38[d]	7.90
				4.30	
59413-90-0	2g	3.81	6.61		7.34

[a] δ values. [b] $C(CH_3)_3$. [c] $CH(CH_3)_2$. [d] $CO_2CH_2CH_3$.

Table III. NMR Spectra of Substituted Furyl Nitriles[a]



Registry no.	Compd	R_1	R_2	CH_3
13714-86-8	3a	7.02	6.17	2.34
59413-91-1	3b	1.33[b]	6.03	2.28
59413-92-2	3c	1.23[c]	6.25	2.83
		2.91		
59413-93-3	3d	6.93	1.23[b]	2.41
59413-94-4	3e		6.25	2.37
59413-95-5	3f	1.38[d]	6.47	2.36
		4.30		

[a] δ values. [b] $C(CH_3)_3$. [c] $CH(CH_3)_2$. [d] $CO_2CH_2CH_3$.

lation of the residue in vacuo gave a clear liquid (bp 54–56 °C, 2.5 mm) which was identified from ir and NMR spectra as a mixture of 4-bromofurfuryl alcohol and *N,N*-dimethylformamide. Distillation of the dark residue under high vacuum gave a viscous liquid which solidified in the condenser. Recrystallization of this solid from carbon tetrachloride afforded 0.63 g (9.5% yield) of **40**: mp 81–82 °C; NMR (CCl_4) δ 7.50 (s, 1 H, H-2), 6.27 (s, 1 H, H-4), 4.43 (s, 2 H, CH_2), and 3.60 (s, 1 H, –OH).

Anal. Calcd for $C_6H_5NO_2$: C, 58.54; H, 4.07; N, 11.38. Found: C, 58.63; H, 4.17; N, 11.47.

5-(Chloromethyl)-3-furonitrile (1g), Scheme VI. A solution of 5-(hydroxymethyl)-3-furonitrile (0.57 g, 0.0046 mol) and pyridine (0.45 g, 0.0057 mol) in 15 ml of anhydrous ether was treated with thionyl chloride (0.66 g, 0.0055 mol) as previously described in the preparation of **1a**. Removal of the solvent and distillation of the residue in vacuo gave 0.33 g (50.1% yield) of **1g** as white crystals: mp 50–50.5 °C; ir (CCl_4) 3150, 3120, 2970, 2890, 2240, 1535, 1425, 1355, 1290, 1255, 1160, 1140, 970, 950, and 720 cm^{-1}; NMR (CCl_4) δ 7.27 (s, 1 H, H-2), 6.67 (s, 1 H, H-4), and 4.55 (s, 2 H, CH_2).

Anal. Calcd for C_6H_4ClNO: C, 50.90; H, 2.83; N, 9.89; Cl, 25.07. Found: C, 51.10; H, 2.78; N, 9.94; Cl, 25.19.

Reactions of Substituted 2-(Chloromethyl)furans, 1a–g, with Potassium Cyanide. The general procedure will be illustrated with the reaction of **1c**. A solution of potassium cyanide (0.51 g, 0.008 mol) in 1 ml of water was prepared in a 10-ml Erlenmeyer flask and placed in an Elberbach water bath shaker. The temperature of the bath was maintained at 37.5 ± 0.5 °C. Freshly distilled 4-isopropyl-2-(chloromethyl)furan (0.79 g, 0.005 mol) was then added to the cyanide solution and the reaction flask was shaken for 28 h. At this point, 10 ml of ether was added to the solution. The ether layer was separated and the aqueous layer was extracted with two 10-ml portions of ether. The ether extracts were combined and evaporated under reduced pressure. After dilution of the residue with carbon tetrachloride, the product mixture was determined by NMR spectroscopy. At 37.5 ± 0.5 °C, the length of time required for the reaction to reach completion varied considerably as shown in Table I.

The reaction of **1d** with aqueous potassium cyanide was also carried out at 70 °C. In this instance, isomeric nitriles **2d** and **3d** as well as an additional product identified as 4-*tert*-butyl-5-methyl-2(5*H*)-furanone (**7**) were observed. The latter compound was separated by preparative vapor phase chromatography: ir (CCl_4) 2970, 2900, 2870, 1780, 1755, 1730, 1620, 1475, 1460, 1395, 1370, 1360, 1290, 1240, 1200, 1195, 1170, 1090, 1060, 950, and 860 cm^{-1}; NMR (CCl_4) δ 5.68 (d, 1 H, H-3, $J_{3,5}$ = 1.5 Hz), 5.46 (q, 1 H, H-5, $J_{CH_3,H\text{-}5}$ = 7, $J_{3,5}$ = 1.5 Hz), 1.53 (d, 3 H, 5-CH_3, $J_{CH_3,H\text{-}5}$ = 7 Hz), and 1.23 [s, 9 H, $-C(CH_3)_3$]; mass spectrum *m/e* (rel intensity) 154 (M^+, 1.0), 139 ($C_8H_{11}O_2^+$, 5), 110 ($C_8H_{14}^+$, 16), 95 ($C_7H_{11}^+$, 44), 57 ($C_4H_9^+$, 100), 41 ($C_3H_5^+$, 66), and 39 ($C_3H_3^+$, 41).

The NMR spectra of the nitriles obtained in these reactions are shown in Tables II and III.

Registry No.—**1a**, 617-88-9; **1b**, 59413-96-6; **1c**, 59413-97-7; **1d**, 59413-98-8; **1e**, 59413-99-9; **1f**, 59414-00-5; **1g**, 59414-01-6; **6a**, 22727-21-5; **7**, 17644-74-5; **8**, 59414-02-7; **9**, 59414-03-8; **10**, 59414-04-9; **11**, 59414-05-0; **12**, 59414-06-1; **13**, 59414-07-2; **14**, 59414-08-3; **15**, 59414-09-8; **16**, 59414-10-7; **17**, 59413-60-7; **18**, 59413-61-5; **19**, 59413-62-6; **20**, 59413-63-7; **21**, 52432-89-0; **22**, 59413-64-8; **23**, 98-01-1; **24**, 16015-07-9; **25**, 33554-12-0; **26**, 59413-65-9; **27**, 6132-37-2; **28**, 59413-66-0; **29**, 59413-67-1; **30**, 59413-68-2; **31**, 59413-69-3; **32**, 59413-70-6; **33**, 2433-85-4; **34**, 2434-03-9; **35**, 3439-02-9; **36**, 59413-71-7; **37**, 3387-26-6; **38**, 488-93-7; **39**, 614-98-2; **40**, 59413-72-8; 2-methyl-3-furancarboxaldoxime, 59413-73-9; 1-(4-*tert*-butyl-2-furoyl)aziridine, 59413-74-0; 4-*tert*-butyl-2-furoic acid anhydride, 59413-76-2; 4-*tert*-butyl-2-furoyl chloride, 59413-75-1; rhodanine, 141-84-4; 4-*tert*-butyl-2-furaldehyde hydrazone, 59413-77-3; 3-*tert*-butyl-5-methyl-2-furaldehyde oxime, 59413-78-4; potassium cyanide, 151-50-8; diethylamine, 109-89-7; piperidine, 110-89-4; morpholine, 110-91-8; thiourea, 62-56-6; diethyl malonate, 105-53-3; diethyl methyl malonate, 609-08-5; ethyl acetoacetate, 141-97-9; sodium azide, 26628-22-8; 2-(azidomethyl)-4-*tert*-butylfuran, 59413-79-5; 2-azido-4-*tert*-butyl-5-methylfuran, 59413-80-8; potassium thiocyanate, 333-20-0; 4-*tert*-butylfurfuryl thiocyanate, 59413-81-9; 4-*tert*-butylfurfuryl isothiocyanate, 59413-82-0; 2-thiocyano-4-*tert*-butyl-5-methylfuran, 59413-83-1; 2-isothiocyano-4-*tert*-butyl-5-methylfuran, 59413-84-2; 5-bromo-2-furoic acid, 585-70-6.

References and Notes

(1) Preliminary communication: S. Divald, M. C. Chun, and M. M. Joullié, *Tetrahedron Lett.*, 777 (1970).
(2) (a) Abstracted in part from the Ph.D. Dissertation of S. Divald, University of Pennsylvania, 1969; (b) Deceased; (c) Abstracted in part from the Ph.D. Dissertation of M. C. Chun, University of Pennsylvania, 1969.
(3) W. R. Kirner and G. H. Richter, *J. Am. Chem. Soc.*, **51**, 3131 (1929).
(4) M. M. Runde, E. W. Scott, and J. R. Johnson, *J. Am. Chem. Soc.*, **52**, 1284 (1930).
(5) T. Reichstein, *Ber.*, **63**, 749 (1930).
(6) T. Reichstein and H. Zschokke, *Helv. Chim. Acta*, **15**, 249, 1124 (1932).
(7) E. W. Scott and J. R. Johnson, *J. Am. Chem. Soc.*, **54**, 2549 (1932).
(8) M. Kland-English and C. L. Wilson, Abstracts, 119th National Meeting of the American Chemical Society, New York, N.Y., April 1951, p 48M.
(9) O. Moldenhauer, G. Trautmann, W. Irion, D. Mastaglio, H. Marwitz, R. Pfluger, and H. Döser, *Justus Liebigs Ann. Chem.*, **583**, 37 (1953).
(10) C. J. Benning, Ph.D. Thesis, Ohio State University, 1953.
(11) J. Egyed and A. Gerecs, *Acta Chim. Acad. Sci. Hung.*, **29**, 91 (1961).
(12) Yu. K. Yur'ev, M. A. Gal'bershtam, and A. F. Prokof'eva, *Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol*, **7**, 419, 558 (1964).
(13) K. Yu. Novitskii, Kh. Gresl, and Yu. K. Yur'ev, *Zh. Org. Khim.*, **1**, 539 (1965).
(14) K. Yu. Novitskii, Kh. Gresl, and Yu. K. Yur'ev, *Khim. Geterotsikl. Soedin.*, **6**, 829 (1966).
(15) Y. Oshiro, H. Tanisake, and S. Komori, *Yuki Gosei Kagaku Kyokai Shi*, **24**, 950 (1966).
(16) E. A. Hill, M. B. Hughes, and M. A. Stasiewicz, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco Calif., April 1968, p 121.
(17) L. A. Spurlock and R. G. Fayter, *J. Org. Chem.*, **34**, 4035 (1969).
(18) F. Yamamoto, M. Hiroyuki, and S. Oae, *Heterocycles*, **3**, 1 (1975).
(19) D. S. Noyce and G. V. Kaiser, *J. Org. Chem.*, **34**, 1008 (1969).
(20) E. L. Eliel and P. E. Peckham, *J. Am. Chem. Soc.*, **72**, 1209 (1950).
(21) (a) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists", Wiley, New York, N.Y., 1961; (b) W. C. Herndon and J. Feuer, *J. Org. Chem.*, **33**, 417 (1968).
(22) K. Yu. Novitskii, Yu. K. Yur'ev, and V. N. Zhingareva, *Zh. Obshch. Khim.*, **32**, 3303 (1962).
(23) V. V. Belogorodskii, L. A. Pavlova, and E. D. Venus-Danilova, *Zh. Obshch. Khim.*, **37**, 2435 (1967).
(24) (a) J. Plucker and E. D. Amstutz, *J. Am. Chem. Soc.*, **62**, 1512 (1940); (b) P. L. Julian and B. M. Sturgis, *ibid.*, **57**, 1126 (1935).
(25) H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).
(26) L. Wolff, *Justus Liebigs Ann. Chem.*, **394**, 86 (1912).
(27) A. L. Mndzhoian, "Synthesis of Heterocyclic Compounds", Vol. 3, Consultants Bureau, New York, N.Y., 1959, p 24.
(28) (a) H. Gilman and N. O. Calloway, *J. Am. Chem. Soc.*, **55**, 4197 (1933); (b) H. Gilman, N. O. Calloway, and R. R. Burtner, *ibid.*, **57**, 906 (1935).

(29) P. Bosshard and C. H. Eugster, *Adv. Heterocycl. Chem.*, **7**, 396 (1966).
(30) J. L. Goldfarb, J. B. Volkenstein, and L. I. Belenkij, *Angew. Chem., Int. Ed. Engl.*, **1**, 519 (1968).
(31) (a) A. F. Shepard, N. R. Winslow, and J. F. Johnson, *J. Am. Chem. Soc.*, **52**, 2083 (1930); (b) L. C. Raiford, *J. Org. Chem.*, **6**, 858 (1941).
(32) H. Gilman and J. A. V. Turck, Jr., *J. Am. Chem. Soc.*, **61**, 473 (1939).
(33) I. J. Rinkes, *Recl. Trav. Chim. Pays-Bas*, **51**, 349 (1932).
(34) Ya. L. Goldfarb, Yu. B. Volkenstein, and B. V. Lopatin, *Zh. Obshch. Khim.*, **34**, 969 (1964).
(35) Ya. L. Goldfarb and L. D. Tarasova, *Izv. Akad. Nauk SSR, Ser. Khim.*, **6**, 1079 (1965).
(36) H. B. Hill and C. R. Sanger, *Justus Liebigs Ann. Chem.*, **507**, 42 (1885).
(37) E. Sherman and E. D. Amstutz, *J. Am. Chem. Soc.*, **72**, 1209 (1950).
(38) A. L. Mndzhoian, "Synthesis of Heterocyclic Compounds", Vol. 1 and 2, Consultants Bureau, New York, N.Y., 1959, p 42.
(39) L. Friedman and H. Schechter, *J. Org. Chem.*, **25**, 877 (1960).

Synthesis of α-Alkoxyacrylonitriles Using Substituted Diethyl Cyanomethylphosphonates

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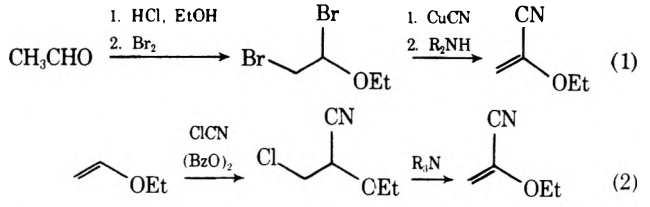
The synthesis of the thiophenoxy, methoxy, and *tert*-butoxy derivatives of diethyl cyanomethylphosphonates $(EtO)_2POCH(Z)CN$ **3** involved either the phenylsulfenylation of the anion of diethyl cyanomethylphosphonate (**4**) to afford **3a** (Z = SPh), the photolysis of the diazo derivative of **4** in methanol to afford **3b** (Z = OMe), or, preferably, the Arbusov reaction of methoxy- or *tert*-butoxybromoacetonitrile with triethyl phosphite to afford **3b** (Z = OMe) or **3c** (Z = O-*t*-Bu), respectively. The latter two phosphonate reagents **3b** and **3c** serve in the Horner–Emmons modification of the Wittig reaction to provide α-alkoxyacrylonitriles RR'C=C(OR'')CN **1** from carbonyl compounds RR'C=O in excellent yield.

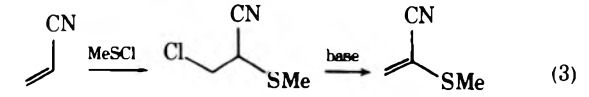
In connection with our interest in the chemistry of α,β-unsaturated nitriles,[1] we required a convenient synthesis of α-alkoxy- or α-thioalkoxyacrylonitriles. Cuvigny and Normant[2] have developed a substitution–elimination sequence for the conversion of aldehydes to α-alkoxyacrylonitriles which parallels a synthesis of α-ethoxyacrylonitrile reported earlier by Price[3] (eq 1). A more direct sequence developed by Vasil'eva[4] utilized the free-radical addition of cyanogen chloride to ethyl vinyl ether but suffered from low overall yields of α-ethoxyacrylonitrile (eq 2).



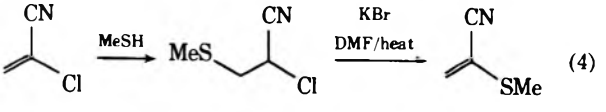
(1)

(2)

In contrast to the syntheses of α-alkoxyacrylonitriles in which the cyano group is introduced subsequent to the alkoxy group, the reported approaches to α-thioalkoxyacrylonitriles invert this order for the introduction of cyano and thioether groups. The addition of methylsulfenyl chloride to acrylonitrile and subsequent dehydrochlorination furnished α-thiomethoxyacrylonitrile[5] (eq 3). Alternatively, Gundermann[6] developed an interesting approach in which the 2-chloro-3-thiomethoxynitrile was dehydrochlorinated with concomitant migration of the thioether group to afford α-thiomethoxyacrylonitrile (eq 4).

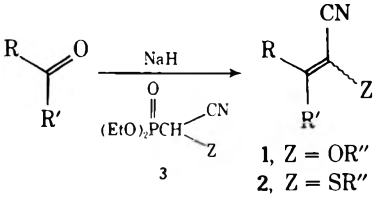


(3)



(4)

To develop a general synthesis of α-alkoxyacrylonitriles **1** and α-thioalkoxyacrylonitriles **2** which would avoid these multistep sequences, we required a Wittig reagent which could introduce the α-alkoxyacrylonitrile or α-thioalkoxyacrylonitrile synthon in a single operation. In particular, we desired the phosphonate Wittig reagents[7] **3** which offer the distinct advantage over phosphorane Wittig reagents of providing water-soluble, phosphate by-products. We now wish to report various synthetic approaches to these phosphonate reagents **3** and their application to the preparation of **1** and **2** (eq 5).

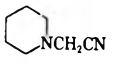


(5)

We have examined three different approaches to the phosphonates **3** (eq 6–8). Initially, we studied the sulfenylation of the anion of diethyl cyanomethylphosphonate (**4**) with phenylsulfenyl chloride and succeeded in obtaining the thiophenoxyphosphonate **3a** as the predominant product (eq 6). Our interest in exploring similarly substituted sulfur derivatives of **4** was dampened by the failure of the anion of **3a** to condense with carbonyl compounds other than nonenolizable aldehydes. For example, although benzaldehyde condensed with the anion of **3a** (1.0 equiv, 10% HMPA–DME, 81 °C, 24 h) to furnish (*E*)- and (*Z*)-2-thiophenoxycinnamonitriles in 68% yield, acetaldehyde failed to provide any of the desired product. The failure of the anion of **3a** to add to the carbonyl group of other aldehydes and ketones was attributed either to the steric bulk of the phosphonate or to the additional thioether stabilization[8] of the anion of **3a** relative to the anion of **4**. We consequently turned to the synthesis of the alkoxy derivatives of **4**.

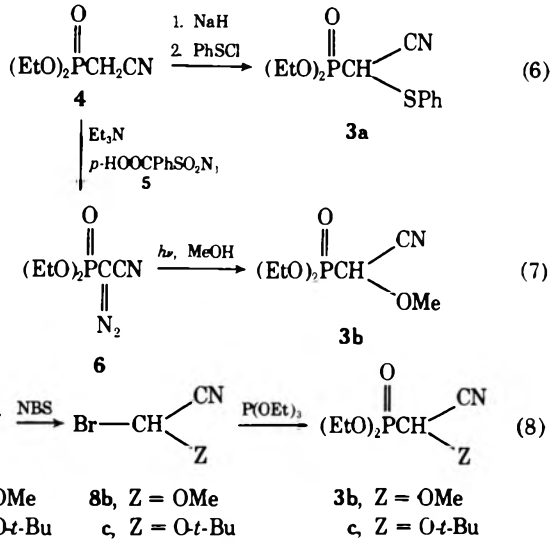
In a second effort to utilize **4** to secure the methoxyphosphonate **3b**, we investigated the reaction of the anion of **4** with *p*-toluenesulfonyl azide[9a] and *p*-carboxybenzenesulfonyl azide[9b] (**5**). Although the infrared spectrum of crude products displayed a signal at 4.74 μ which indicated successful diazo transfer, we were unable to obtain the azophosphonate **6** in

Table I. Substituted Acetonitriles 7

	Acetonitriles 7	Isolated yield, %	Reference to or method of synthesis of 7
a	$MeOC(CH_3)_2OCH_2CN$	57	*b*
b	$MeOCH_2CN$	70–77	*c*
c	$tBuOCH_2CN$	42	*a*
d	$PhCOOCH_2CN$	66	*a*
e	$tBuCOOCH_2CN$	74	*a*
f	$EtOCOOCH_2CN$	48	*a*
g	$EtOCSSCH_2CN$	75	*a*
h	$PhCOSCH_2CN$	66	*a*
i	$MeCOSCH_2CN$	64	*a*
j	$(i\text{-}Pr)_2NCH_2CN$	69	*d*
k		80	*d*

[a] This work. [b] N. B. Lorette and W. L. Howard, *J. Org. Chem.*, 25, 521 (1960). [c] J. A. Scarrow and C. F. H. Allen, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 387. [d] D. B. Luten, Jr., *J. Org. Chem.*, 3, 588 (1939).

yields greater than 30%. We demonstrated, nevertheless, that the photolysis of **6** in methanol provided **3b** (eq 7). The unsatisfactory overall yield of **3b** from **4** led us to examine an alternative approach.



7b, Z = OMe **8b**, Z = OMe **3b**, Z = OMe
c, Z = O-*t*-Bu **c**, Z = O-*t*-Bu **c**, Z = O-*t*-Bu

Dawson and Burger[10] first demonstrated that the Arbusov reaction[11] of chloroacetonitrile and triethyl phosphite would furnish diethyl cyanomethylphosphonate (**4**). To utilize this same approach in the synthesis of phosphonates **3**, we required the substituted haloacetonitriles **8**. The NBS bromination of methoxyacetonitrile (**7b**) or *tert*-butoxyacetonitrile (**7c**) furnished the desired monobromination products **8b** and **8c**, respectively. The Arbusov reaction of **8b** or **8c** with triethyl phosphite afforded the phosphonates **3b** and **3c** in ca. 60% yield from the acetonitriles **7** (eq 8). The success of this approach prompted a survey of the NBS bromination of other oxygen, sulfur, and nitrogen substituted acetonitriles **7**. With the exception of **7b**, **7c**, and **7h**, the substituted acetonitriles shown in Table I afforded intractable mixtures on exposure to NBS. The monobromination product **8h** of cyanomethyl thiolbenzoate (**7h**) failed to participate in the Arbusov reaction with triethyl phosphite.

In contrast to the anion of **3a**, the anions of the phosphonates **3b** or **3c** condensed with aldehydes or ketones to provide α-methoxyacrylonitriles **1b** or α-*tert*-butoxyacrylonitriles **1c**, respectively, in excellent yield (Table II). The success of **3b** and particularly **3c** in this reaction would suggest that the failure of **3a** to condense with carbonyl compounds can be attributed to sulfur stabilization and not to the steric bulk of the anion of **3a**. In summary, we have developed an effective synthesis of α-alkoxyacrylonitriles **1** which should supplant published procedures as the method of choice. Other research groups[2b,12] have demonstrated the synthetic versatility of α-alkoxyacrylonitriles **1**, and we hope to report on new applications of this synthon in future publications.

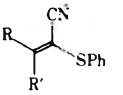
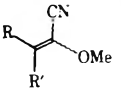
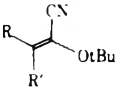
Experimental Section

Infrared spectra were determined on a Perkin-Elmer Model 337 spectrophotometer. NMR spectra were determined on a Varian A-60A spectrometer using tetramethylsilane as an internal standard. Mass spectra were determined on a Varian MAT CH5 mass spectrometer. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected.

***tert*-Butoxyacetonitrile (7c).** A mixture of 16.5 g (0.183 mol) of paraformaldehyde, 42.6 g (45.7 ml, 0.500 mol) of acetone cyanohydrin, 1.2 g of anhydrous potassium carbonate, and 12 ml of methanol saturated with potassium carbonate was stirred at 25 °C for 1.5 h. Sufficient concentrated hydrochloric acid (ca. 3 ml) was added to obtain pH <6. The product was concentrated under reduced pressure, and the residue was diluted with 100 ml of ether, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure (rotary evaporator) to afford 24.0 g of crude glycolonitrile[13] which was used *immediately* in the next step.

To 118 g (200 ml, 2.0 mol) of isobutylene liquefied in a 500-ml Parr shaker bottle at −78 °C was added 24.0 g of glycolonitrile, 100 ml of dichloromethane, and (slowly) 2 ml of concentrated sulfuric acid. The bottle was connected to the Parr shaker and shaken at 25 °C for 48 h or until the mixture was homogeneous. After releasing the pressure, the solution in the Parr bottle was stirred (caution: magnetic stirring bar was slowly lowered into the solution) in a hood at 25 °C until foaming ceased. To the yellow solution was added saturated aqueous sodium carbonate solution until pH 8. The product was extracted with 200 ml of ether. The ether solution was washed successively with two 100-ml portions of water and 100 ml of brine, and dried over anhydrous magnesium sulfate. The product was distilled to afford 23.8 g (42% based on acetone cyanohydrin) of **7c**: bp 50–54 °C (3 mm) [lit.[14] bp 44 °C (5.5 mm)]; ir (TF) shows no CN absorption, which is characteristic of α-alkoxyacetonitriles but has strong absorptions at 7.30, 8.40, and 9.18 μ; NMR ($CDCl_3$) δ 1.28 [s, 9, $C(CH_3)_3$] and 4.18 (s, 2, OCH_2CN); mass spectrum (70 eV) *m/e* (rel intensity) 113 (1), 98 (100), 57 (60), and 43 (61).

Table II. Synthesis of α-Thiophenoxy-, α-Methoxy-, or α-*tert*-Butoxyacrylonitriles

	Carbonyl compd RR'C=O		Isolated yields, %		
					
Registry no.	R	R'	2	1b	1c
100-52-7	Ph	H	68%	81	94
111-71-7	$(CH_2)_5CH_3$	H		71	99
108-94-1	$-(CH_2)_5-$		*a*	81	89
5396-91-8	$(CH_2)_2Ph$	$(CH_2)_2Ph$		96	84
98-86-2	Ph	CH_3	*a*	83	93
119-61-9	Ph	Ph		94	86

[a] No reaction.

Cyanomethyl Benzoate (7d). To 11.4 g (0.20 mol) of glycolonitrile (see preparation of **7c** for details) and 20.3 g (28 ml, 0.20 mol) of anhydrous triethylamine in 250 ml of anhydrous THF at 0 °C was added 28.4 g (22 ml, 0.20 mol) of benzoyl chloride dropwise over a 10-min period. The mixture was stirred for ca. 12 h at 25 °C, filtered to remove triethylamine hydrochloride, and evaporated to remove THF. The oil was dissolved in 100 ml of ether, washed successively with 50 ml of 1 M sodium hydroxide solution, two 100-ml portions of water, and 50 ml of brine, and dried over anhydrous magnesium sulfate. The product was distilled to afford 21.3 g (66%) of **7d:** bp 152–154 °C (11 mm); ir (TF) 5.78 (C=O), 6.25, and 6.31 μ (aromatic); NMR ($CDCl_3$) δ 4.96 (s, 2, OCH_2CN) and 7.25–8.20 (m, 5, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 161 (47), 117 (4), 105 (100), and 77 (55).

Cyanomethyl Pivalate (7e). The procedure described above was repeated using 12.9 g (0.23 mol) of glycolonitrile, 23.2 g (32 ml, 0.23 mol) of triethylamine, and 27.4 g (0.23 mol) of pivalyl chloride to afford 23.5 g (74%) of **7e:** bp 87.5–88.5 °C (16 mm); ir (TF) 5.76 μ (C=O); NMR ($CDCl_3$) δ 1.27 [s, 9, $C(CH_3)_3$] and 4.75 (s, 2, OCH_2CN); mass spectrum (70 eV) *m/e* (rel intensity) 141 (1), 98 (3), 85 (8), and 57 (100).

Cyanomethyl Ethylcarbonate (7f). The procedure described above was repeated using 13.2 g (0.23 mol) of glycolonitrile, 24.0 g (33 ml, 0.24 mol) of triethylamine, and 25.0 g (22 ml, 0.23 mol) of ethyl chloroformate to afford 14.3 g (48%) of **7f:** bp 110–114 °C (28 mm); ir (TF) 5.69 μ (C=O); NMR ($CDCl_3$) δ 1.36 (t, J = 7 Hz, 3, OCH_2CH_3), 4.33 (q, J = 7 Hz, 2, OCH_2CH_3), and 4.80 (s, 2, OCH_2CN); mass spectrum (70 eV) *m/e* (rel intensity) 129 (2), 102 (25), and 101 (40).

Cyanomethyl Ethylxanthate (7g). To 32 g (0.2 mol) of potassium ethylxanthate[15] in 200 ml of acetone at 0 °C under a nitrogen atmosphere was added 15.1 g (0.2 mol) of chloroacetonitrile in 100 ml of acetone dropwise over a 30-min period. The solution was stirred for an additional 6 h at 25 °C and filtered to remove potassium chloride. The filtrate was concentrated and distilled to afford 24.3 g (75%) of **7g:** bp 104.5–107 °C (0.7 mm); ir (TF) 4.45 μ (C≡N); NMR (CCl_4) δ 1.51 (t, J = 7 Hz, 3, OCH_2CH_3), 3.87 (s, 2, SCH_2CN), and 4.75 (q, J = 7 Hz, 2, OCH_2CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 161 (43), 116 (10), 101 (6), 93 (5), 89 (6), 77 (7), 76 (23), and 73 (43).

Cyanomethyl Thiolbenzoate (7h). The procedure described for the preparation of **7g** was repeated using 16.0 g (0.1 mol) of sodium thiolbenzoate and 7.55 g (0.1 mol) of chloroacetonitrile to afford 12.7 g (66%) of **7h:** bp 136.5–140.5 °C (0.85 mm); ir (TF) 4.48 (C≡N), 6.00 (C=O), 6.30, and 6.35 μ (aromatic); NMR (CCl_4) δ 3.84 (s, 2, CH_2CN) and 7.25–8.05 (m, 5, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 177 (1), 161 (5), 122 (4), 105 (100), and 77 (50).

Cyanomethyl Thiolacetate (7i). The procedure described for the preparation of **7g** was repeated using 22.8 g (0.2 mol) of potassium thiolacetate and 15.1 g (0.2 mol) of chloroacetonitrile to afford 14.6 g (64%) of **7i:** bp 66–68 °C (0.7 mm); ir (TF) 4.48 (C≡N) and 5.90 μ (C=O); NMR (CCl_4) δ 2.45 (s, 3, CH_3) and 3.67 (s, 2, CH_2CN); mass spectrum (70 eV) *m/e* (rel intensity) 115 (2), 73 (4), and 43 (100).

Bromo(cyano)methyl Thiolbenzoate (8h). To 177 mg (1.0 mmol) of **7h** in 7.5 ml of anhydrous benzene was added 890 mg (5.0 mmol) of recrystallized[16] *N*-bromosuccinimide. The mixture was irradiated with a 250-W sun lamp for 24 h. The product was cooled, filtered, concentrated, and chromatographed on Merck silica gel F254 in 1:1 ether–hexane to afford 195 mg (76%) of **8h:** R_f 0.61; NMR (CCl_4) δ 6.18 (s, 1, CHBrCN) and 7.35–8.05 (m, 5, aromatic). The use of solvents other than benzene proved unsatisfactory. For example, using carbon tetrachloride (8-h irradiation time) instead of benzene provided none of **8h** and a 14% yield of dibromocyanomethyl thiolbenzoate: NMR (CCl_4) δ 7.25–8.25 (m, 5, aromatic).

Diethyl Cyano(thiophenoxy)methylphosphonate (3a). To 4.55 g (0.11 mol) of sodium hydride (washed with three 20-ml portions of anhydrous hexane to remove mineral oil) in 75 ml of anhydrous THF under a nitrogen atmosphere was added 17.7 g (0.10 mol) of diethyl cyanomethylphosphonate (**4**) in 25 ml of anhydrous THF. The mixture was stirred for 30 min at 25 °C at which time hydrogen gas evolution had ceased. To the solution was added 3.64 g (0.025 mol) of phenylsulfenyl chloride. After 1 h, the reaction mixture was quenched with water and extracted with ether. The ether solutions were washed repeatedly with water to remove 4 selectively, dried, concentrated, and distilled to afford 2.69 g (37% based on PhSCl[17]) of **3a:** bp 162–164 °C (0.2 mm); NMR ($CDCl_3$) δ 1.40 (t, J = 7 Hz, 6, OCH_2CH_3), 4.07 (d, J = 23 Hz, 1, PCH), 4.05–4.60 (two q, 4, OCH_2CH_3), and 7.30–7.85 (m, 5, aromatic); mass spectrum (70 eV) *m/e* 285. In a small-scale experiment, **3a** was conveniently isolated in 47% yield by chromatography on Merck silica gel F254 in 1:9 ether–hexane (R_f 0.6).

Diethyl Cyano(methoxy)methylphosphonate (3b). The procedure described below for the preparation of **3c** was repeated starting with 5.09 g (0.072 mol) of methoxyacetonitrile (**7b**) and 12.6 g (0.071 mol) of recrystallized[16] *N*-bromosuccinimide to afford 9.79 g of crude 8b which displayed a characteristic NMR signal (CCl_4) at δ 6.30 (MeOCHBrCN). The Arbusov reaction of crude **8b** with 10.7 g (0.065 mol) of triethyl phosphite afforded 8.03 g (54% based on **7b**) of **3b:**[18] ir (TF) 7.87, 9.03, 9.53 (sh), and 9.80 μ; NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 6, OCH_2CH_3), 3.61 (s, 3, OCH_3), and 4.0–4.6 (m, 5, OCH_2CH_3 and PCH); mass spectrum (70 eV) *m/e* (rel intensity) 207 (7), 164 (6), 163 (8), 137 (27), and 109 (100).

In an alternate approach to the synthesis of **3b,** 384 mg (2.17 mmol) of **4** in 1 ml of anhydrous acetonitrile was added to a solution of 510 mg (2.25 mmol) of *p*-carboxybenzenesulfonyl azide[9b] and 464 mg (4.58 mmol) of triethylamine in 7 ml of anhydrous acetonitrile. The reaction mixture was stirred for 2 h at 25 °C, diluted with 25 ml of dichloromethane, washed with 20 ml of 5% sodium hydroxide solution and three 20-ml portions of water, and dried over anhydrous magnesium sulfate to afford 203 mg of red oil which contains 28% of **6** by NMR analysis. The crude **6** was photolyzed in methanol for 1 h using a high-pressure 450-W Hanovia lamp. The product (192 mg) was analyzed by GLC–mass spectrometry on a temperature programmed (90–120 °C) 6-ft OV-1 column to identify **3b.**

Diethyl *tert*-Butoxy(cyano)methylphosphonate (3c). To 50 g (0.442 mol) of *tert*-butoxyacetonitrile (**7c**) in 1.5 l. of benzene was added 78.7 g (0.442 mol) of recrystallized[16] *N*-bromosuccinimide. The mixture was irradiated with a 250-W sun lamp for 30 min at which time the orange color had discharged. The product was cooled in an ice bath until the benzene solution just started to solidify and then filtered to remove the precipitated succinimide. The filtrate was evaporated to afford a pale orange oil which was again filtered to afford 76.6 g of crude **8c** which displayed a characteristic NMR signal ($CDCl_3$) at δ 6.35 (*t*-BuOCHBrCN). The crude **8c** was used immediately in the next step.

A mixture of 76.6 g of crude **8c** and 66.4 g (69 ml, 0.40 mol) of triethyl phosphite[21] in a 500-ml three-necked flask equipped with a large-bore, efficient condenser was heated to initiate an exothermic Arbusov reaction. An ice bath was occassionally applied to moderate the reaction. When the reaction subsided (<5 min), the solution was again heated for 15 min at reflux. The condenser was removed, and the flask was connected to a dry ice–acetone trap. Heating was continued (using a 110 °C oil hath) for an additional 15 min under a stream of nitrogen to entrain the ethyl bromide generated in the reaction. The product was distilled through a short-path distillation head to afford 63.3 g (57% based on **7c**) of **3c** as a viscous, pale yellow oil: bp 116–118 °C (0.5 mm); ir (TF) 7.18, 7.31, 7.88, and 9.90 μ; NMR ($CDCl_3$) δ 1.32 [s, 9, $C(CH_3)_3$], 1.40 (t, J = 7 Hz, 6, OCH_2CH_3), 4.08–4.73 (m, 5, OCH_2CH_3 and PCH); mass spectrum (70 eV) *m/e* (rel intensity) 234 (10), 193 (22), 138 (78), and 57 (100).

The following is a typical experimental procedure for the preparation of α-alkoxyacrylonitriles **1.**

(*E*)- and (*Z*)-α-*tert*-Butoxycinnamonitrile (1c, R = Ph; R′ = H). To 93 mg of 57% sodium hydride (washed with three 5-ml portions of anhydrous hexane) in 3 ml of anhydrous THF under a nitrogen atmosphere was added 499 mg (2.0 mmol)[22] of **3c** in 1 ml of anhydrous THF. After the evolution of hydrogen gas had subsided, the solution was refluxed for 15 min to complete the generation of the anion of **3c.** To this solution was added 106 mg (1.0 mmol) of distilled benzaldehyde in 1.0 ml of anhydrous THF. The mixture was refluxed for 3 h, cooled, poured into 50 ml of water and 2 ml of brine, and extracted with three 20-ml portions of ether. The combined ether solutions were washed successively with two 25-ml portions of water and 25 ml of brine and dried over anhydrous magnesium sulfate. The solvent was evaporated to afford 356 mg of oil which was chromatographed on Merck silica gel F254 in 1:3 ether–hexane to afford 188 mg (94%) of **1c** (R = Ph; R′ = H): R_f 0.61; ir (TF) 4.53 (C≡N), 6.18 (C=C), and 6.37 μ (aromatic); NMR (CCl_4) δ 1.41 and 1.49 [two s, 9, $C(CH_3)_3$ of *E* and *Z* isomers], 6.28 and 6.72 (two s, 1, vinyl H of *E* and *Z* isomers), and 7.17–7.75 (m, 5, aromatic H); mass spectrum (70 eV) *m/e* 201, 91, 77, and 57.

1c [R = $(CH_2)_5CH_3$; R′ = H]: ir (TF) 4.52 (C≡N) and 6.10 μ (C=C); NMR ($CDCl_3$) δ 0.72–1.08 [m, 3, $(CH_2)_4CH_3$], 1.08–1.60 [m, 8, $(CH_2)_4CH_3$], 1.32 and 1.41 [two s, 9, $C(CH_3)_3$ of *E* and *Z* isomers], 1.80–2.50 (m, 2, $C=CHCH_2$), 5.80 and 5.93 (two t, J = 8 Hz, 1, $C=CHCH_2$ of *E* and *Z* isomers); mass spectrum (70 eV) *m/e* (rel intensity) 209 (<1) and 57 (100).

1c [R, R′ = $-(CH_2)_5-$]: ir (TF) 4.53 (C≡N) and 6.12 μ (C=C); NMR ($CDCl_3$) δ 1.37 [s, 9, $C(CH_3)_3$], 1.43–1.76 (m, 6, CH_2), and 2.03–2.55 (m, 4, $C=C-CH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 193 (3), 178 (9), 137 (16), 110 (20), 68 (19), and 57 (100).

1c (R = R′ = CH_2CH_2Ph): ir (TF) 4.54 (C≡N), 6.18 (C=C), 6.25 and 6.32 μ (aromatic); NMR ($CDCl_3$) δ 1.29 [s, 9, $C(CH_3)_3$], 2.28–2.95 (m, 8, CH_2), and 7.23 (s, 10, aromatic H); mass spectrum (70 eV) *m/e*

(rel intensity) 318 (1), 176 (18), 159 (35), 133 (39), 120 (67), and 57 (100).

1c (R = Ph; R′ = CH_3): ir (TF) 4.54 (C≡N), 6.21 (C=C), and 6.36 μ (aromatic); NMR ($CDCl_3$) δ 1.22 and 1.49 [two s, 9, $C(CH_3)_3$ of *E* and *Z* isomers], 2.15 and 2.31 (two s, 3, C=C–CH_3 of *E* and *Z* isomers), and 7.40 (s, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 215 (3), 200 (7), 159 (56), 132 (100), and 57 (90).

1c (R = R′ = Ph): mp 96–96.5 °C; ir (KBr) 4.53 (C≡N), 6.28 (C=C), and 6.38 μ (aromatic); NMR ($CDCl_3$) 1.32 [s, 9, $C(CH_3)_3$] and 7.34 (s, 10, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 277 (3), 194 (100), 77 (5), and 57 (59).

1b (R = Ph; R′ = H): ir (TF) 4.47 (C≡N), 6.02 (C=C), and 6.33 μ (aromatic); NMR ($CDCl_3$) δ 3.78 and 3.93 (two s, 3, OCH_3 of *E* and *Z* isomers), 6.18 and 6.56 (two s, 1, vinyl H of *E* and *Z* isomers), and 7.22–7.76 (m, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 159 (100), 144 (82), 116 (75), and 89 (45).

1b (R = $(CH_2)_5CH_3$; R′ = H): ir (TF) 4.49 and 4.53 (C≡N of *E* and *Z* isomers) and 6.11 μ (C=C); NMR ($CDCl_3$) δ 0.65–1.72 [m, 11, $(CH_2)_4CH_3$], 1.72–2.48 (m, 2, C=CHCH_2), 3.63 and 3.73 (two s, 3, OCH_3 of *E* and *Z* isomers), and 5.55 (t, *J* = 8 Hz, 1, C=CHCH_2 of *E* and *Z* isomers); mass spectrum (70 eV) *m/e* (rel intensity) 167 (20) and 43 (100).

1b [R, R′ = $-(CH_2)_5-$]: ir (TF) 4.54 (C≡N) and 6.02 μ (C=C); NMR ($CDCl_3$) δ 1.35–1.82 (m, 6, CH_2), 2.10–2.56 (m, 4, C=C–CH_2), and 3.67 (s, 3, OCH_3); mass spectrum (70 eV) *m/e* (rel intensity) 151 (25), 108 (16), 81 (23), and 68 (100).

1b (R = R′ = CH_2CH_2Ph): ir (TF) 4.53 (C≡N), 6.09 (C=C), and 6.24 μ (aromatic); NMR ($CDCl_3$) δ 2.30–2.98 (m, 8, CH_2), 3.47 (s, 3, OCH_3), and 7.21 (s, 10, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 291 (3), 221 (14), 200 (16), 168 (13), and 91 (100).

1b (R = Ph; R′ = CH_3): ir (TF) 4.56 (C≡N), 6.18 (C=C), and 6.33 μ (aromatic); NMR ($CDCl_3$) δ 2.14 and 2.28 (two s, 3, vinyl CH_3 of *E* and *Z* isomers), 3.69 and 3.81 (two s, 3, OCH_3 of *E* and *Z* isomers), and 7.39 (s, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 173 (100), 158 (85), 130 (33), and 103 (71).

1b (R = R′ = Ph): mp 69.5–70.5 °C; ir (KBr) 4.53 (C≡N), 6.21 (C=C), and 6.38 δ (aromatic); NMR (CCl_4) δ 3.75 (s, 3, OCH_3), 7.25 and 7.32 (two s, 10, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 235 (100), 165 (84), and 77 (10).

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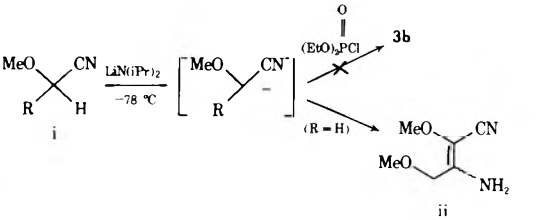
Registry No.—*E*-**1b** (R = Ph; R = H), 59463-29-5; *Z*-**1b** (R = Ph; R′ = H), 59463-30-8; *E*-**1b** (R = $(CH_2)_5CH_3$; R′ = H), 59463-31-9; *Z*-**1b** (R = $(CH_2)_5CH_3$; R′ = H), 59463-32-0; **1b** (R, R′ = $-(CH_2)_5-$), 59463-33-1; **1b** (R = R′ = CH_2CH_2Ph), 59463-34-2; *E*-**1b** (R = Ph; R′ = CH_3), 59463-35-3; *Z*-**1b** (R = Ph; R′ = CH_3), 59463-36-4; **1b** (R = R′ = Ph), 59463-37-5; *E*-**1c** (R = Ph; R′ = H), 59463-38-6; *Z*-**1c** (R = Ph; R′ = H), 59463-39-7; *E*-**1c** (R = $(CH_2)_5CH_3$; R′ = H), 59463-40-0; *Z*-**1c** (R = $(CH_2)_5CH_3$; R′ = H), 59463-41-1; **1c** (R, R′ = $-(CH_2)_5-$), 59463-42-2; **1c** (R = R′ = CH_2CH_2Ph), 59463-43-3; *E*-**1c** (R = Ph; R′ = CH_3), 59463-44-4; *Z*-**1c** (R = Ph; R′ = CH_3), 59463-45-5; **1c** (R = R′ = Ph), 59463-46-6; **3a**, 59463-47-7; **3b**, 59463-48-8; **3c**, 59463-49-9; **4**, 2537-48-6; **6**, 59463-50-2; **7b**, 1738-36-9; **7c**, 59463-51-3; **7d**, 939-56-0; **7e**, 59463-52-4; **7f**, 59463-53-5; **7g**, 59463-54-6; **7h**, 59463-55-7; **7i**, 59463-56-8; **8b**, 59463-57-9; **8c**, 59463-58-0; **8h**, 59463-59-1; acetone cyanohydrin, 75-86-5; glycolonitrile, 107-16-4; isobutylene, 115-11-7; benzoyl chloride, 98-88-4; pivalyl chloride, 3282-30-2; potassium ethylxanthate, 140-89-6; chloroacetonitrile, 107-14-2; sodium thiolbenzoate, 51066-54-7; potassium thiolacetate, 10387-40-3; dibromocyanomethyl thiolbenzoate, 59463-60-4; phenylsulfenyl chloride, 931-59-9; triethyl phosphite, 122-52-1; acetonitrile, 75-05-8.

References and Notes

(1) J. A. Profitt, D. S. Watt, and E. J. Corey, *J. Org. Chem.*, **40**, 127 (1975).
(2) (a) T. Cuvigny and H. Normant, *C. R. Acad. Sci., Ser. C*, **237**, 815 (1953); (b) T. Cuvigny, *Ann. Chim. (Paris)*, **1**, 475 (1956); (c) I. F. Lutsenko, L. P. Badenkova, and V. L. Foss, *Zh, Obshch. Khim.*, **27**, 3261 (1957).
(3) C. C. Price, E. C. Coyner, and D. DeTar, *J. Am. Chem. Soc.*, **63**, 2796 (1941).
(4) E. I. Vasil'eva, B. I. Keda, and R. Kh. Freidlina, *Dokl. Akad. Nauk SSSR*, **154**, 129 (1964).
(5) I. L. Knunyants, M. G. Lin'kova, and N. D. Kuleshova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1069 (1966).
(6) (a) K. D. Gundermann, *Chem. Ber.*, **88**, 1432 (1955); (b) K. D. Gundermann, *ibid.*, **89**, 1263 (1946); and (c) K. D. Gundermann, German Patent 1 035 646 (1958); *Chem. Abstr.*, **55**, 2490a (1961).
(7) J. Boutagy and R. Thomas, *Chem. Rev.*, **74**, 87 (1974).
(8) For a discussion of the sulfur stabilization of carbanions see (a) A. W. Johnson, "Ylid Chemistry", Academic Press, New York, N.Y., 1966; (b) B. M. Trost and L. S. Melvin, Jr., "Sulfur Ylids", Academic Press, New York, N.Y., 1975.
(9) (a) M. Regitz, *Synthesis*, 351 (1972); (b) J. B. Hendrickson and W. A. Wolf, *J. Org. Chem.*, **33**, 3610 (1968).
(10) N. D. Dawson and A. Burger, *J. Am. Chem. Soc.*, **74**, 5312 (1952).
(11) A. N. Pudovik and G. E. Yastrebova, *Russ. Chem. Rev.*, **39**, 562 (1970).
(12) (a) T. Cuvigny, *C. R. Acad. Sci., Ser. C*, **240**, 206 (1955); (b) T. Cuvigny, *Bull. Soc. Chim. Fr.*, 655 (1957).
(13) I. N. Nazarov, A. A. Akhrem, and A. V. Kamernitskii, *Zh. Obshch. Khim.*, **25**, 1345 (1955); *Chem. Abstr.*, **50**, 4950*h* (1956).
(14) W. F. Gresham, U.S. Patent 2 491 659 (Dec 20, 1949); *Chem. Abstr.*, **44**, 3010*e* (1950).
(15) C. Djerassi, M. Gorman, F. X. Markley, and E. B. Oldenburg, *J. Am. Chem. Soc.*, **77**, 568 (1955).
(16) H. J. Dauben, Jr., and L. L. McCoy, *J. Am. Chem. Soc.*, **81**, 3863 (1959).
(17) All efforts to secure **3a** using 1:1 molar ratios of PhSCl and the anion of **4** led to $(EtO)_2POC(SPh)_2CN$ as the predominant product. For example, the addition of the anion of **4** to an equimolar amount of PhSCl in THF gave a 30% yield of $(EtO)_2POC(SPh)_2CN$ and a 2% yield of **3a**.
(18) Yet another approach to the synthesis of **3b** involves the reaction of the anion of methoxyacetonitrile (**7b**) with diethyl chlorophosphate. We were not surprised at the failure of this reaction to furnish **3b**. We have investigated the alkylation of a series (shown in Table I) of substituted acetonitriles such as i (R = H) and have observed the rapid self-condensation of the



i ii

anions of i to give the β-aminoacrylonitriles ii. In sharp contrast, Stork[19] has reported the efficient alkylation of substituted acetonitriles (R = alkyl or aryl group). Recently however, Büchi[20] reported on the successful alkylation of dimethylaminoacetonitrile with an allylic bromide, but we have been unable to generalize this reaction to other systems.
(19) G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **93**, 5286 (1971).
(20) G. Büchi and H. Wüest, *J. Am. Chem. Soc.*, **96**, 7573 (1974).
(21) We have also used trimethyl phosphite to obtain dimethyl *tert*-butoxy(cyano)methylphosphonate, $(MeO)_2POCH(CN)O$-*t*-Bu: NMR ($CDCl_3$) δ 1.33 [s, 9, $C(CH_3)_3$], 3.86 (s, 3, OCH_3), 4.05 (s, 3, OCH_3), and 4.67 (d, *J* = 22 Hz, 1, PCH). No advantage accrued to the use of this phosphonate instead of **3c** in the synthesis of α-*tert*-butoxyacrylonitriles **1c**.
(22) Only 1.5 equiv of the anion of **3b** was required to secure the yields of α-methoxyacrylonitriles **1b** shown in Table II.

A New Furan and Dihydro-4-pyrone Synthesis via Diels–Alder Reactions between Methyl 2-[2′-Acetamido-4′(1′*H*)-pyrimidon-6′-yl]glyoxylate and Diethyl Oxomalonate and Oxygenated 1,3-Dienes

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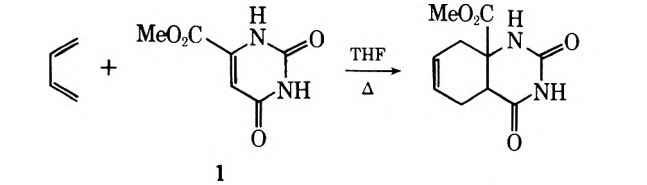
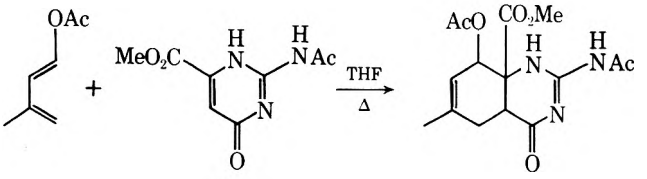
Pyrimidone **3**, required as a potential dienophile for a synthesis of tetrodotoxin, has been prepared by oxidation of **4** with H_2SeO_3. While the desired hydroquinazolines were not produced from the reaction of **3** with dienes **17** and **21**, a new route to substituted furans and dihydro-4-pyrones resulted. Thus, a Diels–Alder reaction between **3** and diene **17** afforded furan **19**. With THF as solvent dihydropyran **20** was formed. Reaction of **3** with diene **21** led to either hydropyrans **22**, **23**, **24**, or **25**, depending on the nature of the hydrolysis or purification step. The generality of these furan and hydropyran producing reactions was shown by employing diethyl oxomalonate (**26**) as the dienophile instead of pyrimidone **3**. Reaction of **26** with diene **17** led to either dihydropyrans **27**, **29** or furan **28**, depending on workup conditions. Furan **28** was independently prepared from furan **30**. Reaction of **26** with diene **21** afforded either hydropyrans **37**, **38**, or **39**, depending on the workup. A mechanistic rationalization is offered for the formation of furan **28** from adduct **27**.

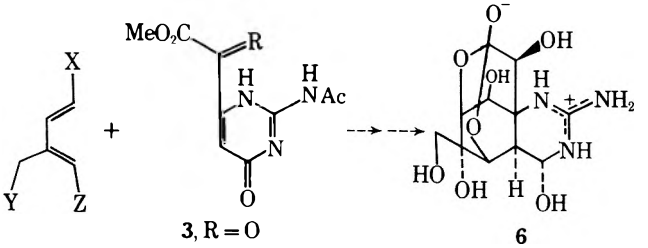
Recently,[2] we described a new route to hydroquinazolines involving the Diels–Alder reaction between pyrimidones **1** and **2** and several 1,3-dienes. The hydroquinazoline ring system is present in tetrodotoxin (**6**),[3] the potent neuropoison of a variety of amphibian and marine animals.[4] Pyrimidone **3** is an attractive dienophile for synthetic studies in this series owing to the presence of the oxygenated two-carbon side chain analogous to that present in tetrodotoxin. In this present paper we describe a convenient synthesis of **3** together with some Diels–Alder reactions of **3** and diethyl oxomalonate with two oxygenated 1,3-dienes. While no hydroquinazolines were produced with **3**, a new route to substituted furans and dihydro-4-pyrones resulted and constitutes the subject of this paper.



1

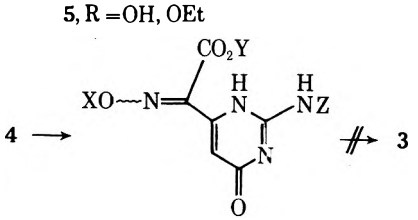


2 (mixture of stereoisomers)



3, R = O
4, R = H, H
5, R = OH, OEt

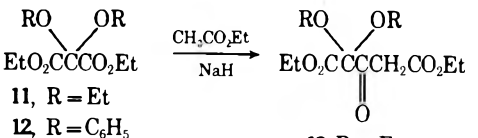
6



7, X = H; Y = *t*-Bu; Z = Ac
8, X = H; Y = Me; Z = Ac
9, X = Z = H; Y = Me
10, X = Z = Ac; Y = Me

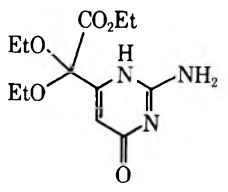
Our first attempt to prepare pyrimidone **3** involved oximination of the readily available pyrimidone **4**[5] using *t*-BuOK and isoamyl nitrite in *t*-BuOH. *tert*-Butyl ester oxime **7** was obtained in 49% yield as a mixture of syn–anti isomers. The methyl ester oxime **8** was obtained in 56% yield from **4** in DMF solvent using NaH and isoamyl nitrite. Unfortunately, every attempt to convert the oxime moiety into a carbonyl group failed. Whereas hydrolysis with 1 N HCl in MeOH led to amine **9** in 84% yield; more vigorous conditions appeared to lead to decarboxylation.[6] Reacetylation of amine **9** led in 84% yield to *O,N*-diacetate **10**, identical with that made in 83% yield by acetylation of oxime **8**, confirming that oxime hydrolysis had not been achieved. Several newer methods[7] of converting oximes to ketones were also not successful with **8** or **10** in our hands.

We then turned to a synthesis of ketal **15** by a method paralleling that of Ross et al.[8] Thus, diethyl diethoxymalonate[9] (**11**) was condensed with ethyl acetate, affording ketoketal **13**. Ester **15** could be obtained directly from the condensation of **13** with guanidine carbonate. Like oxime **8**, ester **15** also proved resistant to acidic hydrolysis and afforded no pyrimidone **3** under a variety of conditions. When the same series of reactions was conducted starting with diethyl di-

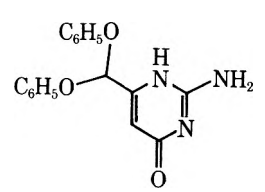


11, R = Et
12, R = C_6H_5

13, R = Et
14, R = C_6H_5



15

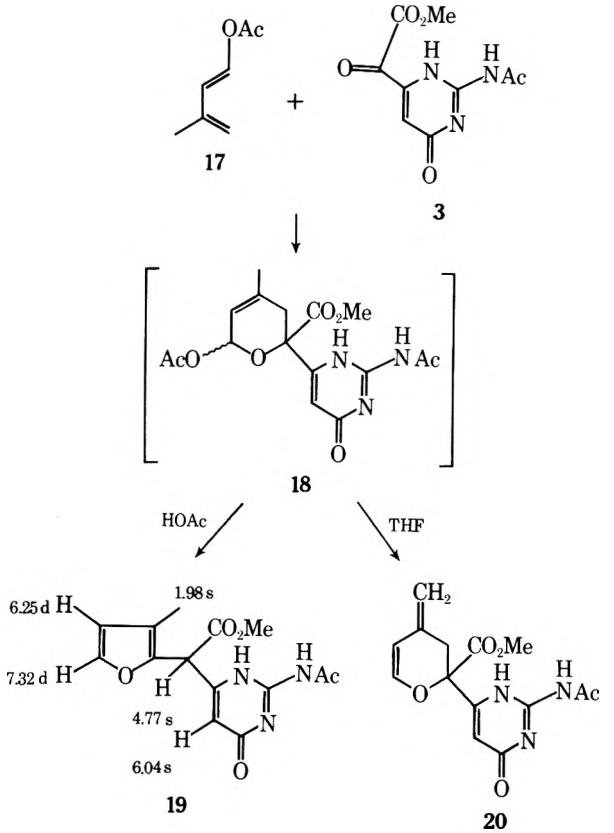


16

phenoxymalonate (12),[10] decarboxylated ketal 16 was formed.

Success was achieved through oxidation of pyrimidone 4 with H_2SeO_3 in HOAc, producing crystalline 3 in 27% yield after chromatography. In the uv spectrum of 3 in dry THF a maximum was observed at 335 nm whereas in EtOH the maximum appeared at 287 nm. This latter absorption corresponds to that of a nonconjugated 6-substituted 2-acetamido-4-pyrimidone[5,11,12] and is attributed to formation of hemiketal 5 in EtOH solution. The NMR spectrum of 3 in anhydrous deuterioacetic acid produced a methyl ester absorption at 3.98 ppm and a vinyl proton at 7.08 ppm. Interestingly, upon addition of D_2O to the sample, the methyl ester absorption shifted to 3.80 ppm and the vinyl proton appeared at 6.66 ppm. The observed change is consistent with a rapid hydration of the α-carbonyl group.[13]

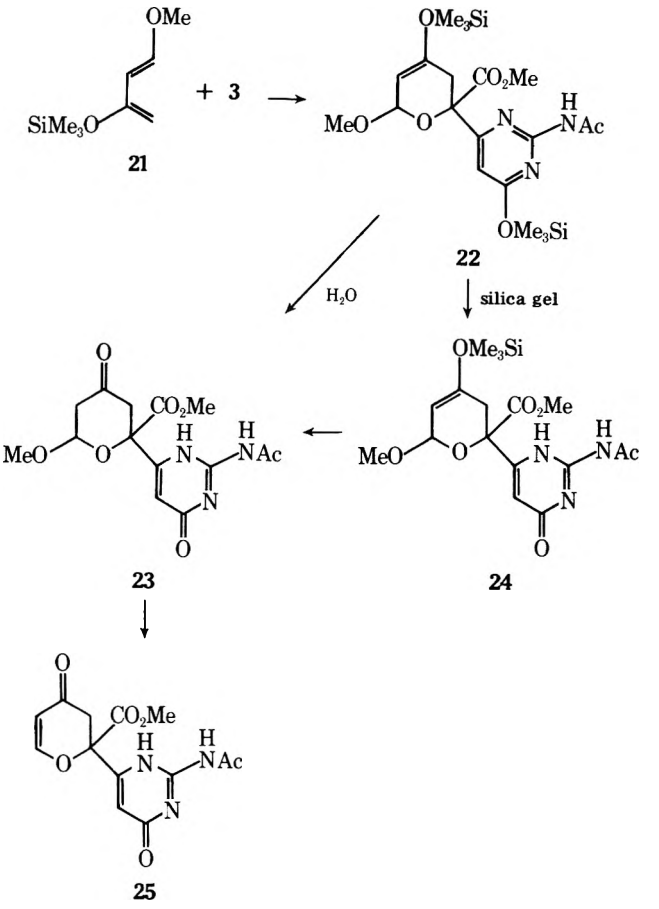
Pyrimidone 3 indeed proved to be a reactive dienophile. However, it was clear from the NMR and uv spectra of the 1:1 dienophile–diene adducts that cycloaddition occurred across the α-carbonyl group of 3 rather than at the double bond.[14] Reaction with 1-acetoxy-3-methyl-1,3-butadiene (17) in HOAc at 100 °C afforded crystalline furan 19 in 20% yield.



Consistent with this structure, the NMR spectrum showed a singlet at 6.04 ppm for the vinyl proton of the pyrimidone ring and a singlet at 4.77 ppm for the side chain methine proton. This proton underwent ready exchange with deuterium in either deuterioacetic acid or MeOH-d_4. The 214-nm maximum observed in the uv spectrum (EtOH) is typical of the furan ring[15] while the maxima at 236 and 285 nm are due to the pyrimidone ring. Absorption at 335 nm is likely due to a small amount of enol or enolate present since addition of a drop of NaOH to the solution gave rise to intense absorption at 335 nm.

The Diels–Alder reaction between 17 and 3 in THF at 120 °C was also accompanied by the elimination of a molecule of HOAc, leading to dihydropyran 20. Together with the usual analytical data, the structure of 20 followed from a comparison of the uv and NMR spectral data (see Experimental Section) with those obtained from the corresponding series of adducts derived from diethyl oxomalonate (see below).

The interesting highly reactive dioxygenated diene 21 recently reported by Danishefsky[16] was also allowed to react

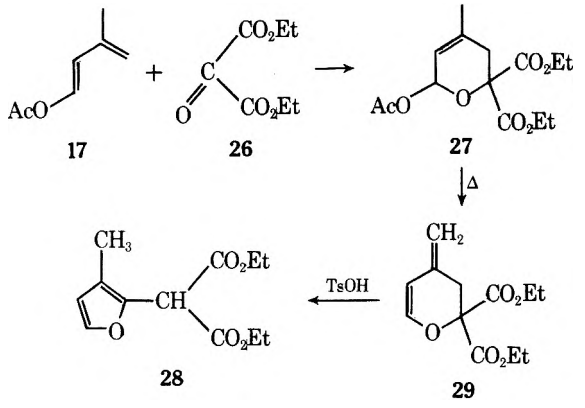


with pyrimidone 3 in THF. Evaporation of the solvent after reaction afforded adduct 22. While adduct 22 suffered hydrolysis upon chromatography, nevertheless, a molecular ion could be obtained in the mass spectrum of the crude oil. The NMR spectrum displayed 18 trimethylsilyl protons and both the pyrimidine ring proton (6.77 ppm) and the acetyl group (2.54 ppm) appeared at lower field than those of mono-Me_3Si derivative 24 (6.54 and 2.28 ppm, respectively), consistent with the presence of a pyrimidine ring in 22.

Passage of a solution of 22 through a silica gel column produced a mixture of mono-Me_3Si derivative 24 and methoxy ketone 23. Attempts to purify 24 were accompanied by further hydrolysis. Ketone 23 was best prepared by direct hydrolysis of 22 with 1 equiv of water in the absence of acid. While the reaction proceeded slowly, the use of neutral conditions avoided problems with the elimination of MeOH from the product. Crystalline 23 could thus be obtained from 22 in near quantitative yield as a single stereoisomer. While mild treatment of a mixture of 23 and 24 with acid produced 25, this latter substance was best obtained by acid hydrolysis of 22 followed by chromatography.

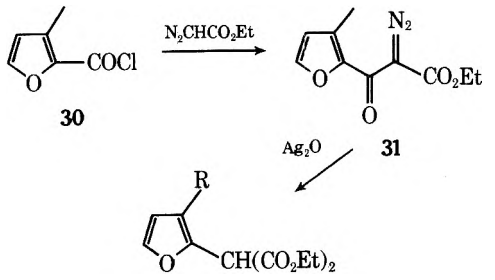
Both to confirm the structure assignments discussed above and to test the generality of these remarkable furan and dihydro-4-pyrone producing reactions, the reaction series was investigated using diethyl oxomalonate (26) as the dienophile rather than pyrimidone 3. Diethyl oxomalonate,[17,18] mesoxalonitrile,[17] and formaldehyde[19] have all served as the dienophile in earlier Diels–Alder reactions with substituted 1,3-dienes.

The reaction between diene 17 and 26 in boiling THF afforded the thermally unstable adduct 27 (by NMR). Distillation afforded methylene dihydropyran 29 as the predomi-



nant product accompanied by some furan **28** [uv max (MeOH) 214 nm (ϵ 6700)[15,20]]. Treatment of **29** with TsOH in benzene also led to furan **28.**

The structure of furan **28** was confirmed by independent synthesis. Thus, reaction of ethyl diazoacetate and 3-methylfuroyl chloride (**30**)[22] afforded diazo ester **31.** An Arndt–

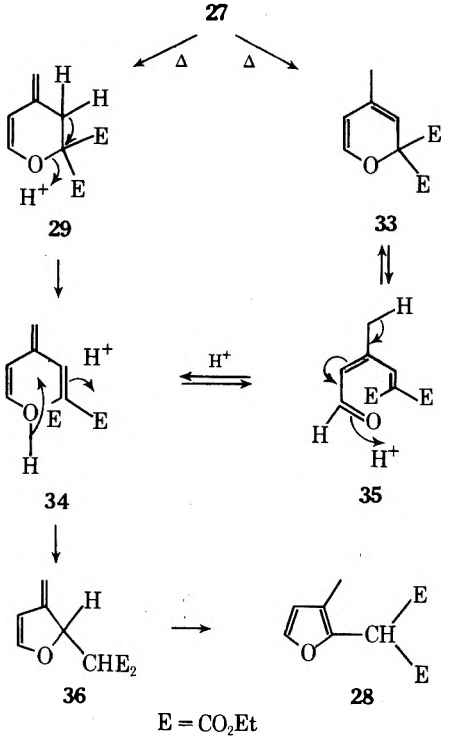


28, R = Me
32, R = H

Eistert reaction of **31** using Ag_2O gave furan **28,** identical with that obtained from the above Diels–Alder reaction. This same synthetic route was employed by Reichstein[23] for the preparation of diethyl fur-2-ylmalonate (**32**).

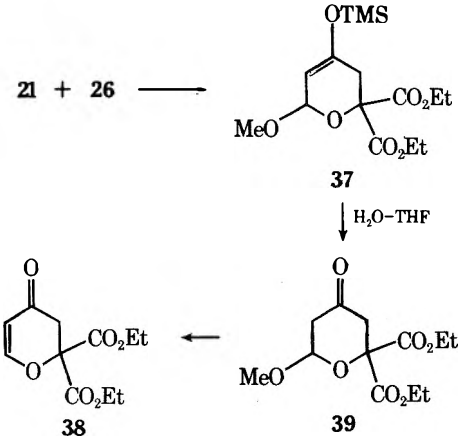
Scheme I outlines two reasonable pathways leading from **27** to furan **28.** Thus, thermal elimination of HOAc from **27** could produce either dihydropyran **29** or pyran **33.** It is not

Scheme I



surprising that we found no pyran **33** among the products in view of the known propensity of this ring system toward ring opening isomerization.[21] Aldehyde **35** is included in the scheme since its presence in the crude distillate of **29** was suggested by NMR. Recyclization of enol **34** would be expected to produce **36,** which would suffer ready isomerization to furan **28.**

The reaction of diethyl oxomalonate (**26**) with Me_3Si diene **21** proceeded analogously to that described above for pyrimidone **3.** Thus, from **26,** hydrolytically unstable Me_3Si ether



37 was formed which could be easily hydrolyzed to tetrahydropyrone **39** using THF–H_2O. This latter substance, when exposed to dilute aqueous HCl in THF, afforded dihydro-4-pyrone **38.** Ketone **38** showed spectral properties in good agreement with those of other 3,4-dihydro-4-pyrones.[24] In general, the uv and NMR spectral properties (see Experimental Section) observed for corresponding compounds derived from pyrimidone **3** and diethyl oxomalonate **26** are also in good agreement, constituting an important confirmation of the structure assignments in the pyrimidone series.

Experimental Section[25]

***tert*-Butyl [2′-Acetamido-4′(1′*H*)-pyrimidon-6′-yl]glyoxylate 2-Oxime (7).**[26] A mixture of 2.00 g (9.30 mmol) of ester **4,** mp 183–184 °C, and 48 ml (60 mmol) of 1.25 N *t*-BuOK in *t*-BuOH was stirred for 3 h at 25 °C. Then 1.36 ml (10.0 mmol) of isoamyl nitrite was added and the resulting solution was stirred for 5.5 h. The mixture was diluted with CH_2Cl_2 and neutralized with 35 ml (60 mmol) of 1.7 N HCl. The usual workup afforded 2.24 g of a yellow solid, recrystallization of which from EtOAc afforded 1.35 g (49%) of **7** as white needles, mp 200 °C dec. A second recrystallization from EtOAc afforded the analytical specimen, mp 205 °C dec, as a 5:2 mixture of syn and anti isomers: major isomer NMR (Me_2SO-d_6) δ 1.51 (s, 9), 2.22 (s, 3), 3.1–3.8 (v br s, 1), 6.28 (s, 1), 11.5–13.0 (m, 2); minor isomer NMR (Me_2SO-d_6) δ 1.57 (s, 9), 2.25 (s, 3), 3.1–3.8 (v br s, 1), 6.34 (s, 1), 11.5–13.0 (m, 2); uv max (EtOH) (mixture) 242 nm (ϵ 23 800) and 307 (4640). Anal. Calcd for $C_{12}H_{16}N_4O_5$: C, 48.64; H, 5.44; N, 18.91. Found: C, 48.83; N, 5.60; N, 18.76.

Methyl [2′-Acetamido-4′(1′*H*)-pyrimidon-6′-yl]glyoxylate 2-Oxime (8).[26] A mixture of 2.44 g (61.0 mmol) of NaH (60% dispersion in mineral oil), 12.3 g (54.5 mmol) of ester **4,** and 275 ml of DMF was heated with stirring at 80 °C for 15 min, cooled to 0 °C, and treated with 6.75 g (58.0 mmol) of isoamyl nitrite dropwise over 10 min. The mixture was then heated at 90 °C for 30 min, cooled to 0 °C, and treated with 3.32 g (61.0 mmol) of HCl in 50 ml of MeOH. The solvent was removed (15 mmol) and the residue was triturated with CCl_4 leaving a solid which was recrystallized from MeOH, affording 7.75 g (56%) of **8,** mp 205–210 °C. Two recrystallizations from MeOH afforded the analytical specimen as a single isomer: mp 227–228 °C dec; NMR (Me_2SO-d_6) δ 2.18 (s, 3), 3.80 (s, 3), 3.0–4.1 (m, 1), 6.28 (s, 1), 11.5–13.2 (m, 2); uv max (EtOH) 241 nm (ϵ 26 000) and 315 (4650). Anal. Calcd for $C_9H_{10}N_4O_5$: C, 42.52; H, 3.97; N, 22.04. Found: C, 42.60; H, 4.03; N, 21.97.

Methyl [2′-Amino-4′(1′*H*)-pyrimidon-6′-yl]glyoxylate 2-Oxime (9). A mixture of 3.40 g (13.4 mmol) of **8,** mp 220–222 °C dec, 20 ml of MeOH, and 20 ml (20 mmol) of 1.0 N HCl was refluxed for 25 min, cooled to 0 °C, and treated with 20 ml (20 mmol) of 1.0 N NaOH. The precipitated amine **9,** 2.42 g, mp 221–223 °C, was twice

recrystallized from MeOH, affording the analytical specimen as a powder: mp 227–230 °C; NMR (Me_2SO-d_6) δ 3.2–3.7 (m, 2), 3.82 (s, 3), 5.93 (s, 1), 12.2–12.6 (m, 1); uv max (EtOH) 227 nm (ε 18 500) and 325 (4930). Anal. Calcd for $C_7H_8N_4O_4$: C, 39.62; H, 3.80; N, 26.41. Found: C, 40.05; H, 4.17; N, 25.85.

Methyl [2′-Acetamido-4′(1′*H*)-pyrimidon-6′-yl]glyoxylate 2-Acetoxime (10). A. From Amine 9. A mixture of 5.0 g of **9**, mp 221–223 °C, and 25 ml of Ac_2O was heated at 130 °C for 7 min and cooled, and the solvent was removed under vacuum. The residue was triturated with CCl_4, affording 5.85 g (84%) of a white solid, mp 184–185 °C. Four recrystallizations from EtOAc afforded the analytical specimen as white needles: mp 202.5–203.5 °C; NMR (Me_2SO-d_6) δ 2.23 (s, 3), 2.28 (s, 3), 3.98 (s, 3), 6.55 (s, 1), 11.7–12.4 (m, 1); uv max (EtOH) 242 nm (ε 26 000) and 316 (4680). Anal. Calcd for $C_{11}H_{12}N_4O_6$: C, 44.60; H, 4.08; N, 18.91. Found: C, 44.87; H, 4.25; N, 18.80.

B. From Oxime 8. A 180-mg sample of oxime **8**, mp 216–219 °C, was treated with 3 ml of Ac_2O at 130 °C for 3 min. The usual workup afforded **10** identical by NMR with that obtained above, in near-quantitative yield.

Ethyl [2′-Amino-4′(1′*H*)-pyrimidon-6′-yl]glyoxylate Diethyl Ketal (15) and *N*-Acetyl Derivative. To 458 mg (19.1 mmol) of NaH was added with stirring at 0 °C a solution of 2.42 g (9.75 mmol) of diethyl diethoxymalonate[9] in 5 ml of THF followed by dropwise addition of 1.1 ml (12 mmol) of EtOAc. After a 30-min stir at 25 °C another 1.1 ml of EtOAc was added and the resulting mixture was stirred at 25 °C for 12 h. The mixture was poured over ice, neutralized to pH 5, and extracted with ether. The combined extracts were washed with water and brine, dried (Na_2SO_4), and evaporated, affording 2.284 g of viscous oil. Vacuum distillation afforded a 385-mg fraction, bp 92 °C (0.01 mm), of ketoketal **13**, pure by NMR. This entire fraction (1.31 mmol) was dissolved in 10 ml of absolute EtOH and treated with 288 mg (1.60 mmol) of guanidine carbonate and the resulting mixture was refluxed for 19 h. The solvent was evaporated, leaving a residue which was triturated with EtOAc. The residue was dissolved in ice water, neutralized to pH 5, and extracted with EtOAc. The sandy precipitate which formed between the layers was collected and dried (150 mg). Two recrystallizations from MeOH afforded 80 mg of pure **15**: mp 238–239 °C; uv max (EtOH) 224 nm (ε 10 000) and 292 (8920). Anal. Calcd for $C_{12}H_{19}N_3O_5$: C, 50.52; H, 6.71; N, 14.73. Found: C, 50.33; H, 6.74; N, 14.57.

A 27-mg portion was treated with 0.6 ml of Ac_2O at 100 °C for 1 h. Preparative TLC of the crude product afforded 23 mg of the *N*-acetyl derivative. Recrystallization from EtOAc–hexane afforded 18 mg of ethyl [2′-acetamido-4′(1′*H*)-pyrimidon-6′yl]glyoxylate diethyl ketal, mp 198–199 °C, as stocky needles: NMR ($CDCl_3$) δ 1.23 (t, 3), 1.25 (t, 6), 2.29 (s, 3), 3.50 (bq, 4), 4.24 (q, 2), 6.67 (s, 1); mass spectrum *m/e* 327.142 (calcd for $C_{14}H_{21}N_3O_6$, 327.143), 282, 254, 226.

6-(Diphenoxymethyl)-2-amino-4(1*H*)-pyrimidone (16). Crude ketoketal **14** was prepared from diethyl diphenoxymalonate[10] following the procedure for ketoketal **13** described above. Reaction (see procedure for **15** above) of 42.3 g (0.110 mol) of **14** with 22.4 g (0.130 mol) of guanidine carbonate afforded 24.0 g of crude **16**, mp 210–216 °C. Recrystallization from EtOH–water afforded the analytical specimen of **16** as white plates: mp 239–241 °C; NMR (Me_2SO-d_6) δ 5.88 (s, 1), 6.41 (s, 1), 6.75 (bs, 2), 6.9–7.5 (m, 10), 10.95 (bs, 1). Treatment of the sample with D_2O caused the signals at δ 6.75 and 10.95 to vanish. Uv max (EtOH) 292 nm (ε 6800); mass spectrum *m/e* 309 (molecular ion). Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 65.67; H, 4.96; N, 13.47.

Methyl 2-[2′-Acetamido-4′(1′*H*)-pyrimidon-6′-yl]glyoxylate (3). A mixture of 25.0 g (0.111 mol) of ester **4**, mp 181–183 °C, 14.9 g (0.115 mol) of H_2SeO_3 (Fisher), and 222 ml of HOAc was heated at 105–120 °C for 5 h; then 25 ml of Ac_2O was added and heating continued for 1 h. Filtration afforded 9.01 g (99%) of black Se. The filtrate was applied to 25 g of silica gel by evaporation of the solvent and azeotropic evaporation with toluene. The silica gel was applied to the top of a column of 100 g of silica gel packed in 3:2 EtOAc–hexanes. Elution with this solvent mixture afforded 7.08 g (27%) of ester **3** (first yellow band on the column) which crystallized directly from the eluant as fine yellow needles, mp 198–200 °C. Recrystallization from EtOAc produced the analytical specimen as white needles: mp 208.5–209 °C; NMR (Me_2SO-d_6) δ 2.15 (s, 3), 3.87 (s, 3), 6.65 (s, 1); (CD_3CO_2D) δ 2.32, 3.98, 7.08; (acetic acid-d_4–D_2O) δ 2.30, 3.80, 6.66; mass spectrum *m/e* 239 (molecular ion), 224, 211, 180, 169; uv max (THF) 335 nm (ε 4500) and 244 (11 000); (EtOH) 287 (6700), 233 (12 300), and 217 (12 700). Anal. Calcd for $C_9H_9N_3O_5$: C, 45.19; H, 3.79; N, 17.57. Found: C, 45.17; H, 3.71; N, 17.54.

Methyl 2-[2′-Acetamido-4′(1′*H*)-pyrimidon-6′-yl]-2-(3″-methylfur-2″-yl)acetate (19). A solution of 1.7 g (7.0 mmol) of keto ester **3**, mp 199–201 °C, 3.5 g (28 mmol) of diene **17**,[2] and 25 mg of 2,6-di-*tert*-butyl-4-methylphenol (Aldrich) in 10 ml of HOAc was heated at 100 °C for 7 h. The reaction mixture was deposited on 5 g of silica gel by evaporation. This was applied to the top of a 14 g silica gel column packed in 1:4 EtOAc–hexanes. Elution with this solvent system produced a total of 423 mg (20%) of good quality furan **19**, mp 200–206 °C. Recrystallization from EtOAc–hexane afforded the analytical specimen: mp 204–205 °C; NMR ($CDCl_3$–CD_3CO_2D) δ 1.98 (s, 3), 2.26 (s, 3), 3.78 (s, 3), 4.79 (s, 1, H-2), 6.04 (s, 1, H-5′), 6.25 (d, *J* = 2 Hz, 1, H-4″) and 7.32 (d, *J* = 2 Hz, 1, H-5″); uv max (EtOH) 335 nm (ε 3360), 285 (6700), 236 (16 000), and 214 (16 800); (pH ~12) 335 nm (intense). Anal. Calcd for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.76. Found: C, 54.84; H, 5.01; N, 13.50.

Methyl 4-Methylene-2,3-dihydro-2-[2′-acetamido-4′(1′*H*)-pyrimidon-6′-yl]-4*H*-pyran-2-carboxylate (20). In a 127-ml pressure reactor were combined 1.00 g (4.18 mmol) of keto ester **3**, mp 199–201 °C, 1.10 g (8.75 mmol) of diene **17**,[2] 50 mg of hydroquinone, and 25 ml of THF. The reactor was sealed and heated at 115–125 °C for 48 h. The mixture was filtered and the filtrate was applied to 5 g of silica gel by evaporation. This was placed on top of a column of 35 g of silica gel packed in 1:9 EtOAc–hexanes. Elution with this solvent system afforded 165 mg (13%) of pyran **20** as fine, white needles. Soxhlet recrystallization from EtOAc–hexanes (1:1) afforded the analytical specimen: mp 235 °C (in at 230 °C); NMR (acetone-d_6–CD_3CO_2D) δ 2.34 (s, 3), 2.83 (bd, *J* = 15 Hz, 1, H-3), 3.21 (bd, *J* = 15 Hz, 1, H-3), 3.70 (s, 3), 4.71 (bs, 1), 4.88 (bs, 1), 5.60 (d, *J* = 6 Hz, 1, H-5), 6.30 (s, 1, H-5′), 6.63 (bd, *J* = 6 Hz, 1, H-6); uv max (MeOH) 286 nm (ε 7630) and 237 (21 800); mass spectrum *m/e* 305 (molecular ion), 273, 263, 246, 245. Anal. Calcd for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.76. Found: C, 54.87; H, 5.02; N, 13.79.

Reaction of Keto Ester 3 with Diene 21. Products of Selective Hydrolysis. A solution of 1.00 g (4.18 mmol) of keto ester **3**, mp 199–201 °C, and 3.60 g (21 mmol) of diene **21**[16,27] in 10 ml of THF was heated at 55 °C for 48 h. A 1.00-ml aliquot was removed and evaporated, affording 192 mg of crude methyl 2-(2′-acetamido-4′-trimethylsilyloxypyrimidin-6′-yl)-6-methoxy-3,6-dihydro-4-trimethylsilyloxy-2*H*-pyran-2-carboxylate (**22**): NMR ($CDCl_3$) δ 0.23 (s, 9), 0.36 (s, 9), 2.54 (s, 3), 2.6 (m, 1), 3.0 (m, 1), 3.49 (s, 3), 3.74 (s, 3), 4.79 (m, 1), 5.42 (m, 1), 6.77 (s, 1); mass spectrum *m/e* 483 (molecular ion), 451, 424.

A second aliquot of the above reaction mixture was passed through a short silica gel column, affording a mixture of ketone **23** (see below) and methyl 2-[2′-acetamido-4′(1′*H*)-pyrimidon-6′-yl]-4-trimethylsilyloxy-6-methoxy-3,6-dihydro-2*H*-pyran-2-carboxylate (**24**): NMR ($CDCl_3$) δ 0.19 (s, 9), 2.28 (s, 3), 2.4 (m, 1), 2.91 (bd, *J* = 17 Hz, 1), 3.44 (s, 3), 3.71 (s, 3), 4.76 (bs, 1), 5.33 (bs, 1), 6.54 (s, 1).

A third 0.50-ml aliquot of the original reaction mixture was treated with 21 mg of water and let stand for 16 h at 25 °C. Chromatography over silica gel and elution with EtOAc afforded 53 mg of crude ketone **23**. Preparative TLC followed by crystallization from EtOAc–hexanes produced the analytical specimen of methyl 2-(2′-acetamido-4′-pyrimidon-6′-yl)-6-methoxy-2,3,5,6-tetrahydro-4-pyrone-2-carboxylate (**23**): mp 191–192 °C dec; NMR ($CDCl_3$) δ 2.29 (s, 3), 2.4–2.9 (m, 2), 2.67 (d, *J* = 18 Hz, 1, H-3), 3.19 (d, *J* = 18 Hz, 1, H-3), 3.54 (s, 3), 3.73 (s, 3), 5.00 (dd, 1, H-6), 6.61 (s, 1); uv max (MeOH) 287 nm (ε 8250) and 235 (14 400); mass spectrum *m/e* 339 (molecular ion), 307, 280, 265. Anal. Calcd for $C_{14}H_{17}N_3O_7$: C, 49.56; H, 5.05; N, 12.38. Found: C, 49.20; H, 5.00; N, 12.35.

Methyl 2-[2′-Acetamido-4′(1′*H*)-pyrimidon-6′-yl]-2,3-dihydro-4-pyrone-2-carboxylate (25). A mixture of 102 mg (0.42 mmol) of keto ester **3**, mp 199–201 °C, 360 mg (2.10 mmol) of diene **21**,[16,27] and 1 ml of THF was heated at 60 °C for 24 h. The solution was cooled, treated with 0.2 ml of 12 N HCl in 10 ml of THF for 40 min at 25 °C, and evaporated. Chromatography over silica gel, elution with 1:4 EtOAc–hexanes, and recrystallization of the crystalline fractions from EtOAc–hexanes afforded 24 mg (18%) of pure ketone **25**: mp 195–198 °C dec; NMR ($CDCl_3$) δ 2.28 (s, 3), 3.01 (d, *J* = 15 Hz, 1, H-3), 3.32 (d, *J* = 15 Hz, 1, H-3), 3.78 (s, 3), 5.53 (d, *J* = 5 Hz, 1, H-5), 6.49 (s, 1, H-5′), 7.41 (d, *J* = 6 Hz, 1, H-6); uv max (MeOH) 288 nm (ε 3070), 258 (4020), and 236 (6100); mass spectrum *m/e* 307.076 (calcd for $C_{13}H_{13}N_3O_6$, 307.080), 265, 248.

Reaction of Diethyl Oxomalonate (26) with Diene 17. A solution of 527 mg (3.03 mmol) of ketone **26** (Aldrich) and 1.00 g (8.00 mmol) of diene **17**[2] in 3 ml of THF was refluxed for 20 h. A 0.3-ml aliquot was removed and pumped down at high vacuum. NMR spectroscopy revealed the presence of diethyl 6-acetoxy-4-methyl-3,6-dihydro-2*H*-pyran-2,2-dicarboxylate (**27**) as the major product: NMR ($CDCl_3$) δ 1.29 (t, 6), 1.87 (bs, 3), 2.02 (s, 3), 2.38 (bd, *J* = 17 Hz, 1), 2.82 (bd, *J* = 17 Hz, 1), 4.0–4.6 (m, 4), 5.49 (bs, 1), 6.51 (bs, 1).

The remainder of the reaction mixture was distilled, affording 222

mg (31%) of bright yellow distillate, bp 100–120 °C (0.15 mm) (bath, 150 °C). Analysis by NMR indicated the oil to be about 50% diene **29** with lesser amounts of furan **28** and possibly aldehyde **25** and tars. Preparative VPC (column B) at 180 °C (t_R 3.0 min) produced a pure sample of diethyl 4-methylene-2,3-dihydro-4*H*-pyran-2,2-dicarboxylate (**29**) as a colorless oil: ir 1745 (s), 1640 cm^{-1} (m); NMR ($CDCl_3$) δ 1.28 (t, 6), 3.01 (bs, 2, H-3), 4.27 (q, 4), 4.74 (bs, 1), 4.88 (bs, 1), 5.51 (d, J = 5 Hz, 1, H-5), 6.53 (bd, J = 6 Hz, 1, H-6); uv max (MeOH) 245 nm (ϵ 12 700); mass spectrum m/e 240.097 (calcd for $C_{12}H_{16}O_5$, 240.100), 211, 194, 167.

A 268-mg sample of crude diene **29** was taken up in 5 ml of benzene containing 1 mg of $TsOH{\cdot}H_2O$ and refluxed for 1 h. Chromatography over silica gel and elution with $CHCl_3$ afforded 180 mg (67%) of crude furan **28**. Preparative TLC (1% EtOAc in benzene) afforded pure diethyl 3-methylfur-2-ylmalonate (**28**) as a colorless oil: NMR ($CDCl_3$) δ 1.27 (t, 6), 2.02 (s, 3), 4.25 (q, 4), 4.76 (s, 1), 6.24 (d, J = 2 Hz, 1, H-4′), 7.32 (d, J = 2 Hz, H-5′); uv max (MeOH) 280 nm (ϵ 540) and 214 (6700); mass spectrum m/e 240.097 (calcd for $C_{12}H_{16}O_5$, 240.100), 168, 95. Furan **28** was best obtained from diene **17** in one step. A 127-ml pressure reactor was charged with 505 mg of diene **17**, 238 mg of ketone **26**, 27 mg of hydroquinone, and 12 ml of THF, sealed, and heated at 120 °C for 36 h. Evaporation at 0.01 mm produced 552 mg (115%) of crude furan **28** as a dark oil. Distillation afforded 60 mg (much hold-up loss) of pure (by NMR) **28**.

Furan 28 by an Arndt–Eistert Synthesis.[23] A solution of 733 mg (5.10 mmol) of 3-methylfuroyl chloride[22] (**30**) and 1.14 g (10.0 mmol) of ethyl diazoacetate was allowed to stand at 25 °C for 5 days. Then 2.00 g (17.5 mmol) more ethyl diazoacetate was added. After 7 days the volatiles were removed at 0.01 mm, producing 614 mg of a yellow oil which by NMR was a 1:1 mixture of **30** and ethyl (3′-methylfuroyl)diazoacetate (**31**). A portion was purified by chromatography over Florisil: NMR (CCl_4) δ 1.33 (t, 3), 2.38 (s, 3), 4.32 (q, 2), 6.44 (d, J = 2 Hz, 1), 7.44 (d, J = 2 Hz, 1). A 518-mg portion of the above yellow oil was heated in 10 ml of EtOH at 160 °C for 1 h with 100 mg of Ag_2O and 1 ml of Newman and Beal's reagent.[28] The reaction mixture was cooled, filtered, and evaporated, and the residue was dissolved in $CHCl_3$ and passed through a short silica gel column. Preparative TLC (2% EtOAc in benzene) produced 67 mg of a pale yellow oil which by NMR and VPC analysis was 25% furan **28** and 75% ethyl 3-methylfuroate. A pure sample of furan **28** was obtained by preparative VPC and was identical with the Diels–Alder product by NMR, uv, and mass spectral analysis.

Reaction of Diene 21 with Diethyl Oxomalonate (26). A solution of 1.10 g (6.40 mmol) of diene **21**[16,27] and 507 mg (2.92 mmol) of keto ester **26** in 3 ml of THF was heated at 55 °C for 23 h. A 0.5-ml aliquot was removed and evaporated (0.01 mm), producing 116 mg (107%) of yellow oily diethyl 6-methoxy-4-trimethylsilyloxy-3,6-dihydro-2*H*-pyran-2,2-dicarboxylate (**37**) (~90% pure by NMR, too unstable for further purification): NMR ($CDCl_3$) δ 0.18 (s, 9), 1.23 (t, 6), 2.32 (bd, J = 17 Hz, 1), 2.79 (d, J = 17 Hz, 1), 3.39 (s, 3), 4.22 (bq, 4), 4.79 (bs, 1), 5.21 (bs, 1); mass spectrum m/e 346.144 (calcd for $C_{15}H_{26}O_7Si$, 346.145), 331, 315, 300, 273.

A 67-mg sample of crude ester **37** was treated with 2 ml of 10% aqueous THF for 2 days at 25 °C followed by a 2-h reflux. Evaporation of the solvent followed by preparative VPC (column A, 132 °C, t_R 3.2 min) afforded pure diethyl 6-methoxy-2,3,5,6-tetrahydro-4-pyrone-2,2-dicarboxylate (**39**): NMR ($CDCl_3$) δ 1.29 (t, 3), 2.66 (m, 2, H-5), 2.81 (d, J = 16 Hz, 1, H-3), 3.23 (d, J = 16 Hz, 1, H-3), 3.49 (s, 3), 4.38 (q, 4), 5.24 (dd, J = 3, 4 Hz, 1, H-6); mass spectrum m/e 274.106 (calcd for $C_{12}H_{18}O_7$, 274.105), 243, 229, 201.

A 1.0-ml aliquot of the initial reaction mixture was treated with 1.0 ml of 0.1 N HCl and 2 ml of THF for 30 min at 25 °C. The solution was diluted with ether, dried (Na_2SO_4), evaporated, taken up in $CHCl_3$, and passed through a short silica gel column. Evaporation followed by preparative VPC (column A, 185 °C, t_R 1.0 min) afforded pure diethyl 2,3-dihydro-4-pyrone-2,2-dicarboxylate (**38**): NMR ($CDCl_3$) δ 1.30 (t, 6), 3.14 (s, 2), 4.33 (q, 4), 5.51 (d, J = 6 Hz, 1, H-5), 7.40 (d, J = 6 Hz, 1, H-6); uv max (MeOH) 257 nm (ϵ 5960); mass spectrum m/e 242.081 (calcd for $C_{11}H_{14}O_6$, 242.079), 197, 169, 97.

Acknowledgment. We thank the National Science Foundation (09413) for generous financial support.

Registry No.—**3**, 59414-11-8; **4**, 22794-57-6; *syn*-**7**, 59414-12-9; *anti*-**7**, 59414-13-0; **8**, 33965-28-5; **9**, 59414-14-1; **10**, 59414-15-2; **11**, 29340-87-2; **12**, 4525-71-7; **13**, 59414-16-3; **14**, 59414-17-4; **15**, 59414-18-5; **15** *N*-acetyl derivative, 59414-19-6; **16**, 59414-20-9; **17**, 17616-47-6; **19**, 59414-21-0; **20**, 59414-22-1; **21**, 59414-23-2; **22**, 59414-24-3; **23**, 59414-25-4; **24**, 59414-26-5; **25**, 59414-27-6; **26**, 609-09-6; **27**, 59414-28-7; **28**, 59414-29-8; **29**, 59414-30-1; **30**, 22601-06-5; **31**, 59414-31-2; **37**, 59414-32-3; **38**, 59414-33-4; **39**, 59414-34-5.

References and Notes

(1) National Institutes of Health RCDA Recipient. Fellow of the Alfred P. Sloan Foundation.
(2) J. F. W. Keana, J. S. Bland, P. E. Eckler, V. Nelson, and J. Z. Gougoutas, *J. Org. Chem.*, **41**, 2124 (1976), and references cited therein.
(3) M. H. Evans, *Int. Rev. Neurobiol.*, **15**, 83 (1972).
(4) Y. H. Kim, G. B. Brown, H. S. Mosher, and F. A. Fuhrman, *Science*, **189**, 151 (1975).
(5) J. F. W. Keana and F. P. Mason, *J. Org. Chem.*, **35**, 838 (1970).
(6) G. N. Mitchell and R. L. McKee, *J. Org. Chem.*, **39**, 176 (1974), have observed that the amino acid corresponding to ester **4** undergoes facile decarboxylation upon attempted nitration or oximination.
(7) For example, E. J. Corey and J. E. Richman, *J. Am. Chem. Soc.*, **92**, 5276 (1970); J. E. McMurry and J. Melton, *J. Org. Chem.*, **38**, 4367 (1973).
(8) L. O. Ross, E. M. Acton, W. A. Skinner, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 3395 (1961).
(9) Y. Otsuji, S. Wake and E. Imoto, *Tetrahedron*, **26**, 4293 (1970).
(10) K. H. Takemura, M. Pulickal, and F. O. Hoff, *J. Org. Chem.*, **36**, 3646 (1971).
(11) F. P. Mason, Ph.D. Thesis, University of Oregon, Eugene, Oregon, 1971.
(12) A. S. Katner and E. A. Ziege, *Chem. Commun.*, 864 (1971).
(13) Other carbonyl groups show a strong propensity toward hydration; see, inter alia, J. Bordner, W. E. Thiessen, A. Bates, and H. Rapoport, *J. Am. Chem. Soc.*, **97**, 6008 (1975).
(14) For other examples, see J. Hamer, "1,4-Cycloaddition Reactions", Academic Press, New York, N.Y., 1967.
(15) W. L. F. Armarego in "Physical Methods in Heterocyclic Chemistry", Vol. 3, A. R. Katritzky, Ed., Academic Press, New York, N.Y., 1971, p 185.
(16) S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7808 (1974).
(17) O. Achmatowicz and A. Zamojski, *Bull. Acad. Pol. Sci., Cl. 3*, **5**, 927 (1957); *Chem. Abstr.*, **52**, 6333*d* (1958).
(18) R. A. Ruden and R. Bonjouklian, *J. Am. Chem. Soc.*, **97**, 6892 (1975).
(19) D. G. Kubler, *J. Org. Chem.*, **27**, 1435 (1962).
(20) it is pertinent to note that the isomeric 2-H pyran structure **33** would be expected to show a uv maximum in the range of 279–284 nm. See J. Royer and J. Dreux, *Bull. Soc. Chim. Fr.*, 707 (1972), and earlier papers.
(21) See, E. N. Marvell, T. Chadwick, G. Caple, T. Gosink, and G. Zimmer, *J. Org. Chem.*, **37**, 2992 (1972), and references cited therein.
(22) H. Ledetschke, *Arch. Pharm. (Weinheim, Ger.)*, **295**, 323 (1962); *Chem. Abstr.*, **58**, 4511*d* (1963).
(23) T. Reichstein and H. J. Morsman, *Helv. Chim. Acta*, **17**, 1119 (1934).
(24) S. Gelin and R. Gelin, *Bull. Soc. Chim. Fr.*, 288 (1968).
(25) The preamble to the Experimental Section of P. N. Strong and J. F. W. Keana, *J. Org. Chem.*, **40**, 956 (1975), applies here. VPC column A was a 6.3 mm × 60 cm copper column packed with 5% SE-30 on 60/80 firebrick. Column B was a 6.3 mm × 90 cm copper column packed with 15% Carbowax 20M on 60/80 Chromosorb W.
(26) This experiment was carried out by F. P. Mason, ref 11.
(27) Diene **21** used in this experiment contained 10 mol % of 4-methoxy-3-buten-2-one by NMR.
(28) M. S. Newman and J. Beal, *J. Am. Chem. Soc.*, **72**, 5163 (1950).

Preparation and Reactions of Bifunctionalized Tetrathiafulvalenes

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Bifunctionalized tetrathiafulvalene (TTF) derivatives suitable for polycondensations were prepared. The desulfurization–coupling of 4-carbomethoxy-1,3-dithiole-2-thione (**3**) with triethyl phosphite gave, in fair yield, 2,6(7)-bis(carbomethoxy)-TTF (**6**), which was converted to TTF-2,6(7)-dicarboxylic acid (**9**), 2,6(7)-bis(hydroxymethyl)-TTF (**18**), the bis acetic anhydride, **19**, of the diacid **9**, and bisanilide **20** of the diacid **9**. The attempted coupling of 1,3-dithiole-2-thione-4-carboxylic acid (**2**) with triethyl phosphite failed to produce diacid **9**, but 4-carboethoxy-1,3-dithiole-2-thione (**10**) was formed. 4-Carbomethoxy-1,3-dithiole-2-thione (**3**), 4,5-biscarboethoxy-1,3-dithiole-2-thione (**1**), and 4-(*p*-nitrophenyl)-1,3-dithiole-2-thione 4-carboxylate (**4**) were each coupled to give their corresponding bifunctionalized TTF derivatives in the presence of trivalent phosphines.

Charge transfer salts of tetrathiafulvalenes (TTF)[1] and tetraselenafulvalenes (TSeF)[2,3] with tetracyanoquinodimethane (TCNQ) have attracted widespread interest owing to their quasi-metallic electrical conductivity. Preparative methods for TTF and TSeF have been reviewed[4] and two groups have recently reported polymers containing TTF structures.[5,6] We report the synthesis of several difunctionalized TTF monomers suitable for polycondensation studies. Thus, TTF-2,6(7)-dicarboxylic acid (**9**), the bis acetic anhydride of TTF-2,6(7)-dicarboxylic acid (**19**), the bisanilide of TTF-2,6(7)-dicarboxylic acid (**20**), and 2,6(7)-bis(hydroxymethyl)-TTF (**18**) were prepared from 2,6(7)-bis(carbomethoxy)tetrathiafulvalene (**6**). Furthermore, 2,6(7)-bis(*p*- and *m*-hydroxyphenyl)tetrathiafulvalenes (**15** and **16**) were prepared by base-catalyzed coupling of 4-(*p*- and *m*-acetoxyphenyl)-1,3-dithiolium perchlorates (**11** and **12**), respectively. In addition, the synthesis and coupling of a series of substituted 1,3-dithiole-2-thiones were carried out.

Results

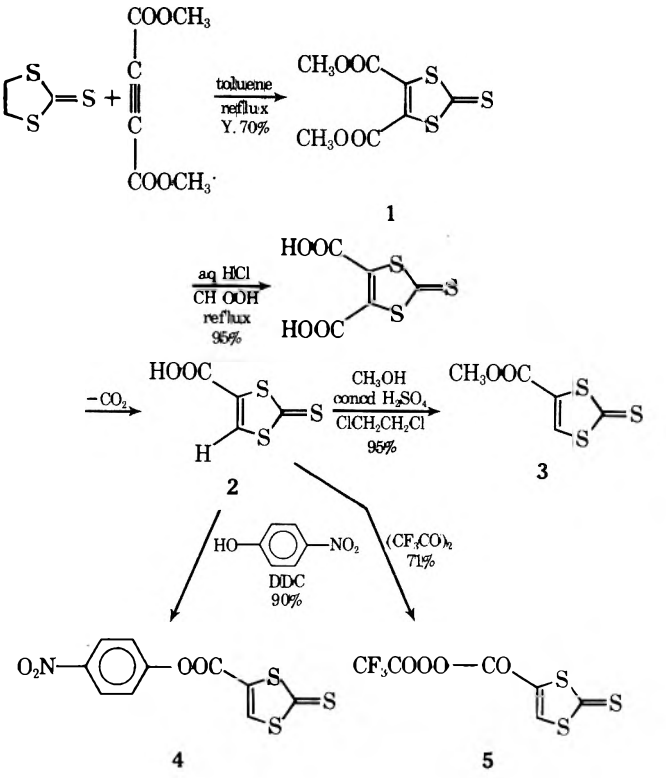
Preparations of 1,3-Dithiole-2-thiones. Several substituted 1,3-dithiole-2-thiones were prepared in order to study their coupling via desulfurization with trivalent phosphorus compounds. It is known that TTF derivatives which have electron-withdrawing substituents may be coupled in fair yields in this manner. Example preparations by this route include 2,3,6,7-tetrakis(trifluoromethyl)-TTF,[7] 2,3,6,7-tetracyano-TTF,[8] and dibenzo-TTF.[9,10]

4-Substituted 1,3-dithiole-2-thiones, precursors of difunctionalized TTFs, were derived from 1,3-dithiole-2-thione-4-carboxylic acid (**2**). Compound **2** was easily obtained by decarboxylation of 1,3-dithiole-2-thione-4,5-dicarboxylic acid,[11] which was prepared by reaction of dimethyl acetylenedicarboxylate with ethylene trithiocarbonate, followed by hydrolysis.[12] The reactions are summarized in Scheme I.

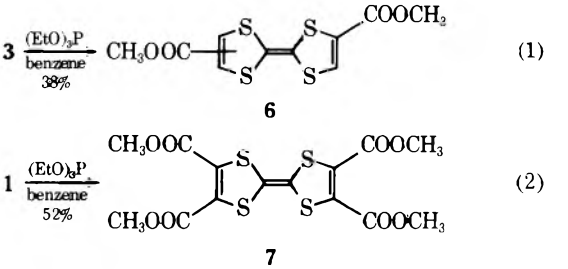
Acid **2** was easily esterified by Clinton's method[13] to give 4-carbomethoxy-1,3-dithiole-2-thione (**3**) in 89% yield. Reaction of **2** and *p*-nitrophenol with dicyclohexylcarbodiimide (DDC) afforded *p*-nitrophenyl 1,3-dithiole-2-thione-4-carboxylate (**4**) in 90% yield, while treatment of **2** with trifluoroacetic anhydride gave the bistrifluoroacetic anhydride, **5**, of the acid **2**, in 71% yield. These 1,3-dithiole-2-thiones were then used for the desulfurization–coupling reactions.

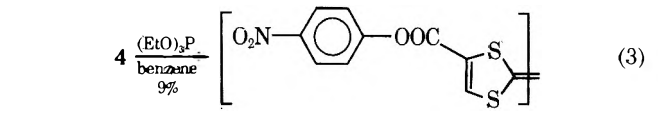
Preparation of Tetrathiafulvalenes by Desulfurization of 1,3-Dithiole-2-thiones. Treatment of either 4-carbomethoxy-1,3-dithiole-2-thione (**3**) or 4,5-bis(carbomethoxy)-1,3-dithiole-2-thione (**1**) with triethyl phosphite in refluxing benzene resulted in the formation of 2,6(7)-bis(carbomethoxy)- and 2,3,6,7-tetrakis(carbomethoxy)tetrathiafulvalenes (**6** and **7**) in 38 and 52% yields, respectively (see eq 1 and 2). The desulfurization–coupling of **1** with triphenylphosphine also gave TTF tetraester **7**, but the yield was only 22%.

Scheme I



TTF diester **6** was also prepared by the reaction of methyl propiolate with carbon disulfide, a known but low-yield route.[12,14] Tetraester **7** was prepared directly from dimethyl acetylenedicarboxylate and carbon disulfide according to the literature.[7] In contrast to the ready coupling of **1** and **3**, desulfurization of 1,3-dithiole-2-thiones **2**, **4**, and **5** did not proceed smoothly. Bis(*p*-nitrophenyl) TTF diester **8** was obtained in only 9% yield in triethyl phosphite promoted coupling of ester **4** (eq 3) and tarry products predominated. Since aromatic nitro compounds are known to react readily with deoxygenating agents such as $(EtO)_3P$,[15] this result is not surprising.

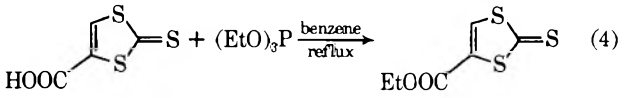




(3)

8

The reaction of 1,3-dithiole-2-thione-4-carboxylic acid with triethyl phosphite did not produce 2,6(7)-tetrathiafulvalenedicarboxylic acid (**9**). Instead 4-carboethoxy-1,3-dithione-2-thione (**1**) was produced in 36% yield (see eq 4). The results of coupling thiones **1**, **2**, and **4** are summarized in Table I.



(4)

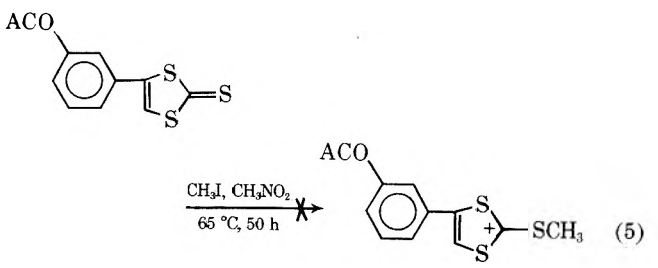
2 **10**

Preparation of 2,6(7)-Bis(*p*- and *m*-hydroxyphenyl)-tetrathiafulvalenes by Deprotonation of 1,3-Dithiolium Cations (Scheme II). The most suitable method for preparation of the bisphenol monomers **15** and **16** appeared to be the coupling of their corresponding 1,3-dithiolium cations (i.e., **11** and **12**) by triethylamine-promoted deprotonation. Thus, **11** and **12** were designated as key intermediates. The overall synthesis is summarized in Scheme II.

Many TTF derivatives, which do not have electron-withdrawing substituents, have been prepared by the coupling reaction of cations upon deprotonation with triethylamine.[4,12,16] It is known that 1,3-dithiolium-2-carbenes, produced by deprotonation of 1,3-dithiolium cations, react rapidly with alcohols to give 2-alkoxy-1,3-dithioles.[7,17] Thus, we prepared 4-(*p*- and *m*-acetoxyphenyl)-1,3-dithiolium perchlorates (**11** and **12**) as intermediates for use in coupling reactions to produce the bisacetates **13** and **14**, respectively. Perchlorates **11** and **12** were obtained as shown in Scheme II according to the procedure of Takamizawa.[18] Perchlorates **11** and **12** were reluctantly chosen as intermediates only after it was shown that hydrogen sulfate salts were difficult to prepare reproducibly.

Preparation of *p*- and *m*-hydroxyphenacylpiperidinocarbodithioate was achieved by reaction of corresponding hydroxyphenacyl bromides with carbon disulfide and piperidine. Acid-catalyzed cyclizations gave 4-(*p*- or *m*-hydroxyphenyl)-1,3-dithiole-2-ylidene piperidinium fluoroborates in good yield. The phenolic hydroxyl groups were acylated by acetic anhydride and then the piperidinium salts were reduced with sodium borohydride. Treatment of the resulting 2-piperidino-1,3-dithioles with perchloric acid gave perchlorate salts **11** and **12**.

We were unsuccessful in obtaining 4-(*m*-acetoxyphenyl)-1,3-dithiolium tetrafluoroborate by the S-methylation of 4-(*m*-acetoxyphenyl)-1,3-dithiole-2-thione with methyl iodide, followed by sodium borohydride reduction and treatment with fluoroboric acid. The S-methylation failed (eq 5). Thus, the

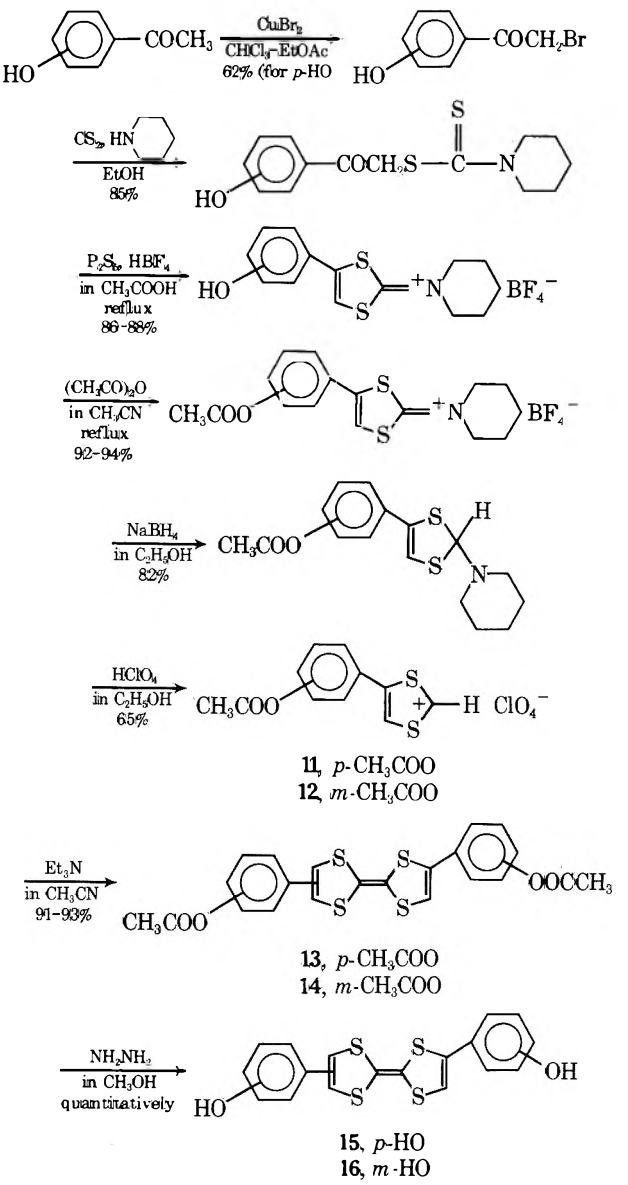


(5)

route involving 2-piperidino-1,3-dithiole intermediates (Scheme II) as the precursors to **11** and **12** was dictated.

Perchlorate salts **11** and **12** were successfully coupled in acetonitrile by treatment with excess triethylamine to produce 2,6(7)-bis(*p*- and *m*-acetoxyphenyl)-TTF (**13** and **14**). Bisacetates **13** and **14** were easily converted to 2,6(7)-bis(*p*- and *m*-hydroxyphenyl)-TTF (**15** and **16**) by treatment with hydrazine in methanol. This scheme constitutes an efficient, high-yield route to monomers **15** and **16**. No attempts were made to optimize the yields of any of the steps in this scheme. Monomers **15** and **16** were prepared for use in the synthesis of TTF-containing polyesters, polyurethanes, and polycarbonates.

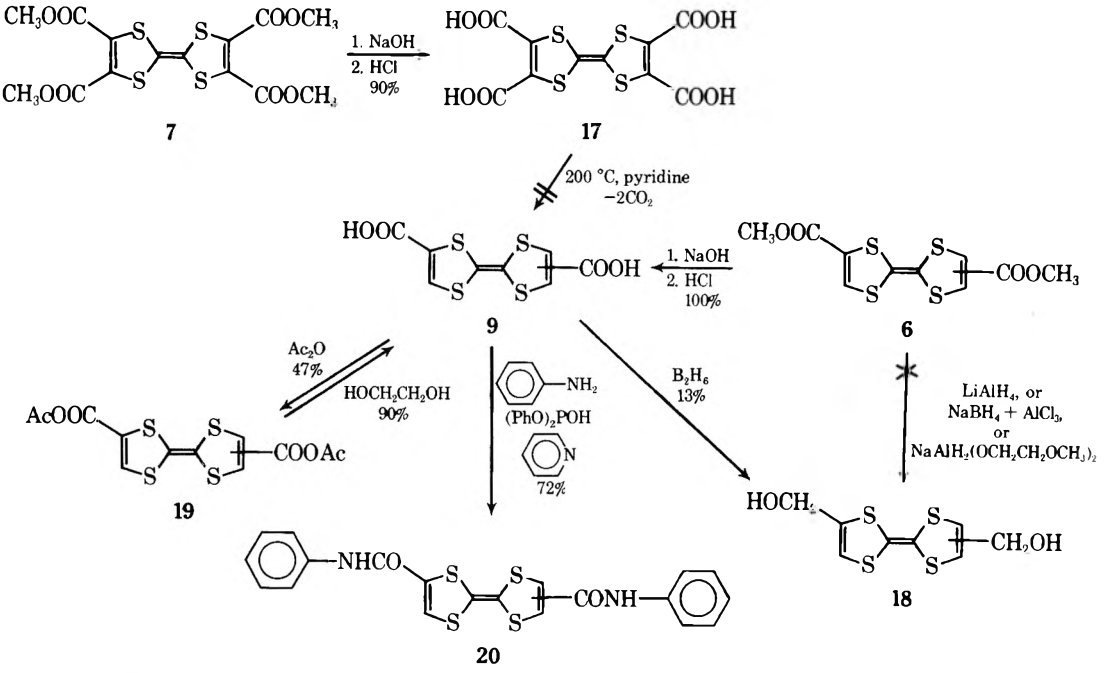
Scheme II

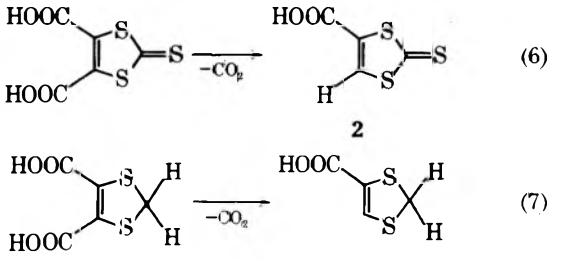


Reactions of Some TTF Derivatives (Scheme III). TTF diester **6** and TTF tetraester **7** were readily hydrolyzed to the corresponding diacid **9** and tetraacid **17** by 1 N NaOH. Decarboxylation of the tetraacid **17** to the diacid **9** was tried at 200 °C in the presence of pyridine, but **17** was quite stable and recovered unchanged. This result was unexpected because both 1,3-dithiole-2-thione-4,5-dicarboxylic acid and 1,3-dithiole-4,5-dicarboxylic acid were readily decarboxylated, without pyridine, to acid **2** and 1,3-dithiole-4-carboxylic acid, respectively, in good yields[11,19] (see eq 6 and 7). Therefore, tetraacid **17** was not a suitable precursor for entry into a series of difunctional TTF monomers.

Diester **6** appeared to be a likely intermediate for the preparation of difunctional monomers such as diol **18**. However, **6** was not reduced by $LiAlH_4$, $LiAlH_4 + AlCl_3$, or $NaAlH_2(OCH_2CH_2OCH_3)_2$ to **18**. These reductions were tried at temperatures below 70 °C in ether, THF, and benzene.[20] This

Scheme III



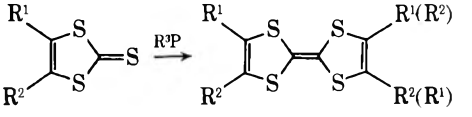


resistance to reduction is puzzling. However, reduction of diacid **9** with diborane in diglyme gave dialcohol **18** in a low yield.

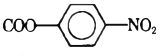
Reaction of diacid **9** with acetic anhydride gave TTF bisanhydride **19** in 47% yield. It was hoped that bisanhydride **19** upon reaction with ethylene glycol would produce 2,6(7)-bis(2-hydroxycarbethoxy)tetrathiafulvalene, a diol which could presumably be polycondensed with diacid **9**. However, reaction of ethylene glycol with **19** gave the TTF diacid **9**. Condensation of diacid **9** with aniline readily give bisanilide **20** in *N,N*-dimethylformamide (D) at 70 °C using diphenyl phosphite–pyridine as a dehydrating reagent. This reagent has previously been used to catalyze polyamide formation.[5,21]

Charge-Transfer Complexes of TTF Derivatives with TCNQ and DDQ. A preliminary study of the ability of TTF derivatives **6**, **13**, **14**, **15**, **16**, **18**, and **20** to form salts or charge-transfer complexes with TCNQ and DDQ was made (Table II). Hot acetonitrile solutions of TCNQ or DDQ were added to hot acetonitrile solutions of the TTF derivative. In the cases of compounds **13**, **14**, **15**, **16**, and **18** complexes with DDQ precipitated when the solutions were slowly cooled to room temperature. TCNQ may form charge-transfer complexes with TTF derivatives **13**, **14**, **15**, **16**, and **18** in solution but precipitation of a complex from acetonitrile occurred only for diols **15**, **16**, and **18**. Compounds **6** and **20**, which have electron-withdrawing substituents, did not form complexes with either TCNQ or DDQ.

Table I. Desulfurization of 1,3-Dithiole-2-thiones



6-8

R¹	R²	R	Yield, %	Product
$COOCH_3$	H	C_2H_5O	38	6
$COOCH_3$	$COOCH_3$	C_2H_5O	52	7
$COOCH_3$	$COOCH_3$	C_6H_5	22[a]	7
	H	C_2H_5O	9	8

[a] 69% of dimethyl 1,3-dithiole-2-thione-4,5-dicarboxylate was recovered.

Table II. Complex Formation of TTF Derivatives with DDQ and TCNQ[a]

TTF donor	Acceptor	Formula	Found (calcd), % C	H	N
13[b]	DDQ	$C_{30}H_{16}N_2O_6S_4Cl_2$	51.36 (51.50	2.31 2.31	4.14 4.00)
14[c]	DDQ	$C_{30}H_{16}N_2O_6S_4Cl_2$	51.42 (51.50	2.41 2.31	4.56 4.00)
18	DDQ	$C_{16}H_8N_2O_4S_4Cl_2$	39.10 (39.42	1.64 1.71	5.70 5.86)[d]
18	TCNQ	$C_{20}H_{12}N_4O_2S_4$	51.51 (51.70	2.43 2.60	11.88 12.06)

[a] TCNQ and DDQ complexes of 15 and 16 did not give satisfactory analyses for 1:1 or 1:2 complexes. [b] Mp 175–177 °C. [c] Mp 137–139 °C. [d] Cl found, 14.68; calcd, 14.43.

The ir spectra of the DDQ complexes with **13, 14, 15, 16,** and **18** showed the expected low frequency $\nu_{C=O}$ at 1550–1560 cm^{-1} expected of the DDQ radical anion. This may be contrasted with $\nu_{C=O}$ 1680 cm^{-1} in DDQ itself, which was not present in the spectra of the complexes. Absorptions at 1480–1470 and 1350–1340 cm^{-1} also were found in each complex. Each of the TCNQ complexes (with **15, 16,** and **18**) contained nitrile stretching bands about 30–40 cm^{-1} lower than the 2310-cm^{-1} band of TCNQ itself. This implies that $TCNQ^-$ has been formed in the complexes. Ueno and Okawara[22] reported that several TTF derivatives reacted with DDQ in mole ratios which depended upon the partilar substituents present in TTF. The DDQ complexes of **13, 14,** and **18** and the TCNQ complex of **18** gave satisfactory analyses for 1:1 complexes, but the analyses for both DDQ and TCNQ complexes of **15** and **16** could not be fit to integral ratios. Phenolic compounds bring about nucleophilic displacement in both TCNQ and DDQ and if a small fraction of the complexes prepared here underwent this reaction, the analytical results would be explained.

Experimental Section

Melting points were uncorrected. Infrared spectra were obtained as potassium bromide disks with a Beckman IR-33. Nuclear magnetic resonance spectra were obtained using a Perkin-Elmer Hatachi Model R-20B spectrometer. *m*- and *p*-hydroxyphenacyl bromide were prepared according to the literature[23] with the single exception that a longer reflux time (3–4 h) was employed.

Methyl 1,3-Dithiole-2-thione-4-carboxylate (3). Esterification of 1,3-dithiole-2-thione-4-carboxylic acid (2) was carried out by Clinton's method.[13] A mixture of 1,3-dithiole-2-thione-4-carboxylic acid (**2,** 35.6 g, 0.2 mol), 20 ml of methanol, 4 ml of concentrated sulfuric acid, and 80 ml of ethylene dichloride was refluxed for 13 h and then chilled in an ice bath. The solid was collected and washed (with aqueous sodium bicarbonate and water, successively) to give 18.2 g of the ester **3.** The filtrate and the washings were combined, and the organic layer was further washed (with aqueous sodium bicarbonate and water). Concentration of the organic layer gave additional crystals of ester **3** (16.0 g) for a total of 34.2 g (89% yield). The aqueous layer was acidified with 3 N HCl to recover 2.8 g of the acid **2.** After recrystallization from carbon tetrachloride, **3** melted at 105–107 °C: ir (KBr) 3060, 3020, 2975, 1715, 1528, 1436, 1295, 1285, 1200, 1072, 1053 cm^{-1}; NMR ($CDCl_3$) δ 3.90 (s, 3 H), 7.96 (s, 1 H). Anal. Calcd for $C_5H_4O_2S_3$: C, 31.23; H, 2.10; S, 50.02. Found: C, 31.27; H, 2.07; S, 50.04.

4-(*p*-Nitrophenyl) 1,3-Dithiole-2-thione-4-carboxylate (4). To a solution of 3.56 g (0.02 mol) of **2** and 3.34 g (0.024 mol) of *p*-nitrophenol in 40 ml of THF was added 4.94 g (0.024 mol) of dicyclohexylcarbodiimide at 0–5 °C under stirring. The reaction mixture was kept at room temperature for 2 h and then filtered. The precipitate was washed with acetone. The filtrate and the washings were combined, and volatiles were removed to give 5.40 g (90%) of the ester **4,** which was purified by recrystallization from toluene: mp 156–157 °C; ir (KBr) 3070, 1715, 1610, 1585, 1505, 1485, 1348, 1263, 1200, 1160, 1075, 1000 cm^{-1}. Anal. Calcd for $C_{10}H_5NO_4S_3$: C, 40.12; H, 1.68; N, 4.68. Found: C, 40.34; H, 1.80; N, 4.51.

Trifluoroacetic Anhydride 5. Tetrahydrofuran (THF, 50 ml) was stirred while 5.34 g (0.03 mol) of **2** and 3.04 g (0.03 mol) of triethylamine were dissolved while stirring. The solution was cooled to 0–5 °C and a solution of 8.4 g (0.04 mol) of trifluoroacetic anhydride in 10 ml of THF was added dropwise at 5–10 °C. The cooling bath was removed and the stirring was continued for 3 h. Volatiles were removed under reduced pressure. The residue was stirred with a little water and filtered to give 5.83 g (71%) of the yellow-brown crystals. Recrystallization from toluene gave crystals which melted at 130–132 °C: ir (KBr) 3095, 3070, 1770, 1705, 1520, 1280, 1225, 1190, 1140, 1060, 990 cm^{-1}. Anal. Calcd for $C_6HF_3O_3S_3$: C, 26.38; H, 0.37; F, 20.78; S, 35.07. Found: C, 26.13; H, 0.56; F, 19.92; S, 36.01. After a second recrystallization from cyclohexane, the mp was 132.5–133 °C. Analysis gave F, 20.42; S, 35.73.

2,6(7)-Bis(carbomethoxy)tetrathiafulvalene (6). A mixture of 21.1 g (0.11 mol) of the ester **3,** 36.4 g (0.22 mol) of triethyl phosphite, and 100 ml of benzene was refluxed for 35 h. A red precipitate was formed which was filtered, while the solution was hot, and washed with benzene to give 3.5 g of TTF **6,** mp 242–244 °C. Recrystallization from glyme gave material which melted at 244–246 °C (lit.[12] 244–245 °C). The filtrate and the washings were combined and concentrated under vacuum. To the residue was added 300 ml of methanol to precipitate orange crystals of **6** (3.2 g).[24]

2,3,6,7-Tetrakis(carbomethoxy)tetrathiafulvalene (7). A mixture of 10.0 g (0.04 mol) of dimethyl 1,3-dithiole-2-thione-4,5-dicarboxylate, 10.0 g (0.06 mol) of triethyl phosphite, and 80 ml of benzene was refluxed for 10 h. After cooling to room temperature, benzene was removed under vacuum. To the residue was added 50 ml of ethanol to precipitate the tetraester **7.** The yield was 4.4 g (52%), mp 167–169 °C. Recrystallization from methanol gave red-purple crystals (3.9 g), mp 169–170 °C (lit.[7] 169–170 °C). A mixture of 2.5 g (0.01 mol) of diester **1,** 3.9 g (0.015 mol) of triphenylphosphine, and 20 ml of benzene was refluxed for 24 h. The mixture was developed by dry column chromatography (silica gel) with benzene eluent to separate 2.45 g of triphenylphosphine, 1.73 g (69%) of diester **1,** and 0.48 g (22%) of tetraester **7.**

2,6(7)-Bis(*p*-nitrophenyloxycarbonyl)tetrathiafulvalene (8). A mixture of 5.98 g (0.02 mol) of ester **4,** 6.67 g (0.04 mol) of triethyl phosphite, and 100 ml of benzene was refluxed for 60 h. Precipitates were filtered to give 0.50 g (9%) of crude product, which was twice recrystallized from toluene: mp 280 °C dec; ir (KBr) 1720, 1610, 1590, 1540, 1518, 1485, 1344 cm^{-1}. Anal. Calcd for $C_{20}H_{10}N_2O_8S_4$: C, 44.94; H, 1.89; N, 5.24; S, 23.99. Found: C, 45.36; H, 2.08; N, 5.31; S, 24.42.

Reaction of 1,3-Dithiole-2-thione-4-carboxylic Acid (2) with Triethyl Phosphite. A mixture of 1.78 g (0.01 mol) of **2,** 1.67 g (0.01 mol) of triethyl phosphite, and 20 ml of benzene was refluxed for 30 h. Volatiles were removed in vacuo. The residue was dissolved in chloroform, and developed on dry column (silica gel) with chloroform elution to separate 0.78 g (36%) of ethyl 1,3-dithiole-2-thione-4-carboxylate (**10**). Recrystallization from cyclohexane gave material which melted at 39–41 °C: ir (KBr) 1710, 1540, 1300, 1225, 1090, 1075 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (t, 3 H), 4.35 (q, 2 H), 7.92 (s, 1 H). Anal. Calcd for $C_6H_6O_2S_3$: C, 34.93; H, 2.93; S, 46.62. Found: C, 34.90; H, 2.96; S, 46.58.

***m*-Hydroxyphenacylpiperidinocarbodithioate.** To a solution of piperidine (0.6 mol) in 300 ml of ethanol was added a solution of CS_2 (30 ml) in ethanol (200 ml) under rapid stirring at 5 °C. Crystals of the salt precipitated but the salt was not isolated. A mixture of *m*-hydroxyphenacyl bromide[23] (65 g, 0.30 mol), 75 g (0.30 mol) of piperidinium piperidinocarbodithioate, and 500 ml of ethanol was refluxed for 2 h. After cooling, ethanol was removed in vacuo. Addition of water to the residue resulted in the precipitation of a crystalline material (75.5 g, 85%). Recrystallization from ethanol gave *m*-hydroxyphenacylpiperidinocarbodithioate which melted at 175–176 °C: ir (KBr) 3280, 2940, 1660, 1600, 1575, 1479, 1442, 1423, 1345, 1313, 1272, 1234, 1216, 1160, 1127, 1102, 1028, 1012, 990 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_2S_2$: C, 56.94: H, 5.80; N, 4.74. Found: C, 57.56; H, 5.82; N, 4.73. *p*-Hydroxyphenacylpiperidinocarbodithioate was prepared in an identical fashion and gave satisfactory analyses and spectra.

4-(*p*- and *m*-Hydroxyphenyl)-1,3-dithiole-2-ylidenepiperidinium Fluoroborates. A mixture of either *p*- or *m*-hydroxyphenacylpiperidinocarbodithioates (29.5 g, 0.10 mol), 20 ml of hydrofluoroboric acid (42%), 13.0 g of P_4S_{10}, and 300 ml of glacial acetic acid was refluxed for 20 h. Treatment of the solution with charcoal, followed by evaporation of solvent and addition of ethanol to the residue, gave pink crystals. Recrystallization from ethanol gave the pure salt.

4-(*p*-Hydroxyphenyl)-1,3-dithiole-2-ylidenepiperidinium fluoroborate: yield 32.2 g (88%); mp 172–174 °C; ir (KBr) 3400, 1605, 1573, 1532, 1510, 1445, 1372, 1280, 1255, 1228, 1210, 1078, 1110–1020 cm^{-1}. Anal. Calcd for $C_{14}H_{16}NOS_2BF_4$: C, 46.04; H, 4.42; N, 3.84. Found: C, 46.16; H, 4.23; N, 3.93.

4-(*m*-Hydroxyphenyl)-1,3-dithiole-2-ylidenepiperidinium fluoroborate: yield 31.4 g (86%); mp 185–186 °C; ir (KBr) 3420, 3080, 2940, 1603, 1567, 1532, 1490, 1478, 1464, 1446, 1320, 1280, 1180, 1110–1030, 852, 796, 775 cm^{-1}. Anal. Calcd for $C_{14}H_{16}NOS_2BF_4$: C, 46.04; H, 4.42; N, 3.84. Found: C, 46.24; H, 4.41; N, 3.95.

4-(*p*- and *m*-Acetoxyphenyl)-1,3-dithiole-2-ylidenepiperidinium Fluoroborates. A mixture of 18.3 g (0.05 mol) of the 4-(*p*- or *m*-hydroxyphenyl)-1,3-dithiole-2-ylidenepiperidinium fluoroborate, 30 ml of acetic anhydride, and 300 ml of acetonitrile was refluxed for 20 h. Volatiles were removed in vacuo. To the residue was added ethanol to give pink crystals. Recrystallization from ethanol gave the pure material.

4-(*p*-Acetoxyphenyl)-1,3-dithiole-2-ylidenepiperidinium fluoroborate: yield 18.2 g (94%); mp 161–163 °C (methanol); ir (KBr) 3020, 2950, 2840, 1755, 1567, 1526, 1496, 1437, 1372, 1210, 1167, 1120–1030, 914, 857, 786 cm^{-1}. Anal. Calcd for $C_{16}H_{18}NO_2S_2BF_4$: C, 47.19; H, 4.45; N, 3.44. Found: C, 46.74; H, 4.35; N, 3.48.

4-(*m*-Acetoxyphenyl)-1,3-dithiole-2-ylidenepiperidinium fluo-

roborate: yield 18.7 g (92%); mp 159–160 °C (ethanol); ir (KBr) 2980, 2950, 1760, 1565, 1525, 1472, 1437, 1372, 1210, 1160, 1120, 1030, 923, 904 cm^{-1}. Anal. Calcd for $C_{16}H_{18}NO_2S_2BF_4$: C, 47.19; H, 4.45; N, 3.44. Found: C, 46.65; H, 4.35; N, 3.86.

4-(*p*-Acetoxyphenyl)-2-piperidino-1,3-dithiole. To a suspension of 8.2 g (0.02 mol) of 4-(*p*-acetoxyphenyl)-1,3-dithiole-2-ylidenepiperidinium fluoroborate in 200 ml of ethanol, 3.0 g of sodium borohydride was added in small portions. The reaction mixture was stirred for 30 min at 0 °C. Addition of water precipitated 5.3 g (82%) of yellow solid. Recrystallization from ethanol–water gave yellow crystals (4.8 g) which melted at 77–79 °C: ir (KBr) 2940, 2850, 2805, 1765, 1748, 1541, 1503, 1438, 1370, 1308, 1215, 1195, 1167, 1095, 990 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_2S_2$: C, 60.04; H, 5.88; N, 4.49. Found: C, 59.78; H, 5.96; N, 4.36. 4-(*m*-Acetoxyphenyl)-1,3-dithiole-2-ylidenepiperidinium fluoroborate was prepared in a similar manner. After the addition of water (500 ml in a 20-mmol scale preparation), the product was extracted with ether and dried (Na_2SO_4), and the ether was removed in vacuo. The residue was dissolved in 80 ml of ethanol and this was used directly, without further purification, to produce dithiolium salts **11** or **12** described below.

2,6(7)-Bis(*p*- and *m*-acetoxyphenyl)tetrathiafulvalenes (13 and 14). To a suspension of 1.61 g (0.5 mmol) of 4-(*p*-acetoxyphenyl)-2-piperidino-1,3-dithiole in 20 ml of ethanol, 3 ml of perchloric acid (60%) was added dropwise with stirring at 0–5 °C to form yellow crystals. Filtration and washing with ether gave 1.1 g (65%) of the 4-(*p*-acetoxyphenyl)-1,3-dithiolium perchlorate salt, **11**. 4-(*m*-Acetoxyphenyl)-1,3-dithiolium perchlorate (**12**) was obtained from 4-(*m*-acetoxyphenyl)-2-piperidino-1,3-dithiole by the same procedure with an overall yield from 4-(*m*-acetoxyphenyl)-1,3-dithiole-2-ylidenepiperidinium fluoroborate of 87%. Salts **11** and **12** had ir absorption bands at 3020, 1755, 1370, 1215, 1205, 1142, 1115, 1090 cm^{-1}. *Caution!* the reaction scale should be kept to about 0.5 mmol (1.61 g) of 4-(*p*- or *m*-acetoxyphenyl)-2-piperidino-1,3-dithiole, and salts **11** and **12** should be precipitated in a few minutes, where filtered. They should be washed thoroughly with ether. In our hands, 1-g lots of **11** and **12** could be stored safely, but caution should be always exercised and several small lots should not be combined.[25] Perchlorate salts **11** and **12** are stable in solution, and larger scale preparations of **13** and **14** than those described below can be conducted. For example, reactions on a 5-g (of **11** or **12**) scale were conducted.

Perchlorate salt **11** (1 g) was dissolved in 40 ml of acetonitrile. The solution was magnetically stirred at 0 °C and 2 g triethylamine in 10 ml of acetonitrile was added. After stirring for 1 h, water was added, precipitating crystals (0.64 g, 91%) identified as diacetate **13**. Diacetate **14** was obtained in 93% yield by the same method.

2,6(7)-Bis(*p*-acetoxyphenyl)tetrathiafulvalene (**13**): orange crystals, mp 228–230 °C (benzene); ir (KBr) 1738, 1550, 1505, 1375, 1220–1195, 1167, 1017, 911, 843, 780, 762 cm^{-1}. Anal. Calcd for $C_{22}H_{16}O_4S_4$: C, 55.91; H, 3.41. Found: C, 55.42; H, 3.52.

2,6(7)-Bis(*m*-acetoxyphenyl)tetrathiafulvalene (**14**): orange crystals, mp 185–186 °C (ethanol); ir (KBr) 1760, 1603, 1370, 1205, 1147, 1016, 918, 760 cm^{-1}. Anal. Calcd for $C_{22}H_{16}O_4S_4$: C, 55.91; H, 3.41. Found: C, 55.99; H, 3.35.

2,6(7)-Bis(*p*- and *m*-hydroxyphenyl)tetrathiafulvalenes (15 and 16). To a suspension of 0.47 g (1.0 mmol) of **13** in 20 ml of methanol, 3 ml of hydrazine hydrate was added. The reaction mixture was stirred at room temperature. Methanol was removed in vacuo. The residue was cooled to ~5 °C and filtered, and the filtrate was washed with small amounts of methanol and acetonitrile to give orange crystals of **15** in quantitative yield. Similarly, **16** was obtained quantitatively.

2,6(7)-Bis(*p*-hydroxyphenyl)tetrathiafulvalene (**15**): mp 207–208 °C (methanol); ir (KBr) 1600, 1548, 1502, 1455, 1382, 1248, 1172, 919, 825, 760 cm^{-1}. Anal. Calcd for $C_{18}H_{12}S_4O_2$: C, 55.64; H, 3.11. Found: C, 55.43; H, 3.25.

2,6(7)-Bis(*m*-hydroxyphenyl)tetrathiafulvalene (**16**): mp 224–225 °C (methanol); ir (KBr) 1595, 1548, 1445, 1268, 1226, 1169, 990, 842 cm^{-1}. Anal. Calcd for $C_{18}H_{12}S_4O_2$: C, 55.64; H, 3.11. Found: C, 56.03; H, 3.37.

Hydrolysis of Esters 6 and 7. Hydrolysis of diester **6** was conducted as reported previously[12] giving **9** quantitatively. The dark purple solid was recrystallized from pyridine to give yellow-orange crystals, which became dark purple upon drying at 70–80 °C under vacuum, mp >350 °C (lit.[12] >350 °C). Anal. Calcd for $C_8H_4O_4S_4$: C, 32.87; H, 1.38. Found: C, 32.74; H, 1.32. TTF ester **7** was hydrolyzed under similar conditions, yield 90%. Recrystallization from water gave purple, crystalline material, which did not melt below 300 °C: ir (KBr) 1650, 1570, 1360, 1095, 755 cm^{-1}. Anal. Calcd for $C_{10}H_4O_8S_4$: C, 31.58, H, 1.06; S, 33.71. Found: C, 31.82; H, 1.21; S, 33.19.

2,6(7)-Bis(hydroxymethyl)tetrathiafulvalene (18). Diacid **9** (5.84 g, 0.02 mol) was cautiously added to sodium borohydride (2.76 g, 70 ml of 1.0 M solution in diglyme) after a thorough nitrogen purge. A 200-ml three-necked flask equipped with a pressure-equalized dropping funnel, magnetic stirrer, nitrogen inlet, and an outlet for hydrogen and excess diborane was used for this reaction. The diborane outlet capillary was connected to a mercury-immersed capillary safety release valve. Boron trifluoride etherate (5.7 g, 0.04 mol) in 30 ml of diglyme was added to the solution over a period of 1 h through the separatory funnel. After an additional 3 h at room temperature, the reaction mixture was poured onto crushed ice and kept in a refrigerator overnight. This caused the precipitation of a solid which was collected on a filter, washed with ice–water, and dried. The yield of the crude product was 0.67 g (13%), mp 172–176 °C dec. Recrystallization from ethanol gave yellow-brown crystalline material, which melted at 178–180 °C dec: ir (KBr) 3350, 3260, 3070, 3030, 2960, 2930, 1580, 1460, 1372, 1232, 1090, 1013 cm^{-1}; NMR (Me_2SO-d_6) δ 4.24 (d, 2, OCH_2), 5.49 (t, 1, CH), 6.53 (s, 1, OH). Anal. Calcd for $C_8H_8O_2S_4$: C, 36.34; H, 3.05; S, 48.50. Found: C, 35.87; H, 3.15; S, 48.10.

Bis Acetic Anhydride of Tetrathiafulvalene-2,6(7)-dicarboxylic Acid (19). In a mixture of 20 ml of acetic anhydride and 30 ml of THF, 1.18 g (4 mmol) of diacid **9** was suspended. This suspension was refluxed for 24 h and then the remaining diacid was filtered (0.41 g of diacid **9**). The filtrate was evaporated in vacuo to give a residue which was recrystallized from acetonitrile to give 0.46 g of **19**, mp ~350 °C (gradually dec). The yield was 47% based on diacid **9** originally charged to the reactor: ir (KBr) 3060, 3030, 1803, 1705, 1545, 1380, 1275, 1150, 1015, 990 cm^{-1}. Anal. Calcd for $C_{12}H_8O_6S_4$: C, 38.29; H, 2.14. Found: C, 37.64; H, 2.18.

Reaction of Bis Acetic Anhydride 19 with Ethylene Glycol. To 20 ml of THF was added 0.02 g of **19** and 2 ml of ethylene glycol. This solution was refluxed for 3 h; THF was removed, and to the residue was added a small amount of methanol. A solid was collected on a filter and identified[12] as diacid **9**, 0.14 g (90%).

Bisanilide 20 of Tetrathiafulvalene-2,6(7)-dicarboxylic Acid (9). To 0.59 g (2 mmol) of diacid **9** and 0.38 g (4 mmol) of aniline in 20 ml of *N,N*-dimethylformamide (DMF) was added 5 ml of pyridine and 1.40 g (6 mmol) of diphenyl hydrogen phosphonate. The reaction mixture was stirred at 70 °C for 10 h. The mixture was poured into water and a precipitate was collected by filtration and washed with acetone. After drying, the yield of **9** was 0.64 g (72%), mp 224 °C dec. Recrystallization from acetonitrile gave diacid **9**: mp 224–226 °C dec; ir (KBr) 3330, 3060, 3020, 1630, 1595, 1540, 1495, 1440, 1320, 1260 cm^{-1}. Anal. Calcd for $C_{20}H_{14}N_2O_2S_4$: C, 54.28; H, 3.19; N, 6.33. Found: C, 54.24; H, 3.48; N, 6.24.

Charge Transfer Complexes of TTF Derivatives with TCNQ and DDQ. To a hot solution of the TTF derivative (0.2 mmol) in 30 ml of acetonitrile was added a hot solution of TCNQ (0.4 mmol) or DDQ (0.4 mmol) in acetonitrile. The mixture slowly cooled to room temperature, was filtered, washed with acetonitrile, and vacuum dried. The results are summarized in Table II.

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Registry No.—**1**, 7396-41-0; **2**, 1004-08-6; **3**, 55526-01-7; **4**, 59269-67-9; **5**, 59269-68-0; **6**, 51751-18-9; **7**, 26314-39-6; **8**, 59269-69-1; **9**, 51751-19-0; **10**, 59269-70-4; **11**, 59269-72-6; **12**, 59269-74-8; **13**, 59269-75-9; **14**, 59269-76-0; **15**, 59269-77-1; **16**, 59269-78-2; **17**, 59269-79-3; **18**, 58268-45-4; **19**, 59269-80-6; **20**, 59269-81-7; *p*-nitrophenol, 100-02-7; trifluoroacetic anhydride, 407-25-0; triethyl phosphite, 122-52-1; *m*-hydroxyphenacyl bromide, 2491-38-5; piperidinium piperidinocarbodithioate, 98-77-1; *m*-hydroxyphenacylpiperidinocarbodithioate, 59269-82-8; *p*-hydroxyphenacylpiperidinocarbodithioate, 24372-67-6; 4-(*p*-hydroxyphenyl)-1,3-dithiole-2-ylidenepiperidinium fluoroborate, 59269-83-9; 4-(*m*-hydroxyphenyl)-1,3-dithiole-2-ylidenepiperidinium fluoroborate, 59269-85-1; 4-(*p*-acetoxyphenyl)-1,3-dithiole-2-ylidenepiperidinium fluoroborate, 59269-87-3; 4-(*m*-acetoxyphenyl)-1,3-dithiole-2-ylidenepiperidinium fluoroborate, 59269-89-5; 4-(*p*-acetoxyphenyl)-2-piperidino-1,3-dithiole, 59269-90-8; perchloric acid, 7601-90-3; acetic anhydride, 108-24-7; aniline, 62-53-3; 4-(*m*-acetoxyphenyl)-2-piperidino-1,3-dithiole, 59269-91-9.

References and Notes

(1) A. F. Garito and A. J. Heeger, *Acc. Chem. Res.*, **7**, 232 (1974); D. B. Tanner, C. S. Jacobson, A. F. Garito, and A. J. Heeger, *Phys. Rev. Lett.*, **32**, 1301

(1974), and references cited therein.
(2) E. M. Engler and V. V. Patel, *J. Am. Chem. Soc.*, **96**, 7376 (1974).
(3) K. Bechgaard, D. O. Cowan, and A. M. Bloch, *J. Chem. Soc., Chem. Commun.*, 937 (1974).
(4) M. Narita and C. U. Pittman, Jr., *Synthesis*, in press.
(5) C. U. Pittman, Jr., M. Narita, and Y. F. Liang, *Macromolecules*, **9**, 360 (1976).
(6) Y. Ueno, Y. Masuyama, and M. Okawara, *Chem. Lett.*, 603 (1975).
(7) H. D. Hartzler, *J. Am. Chem. Soc.*, **95**, 4379 (1973).
(8) M. G. Miles, J. D. Wilson, D. J. Dahm, and J. H. Wagenkneckt, *J. Chem. Soc., Chem. Commun.*, 751 (1974); Z. Yoshida, T. Kawase, and S. Yoneda, *Tetrahedron Lett.*, 331 (1975).
(9) G. Scherowsky and J. Weiland, *Chem. Ber.*, **107**, 3155 (1974); S. Hunig, G. Kieplich, H. Quast, and D. Scheutzow, *Justus Liebigs Ann. Chem.*, 310 (1973).
(10) The gas-phase ionization potential of dibenzo-TTF was reported to be 6.81 eV which is the same as that of TTF (see J. Spanget-Larsen, *Chem. Phys. Lett.*, **37**, 29 (1976). Thus, the dibenzo derivative should not be classified with the others as an electron-deficient example.
(11) E. Klingsberg, *J. Am. Chem. Soc.*, **86**, 5290 (1964).
(12) L. R. Melby, H. D. Hartzler, and W. A. Sheppard, *J. Org. Chem.*, **39**, 2456 (1974).
(13) R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).
(14) A superior single step preparation of **6** in 21% yield was reported in ref 7.
(15) J. I. G. Cadogan, *Q. Rev., Chem. Soc.*, **22**, 222 (1968).
(16) F. Wudl, M. L. Kaplan, E. J. Hufnagel, and E. W. Southwick, Jr., *J. Org. Chem.*, **39**, 3608 (1974); J. P. Ferraris, T. O. Poehler, A. N. Bloch, and D. O. Cowan, *Tetrahedron Lett.*, 2553 (1973).
(17) J. Nakayama, *Synthesis*, 168 (1975).
(18) A. Takamizawa and K. Harai, *Chem. Pharm. Bull.*, **17**, 1924 (1969).
(19) C. U. Pittman, Jr., and M. Narita, *J. Chem. Soc., Chem. Commun.*, 960 (1975).
(20) A reviewer has indicated that diester **6** may be cleanly reduced by an excess of $LiAlH_4$ or $NaAlH_2(OCH_2CH_2OCH_3)_2$ in refluxing glyme. This would then be the method of choice to prepare diol **18.**
(21) N. Yamazaki and F. Higashi, *Polym. Lett.*, **12**, 185 (1974).
(22) Y. Ueno and M. Okawara, *Chem. Lett.*, 1135 (1974).
(23) L. C. Knig and G. K. Ostrum, *J. Org. Chem.*, **29**, 3459 (1964).
(24) Recrystallization of the orange solid from benzene gave material which melted at 198–200 °C. The difference in ir spectra between this solid and **6** forms is that **6** has a band at 910 cm^{-1}. Hydrolysis of both materials gave the diacid **9.**
(25) The formation of hexafluorophosphate salts would probably be a preferable route, but it was not done in this study.

Tetrazolo[1,5-*b*]-1,2,4-triazines. Syntheses and Structure Determination

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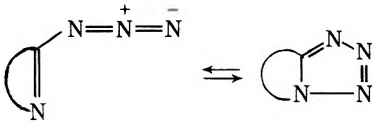
Several 3-azido-1,2,4-triazines were prepared by treating the corresponding 3-hydrazino derivatives with nitrous acid. The azidotriazines spontaneously cyclized into a tetrazolo isomer. These transformations were studied using nuclear magnetic resonance and infrared spectroscopic methods. The tetrazolo isomers were proven to be tetrazolo[1,5-*b*]-1,2,4-triazines by an x-ray crystallographic study on the 5-*p*-chlorophenyl derivative.

Azido-substituted π-deficient nitrogen heterocyclic systems have been extensively investigated.[1] These studies have established that the equilibrium

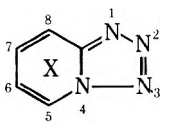


1 2

is strongly controlled by (a) the π deficiency of the nitrogen heterocycle; (b) the polarity of the solvents; and (c) to some extent, temperature. The following interpretive statement has been made:[1]

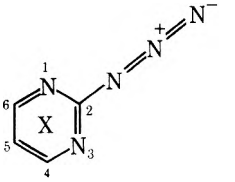
"In azolazines, the azine part of the molecule is responsible for the magnitude of the charge on the N-atom common to both rings. If the negative charge can be further delocalized on other N-atoms in the *m*-position of the azine ring, this enhances the stability of the azido form."

By way of recapitulating the data, the following compounds exist, in dimethyl sulfoxide, as the tetrazolo derivatives:[2-6]



3, X = nil
4, X = N, at position 5
5, X = N, at position 6
6, X = N, at position 7

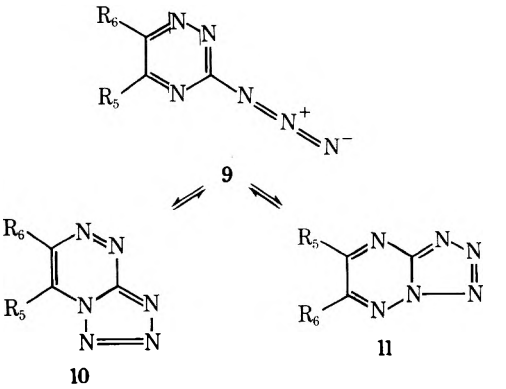
When a nitrogen is substituted at position 8 in the above structure, the azido heterocycles are formed in dimethyl sulfoxide.[7] For example:



7, X = nil (10% in this form)
8, X = N, at position 5 (100% in this form)

The formation of these azido compounds is greatly enhanced by nonpolar solvents (compound **7** in chloroform solution is reported to exist totally in the azido form).[8]

In view of our extensive interest in 1,2,4-triazines and the potential dual possibility of cyclization (**10, 11**), we decided to study the behavior of some 3-azido-1,2,4-triazines (**9**).



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10 11

Table I. Infrared Absorption Spectra (cm^{-1})

Registry no.	Compd	Phase	Azido bands	Tetrazolo bands
32484-95-0	**11a**	CH_2Cl_2	2150 (s)	
		Nujol		1285 (m), 1085 (m), 980 (m)
59318-29-5	**11b**	CH_2Cl_2	2140 (s)	
		Nujol		1275 (m), 1070 (s), 980 (m)
59318-30-8	**11c**	$CHCl_3$	2120 (s), 2140 (s)	
		Nujol		1285 (s), 1090 (s), 980 (m)
59318-31-9	**11d**	$CHCl_3$	2120 (s)	
		KBr		1295 (s), 1100 (s), 995 (m)
59318-32-0	**11e**	Nujol		1285 (2), 1085 (m), 980 (m)
59318-33-1	**11f**	Nujol		1290 (s), 1090 (s), 985 (m)
59318-34-2	**11g**	Nujol		1300 (s), 1080 (m), 975 (m)
59318-35-3	**11h**	Nujol		1285 (m), 1080 (m), 985 (m)

Table II. Least-Squares Plane Calculations for 5-*p*-Chlorophenyltetrazolo[1,5-*b*]-1,2,4-triazine[a]

Plane	Equation of Plane
A	$0.2881X - 0.8435Y - 0.4533Z + 5.9192 = 0$
B	$0.3081X - 0.8237Y - 0.4760Z + 6.2565 = 0$
C	$0.2911X - 0.8793Y - 0.3770Z + 5.1171 = 0$
D	$0.2949X - 0.8636Y - 0.4089Z + 5.3641 = 0$

Deviation of Atoms from Planes (Å)

Atom	Plane A	Atom	Plane B	Atom	Plane C	Atom	Plane D
C1	−0.004	C1	0.003	C4	−0.005	Cl	0.075
C2	−0.009	N1	−0.004	C5	0.003	C1	−0.057
C3	0.015	N2	0.003	C6	0.003	C2	−0.035
N4	0.011	N3	−0.000	C7	−0.007	C3	−0.079
N5	−0.004	N4	−0.002	C8	0.005	C4	−0.052
N6	−0.009			C9	0.001	C5	−0.002
						C6	0.043
						C7	0.036
						C8	0.009
						C9	−0.040
						N1	−0.024
						N2	0.089
						N3	0.113
						N4	0.019
						N5	0.021
						N6	−0.116

[a] The maximum deviation of any atom from the least-squares plane of the entire molecule was 0.12 Å.

Table III. Bond Angles (deg) for Compound 11f

C1–N1–N2	105.6 (2)	N1–N2–N3	112.3 (2)
N2–N3–N4	104.6 (2)	N3–N4–C1	109.7 (2)
N4–C1–N1	107.8 (2)	N1–C1–N6	130.4 (2)
N3–N4–N5	124.1 (2)	C1–N4–N5	126.2 (2)
N4–N4–C2	111.9 (2)	N5–C2–C3	124.2 (2)
C2–C3–N6	120.9 (2)	C3–N6–C1	115.0 (2)
N4–C1–N6	121.8 (2)	C4–C3–N6	118.4 (2)
C2–C3–C4	120.7 (2)	C3–C4–C9	121.5 (2)
C3–C4–C5	119.6 (2)	C4–C5–C6	120.7 (2)
C5–C4–C9	118.8 (2)	C6–C7–C8	121.8 (2)
C5–C6–C7	119.1 (2)	C8–C9–C4	120.7 (2)
C7–C8–C9	118.9 (2)	C1–C7–C8	118.8 (1)
Cl–C7–C6	119.6 (1)		

The desired compounds (cf. Scheme I) were prepared by treatment of the appropriate 3-hydrazino-1,2,4-triazines with nitrous acid. The Nujol infrared spectra of all of the compounds were devoid of any azido peaks. Consequently, in the solid state at least, we are dealing with the tetrazolo form **10**

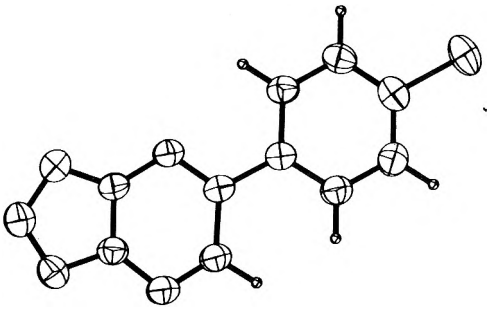
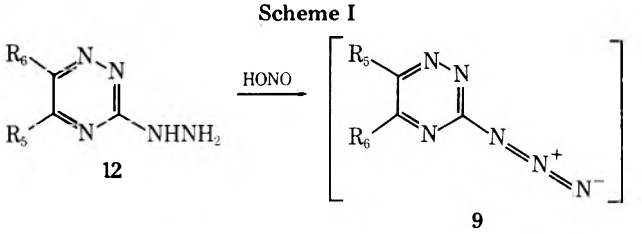


Figure 1. Molecular structure of compound **11f** with the atoms displayed as 40% probability ellipsoids for thermal motion. The standard deviations in the bond lengths are less than 0.003 Å.

or **11**. Since all of the compounds show the same tetrazolo frequencies (see Table I) we conclude that they all have cyclized in identical fashion. In order to ascertain whether we are dealing with the tetrazolo[1,5-*b*]-1,2,4-triazines (**11**) or their isomers **10** it became necessary to establish the structure by x-ray crystallography. The most appropriate derivative for this study was the *p*-chlorophenyl derivative **12f**.

Scheme I



12 **9**

	R_5	R_6		R_5	R_6
a	H	H	**e**	C_6H_5	H
b	H	CH_3	**f**	*p*-ClC_6H_4	H
c	CH_3	H	**g**	*p*-$CH_3OC_6H_4$	H
d	CH_3	CH_3	**h**	*p*-$NO_2C_6H_4$	H

Structure of the Tetrazolo Derivative of 3-Azido-5-*p*-chlorophenyl-1,2,4-triazine. The crystal data, final fractional coordinates, and anisotropic thermal parameters of the compound are available as microfilm supplement. The bond angles are listed in Table III, while the bond distances are shown in Figure 1. These data clearly prove that we are dealing with the tetrazolo[1,5-*b*]-1,2,4-triazine (**11**), rather than the N-4 cyclized isomer **10**. The cyclization into N-2 is not unexpected in view of the fact that, as we have previously shown,[9] given a choice, the 1,2,4-triazines will form structures which do not have a formal N=N. However, it is somewhat surprising that the five-nitrogen chain (structure **11**) is more stable, in this instance, than a four-nitrogen one (structure **10**).

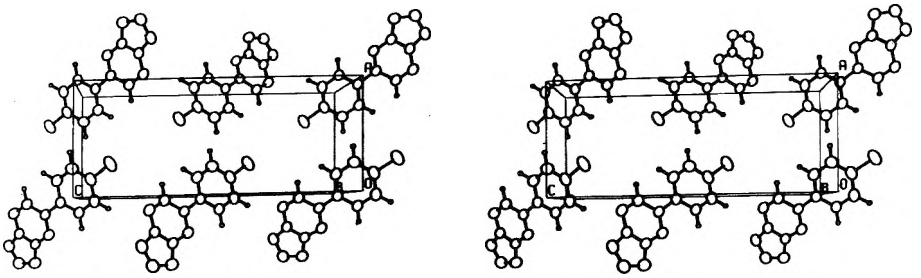


Figure 2. Stereoscopic view of the unit cell packing in **11f**.

Table IV. ^{1}H NMR Spectra of Some Tetrazolo[1,5-*b*]-1,2,4-triazines (Chemical Shifts in τ)

Compd	Solvent[a]	R_6	R_5	J_{AB}, Hz
11a	Me_2SO-d_6	0.96	0.88	1.0
11b	Me_2SO-d_6	7.20	0.83	
	$CDCl_3$	7.12	1.13	
11c	Me_2SO-d_6	0.95	7.18	
	$CDCl_3$	1.31	7.06	
11d	Me_2SO-d_6	7.26	7.23	
	$CDCl_3$	7.22	7.19	
11e	Me_2SO-d_6	0.20	1.52–1.62 (m), 2.27–2.35 (m)	
11f	Me_2SO-d_6	0.24	2.22 (d), 1.52 (d)	
11g	Me_2SO-d_6	0.21	1.52 (d), 2.75 (d), 6.02 (s)	5.5
11h	Me_2SO-d_6	0.10	1.34 (d), 1.54 (d)	4.5

[a] Dilute solutions in indicated solvents; see Scheme I for structure identifications. A Varian HA-100 spectrometer was used to obtain these spectra.

Some other points of interest are (1) the great similarity of all of the nitrogen to nitrogen bond lengths (1.304–1.352 Å); (2) the considerable bond delocalizations in the molecule; (3) the essentially total planarity of the ring system (see Table II).

Thus, by all "classical" definitions, the compound is aromatic.

Infrared Spectral Data. The infrared spectrum of the chloroform extract of the oxidation product of 3-hydrazino-5,6-dimethyl-1,2,4-triazine, taken immediately after completion of the oxidation reaction, shows the presence of an azido group (2120 cm^{-1}). This peak disappears within 50 min and is replaced by the typical tetrazolo peaks (see Table I). Thus, in this compound at least, the tetrazolo structure is the preferred one in chloroform. Chloroform solutions of the oxidation products of the 3-hydrazino-1,2,4-triazine, the 5-methyl and 6-methyl derivatives, again show the presence of an azido group in the infrared spectrum. However, within a very short time, the solution becomes turbid and ultimately no material remains in solution. The precipitated compound in each case is the tetrazolo derivative as established by an examination of the Nujol infrared spectrum. As a result of the insolubility of the tetrazole in chloroform we cannot establish whether there exists an equilibrium between the azido form and the tetrazolo structure of these compounds.

Nevertheless, in view of the behavior of the dimethyl derivative, it seems reasonable to state that, in chloroform at least, the azido structures are unstable and are converted to the tetrazolo forms exclusively.

It is impossible to "trap" the azido forms by evaporation of the freshly prepared chloroform extracts of the oxidation reactions, since the Nujol mull infrared spectra of the solid residues are devoid of azido absorption bands. In fact, the Nujol mull spectra of all of the compounds examined (see Table I) show only typical tetrazolo absorptions.

Table V. ^{1}H NMR Spectra of Some 3-Azido-1,2,4-triazines

Registry no.	Compd[a]	R_5	R_6
59318-36-4	**9b**	7.29	1.61
59318-37-5	**9c**	1.06	7.42
59318-38-6	**9d**	7.36	7.46

[a] Dilute solution in deuteriochloroform. As mentioned in the text, these compounds rapidly cyclize to the tetrazolo structures.

^{1}H NMR Spectral Data. The ^{1}H NMR spectrum of the deuteriochloroform extract of the oxidation product of 3-hydrazino-5,6-dimethyl-1,2,4-triazine taken immediately after oxidation is completed shows four methyl peaks. The intensities of the major two peaks (τ 7.36, 7.46) decrease rapidly and those of the minor 2 peaks (τ 7.19, 7.22) increase correspondingly. Thus, based upon the infrared data, the former peaks belong to the azido form, and the latter to the tetrazolo structure. Again, the methyl peaks due to the azido form disappear totally within 50 min. Since it takes some time to adjust the NMR instrument, the first ^{1}H NMR spectrum cannot be obtained as rapidly as is the case for the infrared spectra. Consequently, the first spectrum (obtained 10 min after completion of the oxidation reaction) shows the azido compound to be present at 35% vs. 65% for the tetrazolo derivative. After 50 min, no azido compound is left. Even though the tetrazolo derivatives of the 5-methyl- and 6-methyl-1,2,4-triazines are rather insoluble in deuteriochloroform, one can nevertheless obtain the ^{1}H NMR spectral data for the azido as well as tetrazole compounds prior to their precipitation from solution. These data are given in Tables IV and V.

The ^{1}H NMR spectra in perdeuteriodimethyl sulfoxide of all of the compounds examined show the presence of only *one* "isomer". Fortunately, the methyl group absorptions in $CDCl_3$ and in Me_2SO-d_6 are nearly the same. Thus, it is clear that in the latter solvent, we are dealing with the tetrazolo compound exclusively (τ 7.23, 7.26). Given this information, we can now compare the chemical shifts of the monomethyl derivatives with those of the dimethyl tetrazolo derivative. The methyl group of the 5-methyl derivative absorbs at τ 7.18 and that of the 6-methyl derivative at τ 7.20. The ring protons, H-6 and H-5, absorb at τ 0.95 and 0.83, respectively. The ^{1}H NMR spectrum of the "parent" tetrazole in perdeuteriodimethyl sulfoxide shows only two protons (τ 0.96 and 0.88, respectively) as an AB system (J_{AB} = 1.0 Hz). Thus, we are again dealing with the tetrazolo derivative.

The question of a rapid equilibrium between the azido and tetrazolo compounds can easily be disposed of by the observation that, in Me_2SO-d_6 at least, these ^{1}H NMR spectra are temperature insensitive (35–150 °C).

Conclusion

This study has established the following facts.

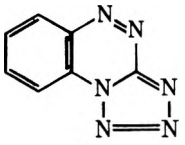
(1) 3-Azido-1,2,4-triazines are unstable and cyclize to the tetrazolo isomers.

(2) The cyclization affords the tetrazolo[1,5-*b*]-1,2,4-triazines exclusively.

(3) The structure assigned to the 5,6-diphenyl derivative without any proof is probably correct.[10]

(4) The tetrazolo[1,5-*b*]-1,2,4-triazine ring system is planar and aromatic by the classical as well as ^{1}H NMR criteria.

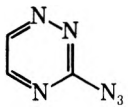
(5) The structure assignment of the tetrazolo[5,1-*c*]-benzo-1,2,4-triazines (**14**), resulting from cyclization of an



14

azido group into N-4 rather than N-2, may well be in error and should be reexamined.[11]

(6) The "addition" of the electron-withdrawing nitrogen to a 2-azidopyrimidine (**16** vs. **15**) is expected to decrease the



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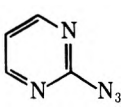

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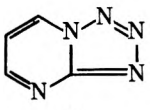
electron-donating capacity of the π-deficient heterocyclic ring and consequently should stabilize the azido form.[12] Yet 3-azido-1,2,4-triazines are *not* stable and exist only as these tetrazolo isomers.

In view of the fact that we are dealing with facile interconversions, we must not only consider the stabilities of the azido structures, but also those of the tetrazolo isomers. If we keep this in mind, it is clear that the tetrazolopyrimidine **17** is going to be less stable than the tetrazolotriazine **18** because of the



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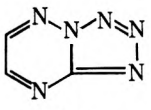
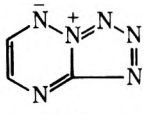
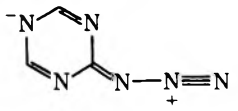


18a



18b

involvement of the extra nitrogen atom in the ground-state stabilization of the bicyclic ring system (**18a,b**). On the other hand, the extra nitrogen in the 3-azido-1,3,5-triazine, reported[8] to be the stable isomer in this ring system, will lend greater stabilization (**19**) to the azido form rather than to the bicyclic structure **20**, where the extra nitrogen would con-



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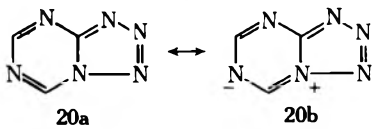

20a **20b**

tribute considerably less to the stabilization (**20a,b**) of the bicyclic system than to the azido form (**19**).

Experimental Section

Tetrazolo[1,5-*b*]1,2,4-triazines. General Procedure. The appropriate hydrazino compound (**12a–h**) (2 mmol) was dissolved in 6 ml of 5 N HCl, the solution was cooled to 0–5 °C, and aqueous $NaNO_2$ (140 mg in 1 ml of H_2O) was added dropwise. The solution was stirred for an additional 15 min while maintaining the temperature at 0–5 °C. The crude tetrazole was separated either by filtration (compounds **11e–h**) or by extraction with $CHCl_3$ (**11a–d**). The compounds thus obtained were recrystallized from absolute methanol (see Table VI).

Table VI. Tetrazolo[1,5-*b*]-1,2,4-triazines[a]

Molecular formula (compd)	Mp, °C	% yield
$C_3H_2N_6$ (**11a**)	174–175	33
$C_4H_4N_6$ (**11b**)	130–131	50
$C_4H_4N_6$ (**11c**)	140–142	82
$C_5H_6N_6$ (**11d**)	138–139	70
$C_9H_6N_6$ (**11e**)	192–193	58
$C_9H_5N_6Cl$ (**11f**)	217–219	90
$C_{10}H_8N_6O$ (**11g**)	194–196	60
$C_9H_5N_7O_2$ (**11h**)	184–186	62

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all compounds in table. Ed.

The ^{1}H NMR spectra for the azido compounds were obtained by extracting the above reaction mixtures with $CDCl_3$ in place of $CHCl_3$.

X-Ray Data Collection. Single crystals of the compound were sealed in thin-walled glass capillaries. The final lattice parameters in Table II were determined from a least-squares refinement of the angular settings of 15 accurately centered reflections ($\theta > 20°$).

Data were taken on an Enraf-Nonius CAD-4 diffractometer with graphite crystal monochromated molybdenum radiation. The diffracted intensities were collected by the ω–2θ scan technique with a takeoff angle of 3.0°. The scan rate was variable and was determined by a fast (20° min^{-1}) prescan. Calculated speeds based on the net intensity gathered in the prescan ranged from 7 to 0.3° min^{-1}. Moving-crystal moving-counter backgrounds were collected for 25% of the total scan width at each end of the scan range. For each intensity the scan width was determined by the equation

$$\text{scan range} = A + B \tan\theta$$

where $A = 0.70°$ and $B = 0.20°$. Aperture settings were determined in a like manner with $A = 4$ mm and $B = 0.87$ mm. Other diffractometer parameters and the method of estimation of the standard deviations have been described previously.[12] As a check on the stability of the instrument and the crystal, two reflections, the (200) and (020), were measured after every 30 reflections; no significant variation was noted.

One independent quadrant of data was measured out to $2\theta = 50°$; a slow scan was performed on a total of 1242 unique reflections. Since these data were scanned at a speed which would yield a net count of 4000, the calculated standard deviations were all very nearly equal. No reflection was subjected to a slow scan unless a net count of 20 was obtained in the prescan. Based on these considerations, the data set of 1242 reflections (used in the subsequent structure determination and refinement) was considered observed, and consisted in the main of those for which $I > 3\sigma(I)$. The intensities were corrected for Lorentz and polarization effects.

Fourier calculations were made with the FOURIER program.[13] The full-matrix, least-squares refinement was carried out using the Busing and Levy program ORFLS.[14] The function $w(|F_o| - |F_c|)^2$ was minimized. No corrections were made for extinction. Atomic scattering factors for Cl, N, and C were taken from Cromer and Waber.[15] Scattering factors for hydrogen were from "International Tables for X-Ray Crystallography".[16] Final bond distances, angles, and errors were computed with the aid of the Busing, Martin, and Levy ORFFE program.[17] Crystal structure illustrations were obtained with the program ORTEP.[18]

Structure Solution and Refinement. The location of the chlorine atom was revealed by the inspection of a Patterson map. The coordinates of all nonhydrogen atoms were deduced from a Fourier map phased on the chlorine atom. Subsequent isotropic least-squares refinement led to an R value of 0.10. Anisotropic refinement gave values of $R_1 = 0.052$ and $R_2 = 0.067$ where

$$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$$

$$R_2 = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$$

Unit weights had been used up to this point. Application of a weighting scheme which reduced to contribution of the ten most in-

tense reflections to 1/25, together with the removal of the (1̄22) and (102) because of extinction afforded $R_1 = 0.042$ and $R_2 = 0.045$. The addition of the five hydrogen atoms in calculated positions (the C–H bond length was assumed to be 1.00 Å) and further anisotropic refinement gave final values of $R_1 = 0.032$ and $R_2 = 0.034$. Unobserved reflections were not included. The largest parameter shifts in the final cycle of refinement were less than 0.01 of their estimated standard deviations. The value of the standard deviation of an observation of unit weight was 0.91. A final difference Fourier map showed no peak larger than 0.2 e/Å^3. The final values of the positional and thermal parameters are given in the microfilm supplement.[19]

Registry No.—**12a,** 28735-23-1; **12b,** 59318-39-7; **12c,** 28735-26-4; **12d,** 19542-09-7; **12e,** 28735-29-7; **12f,** 59318-40-0; **12g,** 59318-41-1; **12h,** 59318-42-2.

Supplementary Material Available. A listing of the crystal data, final fractional coordinates, and anisotropic structure factors (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) M. Tisler, *Synthesis*, 123 (1973).
(2) J. H. Boyer and H. W. Hyde, *J. Org. Chem.*, **25,** 458 (1960).
(3) B. Stanovnik and M. Tisler, *Chimia*, **24,** 272 (1971).
(4) T. Sasaki, K. Kanematsu, and M. Murata, *Tetrahedron*, **27,** 5121 (1971).
(5) C. Wentrup, *Tetrahedron*, **26,** 4969 (1970).
(6) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *J. Org. Chem.*, **30,** 829 (1965).
(7) C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **30,** 826 (1965).
(8) J. Kobe, B. Stanovnik, and M. Tisler, *Montash. Chem.*, **101,** 724 (1970).
(9) W. W. Paudler and J. Lee, *J. Org. Chem.*, **36,** 3923 (1971).
(10) M. F. G. Stevens, *J. Chem. So, Perkin Trans. 1,* 1221 (1972).
(11) A. Messmer, G. Hajos, P. Benko, and L. Pallos, *J. Heterocycl. Chem.*, **10,** 575 (1973).
(12) J. L. Atwood and K. D. Smith, *J. Am. Chem. Soc.*, **95,** 1488 (1973).
(13) D. J. Hodgson's version of Dellaca and Robinson's FOURIER Program, as locally implemented for the UNIVAC 1110, University of Alabama.
(14) W. R. Busing, K. O. Martin, and H. A. Levy, "ORFLS, a Fortran Crystallographic Least-Squares Program," Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1964.
(15) D. T. Cromer and J. T. Waber, *Acta Crystallogr.*, **18,** 104 (1965).
(16) "International Tables for X-Ray Crystallography", Vol. III, Kynoch Press, Birmingham, England, 1962, p 202.
(17) W. R. Busing, K. O. Martin, and H. A. Levy, "ORFFE, a Fortran Crystallographic Function and Error Program", Report ORNL-TM-306, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1964.
(18) C. K. Johnson, "ORTEP, a Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations", Report ORNL-3794, Revised, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(19) See paragraph at end of paper regarding supplementary material.

Synthesis of 2-Azaestratrienes

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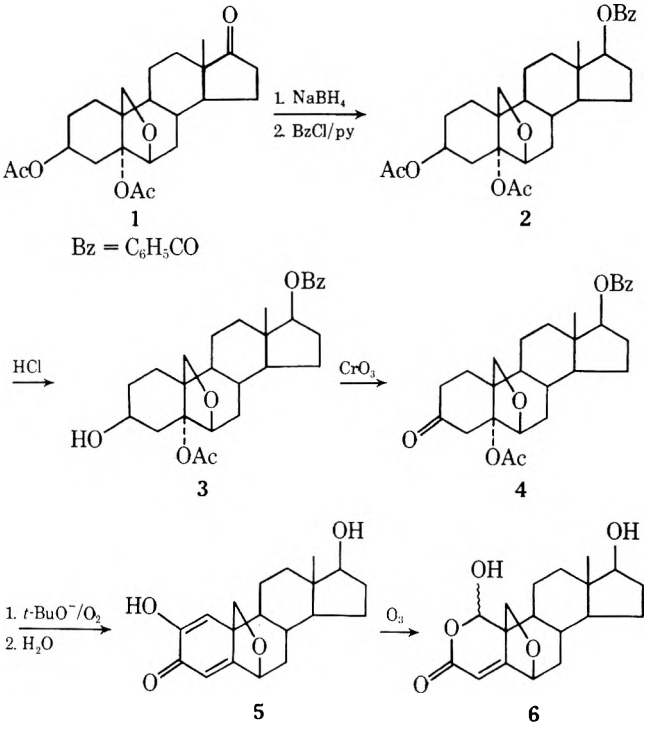
From readily available 3β,5α-dihydroxy-6β,19-oxidoandrostan-17-one 3,5-diacetate (1) a facile synthesis of 1,17-dihydroxy-6β,19-oxido-2-oxaandrost-4-en-3-one (6) was developed. The key step in this sequence was the regioselective ozonolysis of the bridged, unsaturated α-diketone 5 to the bridged lactol 6 in good yield. This cyclic acid aldehyde 6 was utilized for the preparation of 3-methoxy- and 1,3-dimethoxy-2-azaestratrienes. The 17α-ethynyl-17β-hydroxy derivatives of the 3-methoxy- as well as the 3-cyclopentoxy-2-azaestratrienes were prepared via an alternate pathway from 2-oxaestra-5(10)-ene-3,17-dione (17). While these series were devoid of hormonal activity they manifested hypolipemic as well as antiviral properties.

In an earlier communication[1] we had reported the syntheses of several series of 2-aza steroids. This study was an extension of work aimed at determining the effect on biological activity of a heteroatom at the 2 position of the steroid nucleus.[2] In this paper we wish to report in greater detail our investigations into the synthesis of 2-azaestratrienes, the thrust of which has been provided by the interesting biological profile of the 3-methyl ether series (vide infra). Thus, the structural modifications made at the 1 and 3 positions of the aromatic nucleus were attempts to enhance the observed biological properties of this series.

Our initial approach to the 2-aza analogue of estradiol-3-methyl ether utilized the readily available 3β,5α-dihydroxy-6β,19-oxidoandrostan-17-one 3,5-diacetate (**1**)[3] which was converted to the 17-benzoate derivative **2** by treatment with sodium borohydride in methanol[4] and subsequent benzoylation with benzoyl chloride in pyridine, in 85% yield from **1** (Scheme I). Selective hydrolysis of the 3-acetate was accomplished with anhydrous hydrogen chloride in methanol at room temperature providing **3** in 95% yield. Subsequent oxidation of the bridged alcohol **3** with Jones reagent[5] afforded the keto diester **4** in 93% yield.

Following the procedure of Hanna and Ourisson,[6] this material was oxygenated subsequent to the in situ elimination of the 5-acetoxy group by *tert*-butoxide. The conjugated system thus formed enabled oxygenation to occur exclusively at the 2 position generating the bridged α-diketone **5** in yields

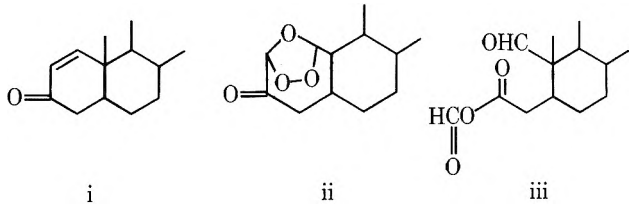
Scheme I



up to 70% after subsequent hydrolysis of the 17-benzoate group.[7] The highly enolic character of this material is demonstrated by the presence of the two vinylic protons of the C-1 and C-4 carbon atoms appearing as singlets in its NMR spectrum at δ 6.23 and 6.27 ppm. It was the enolic character of this compound which enabled its facile conversion to the desired lactol by the method described (vide infra).

On the basis of the work by Hanna and Ourisson,[6] we had originally expected that this α-diketone **5** would provide the bridged lactol **6** upon further oxygenation and this intermediate would readily be converted to the A-ring lactam which we desired. However, further treatment of **5** with base in the presence of oxygen afforded only low yields of the desired product **6**. An investigation of alternate methods for this transformation led to the discovery that ozonolysis of **5** in ethyl acetate at −70 °C followed by warming to room temperature caused rearrangement of the intermediate ozone adduct giving the desired lactol **6** in 60% yield.

This conversion of **5** to **6** via ozone was based on an earlier observation made in these laboratories.[8] It had been found that the ozonide ii of 17β-hydroxy-17α-methyl-5α-androst-1-en-3-one (i) gave the mixed anhydride iii upon warming to



i ii iii

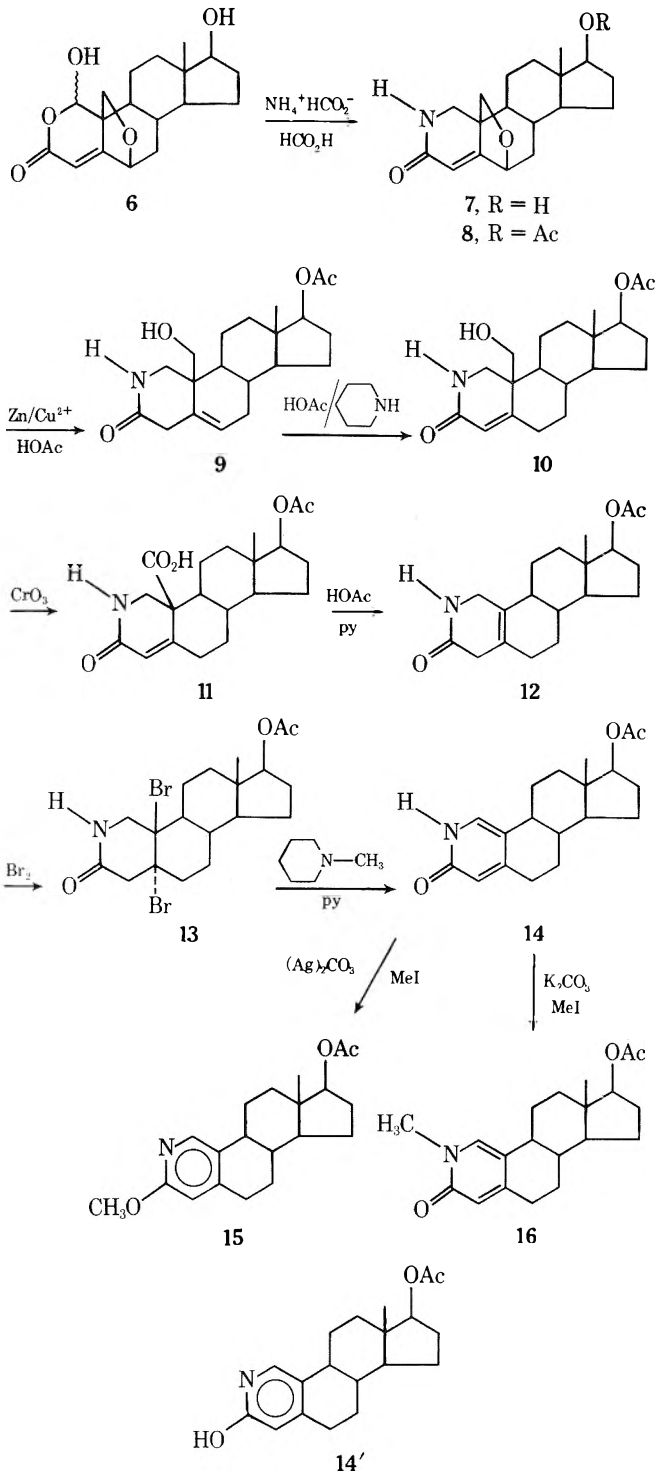
room temperature. This transformation must obviously proceed through a Baeyer–Villiger type rearrangement of the intermediate ozonide ii. On the basis of this mechanism compound **5** must also form an ozonide which rearranges to the mixed anhydride of carbonic acid which in turn spontaneously liberates carbon dioxide to form compound **6**.

We attribute the regioselectivity of ozone for the 1,2 double bond of **5** to the steric shielding of the β face of the 4,5 double bond by the bridged ether, as well as activation of the 1,2 double bond by the 2-hydroxyl group. Experiments in our laboratories and by other investigators[9,10] have demonstrated that ozonolysis of 1,4-diene systems results in a mixture of products due to the indiscriminant attack of the ozone on both double bonds.

Introduction of nitrogen into the steroid ring system was accomplished by treating **6** with ammonium formate and formic acid with no apparent reduction of the conjugated double bond (Scheme II).[11] Thus, Leukart treatment of **6** followed by saponification of the 17-formyloxy substituent gave the A-ring lactam **7** in 50% yield. Acetylation of this bridged lactam **7** in acetic anhydride and pyridine afforded the 17-acetoxy derivative **8** which underwent smooth cleavage of the ethereal bridge with zinc–copper couple in aqueous alcoholic acetic acid solution to provide the 19-hydroxy-Δ^5-lactam **9**. This compound was then isomerized to the conjugated lactam **10** in refluxing acetic acid–piperidine solution in high yield. The conversion of 17,19-dihydroxy-2-azaandrost-4-en-3-one 17-acetate (**10**) to the 19-nor system was accomplished by the methods described in the 2-oxa series.[2d] Oxidation of the alcohol **10** with Jones reagent[5] gave the 10-carboxy derivative **11** which was not purified but rather decarboxylated in pyridine–acetic acid solution to afford the $\Delta^{5(10)}$-lactam **12** in 63% yield from **10**.

The construction of the A-ring pyridone was achieved by bromination of **12** in chloroform which gave the 5,10-dibromo compound **13**.[12] Dehydrobromination with *N*-methylpiperidine produced **14**, exclusive of the cross-conjugated $\Delta^{4,9(10)}$-diene as evinced by spectral data indicative of the A-ring pyridone. The uv spectrum of **14** exhibited λ_{max} at 305 and 231

Scheme II



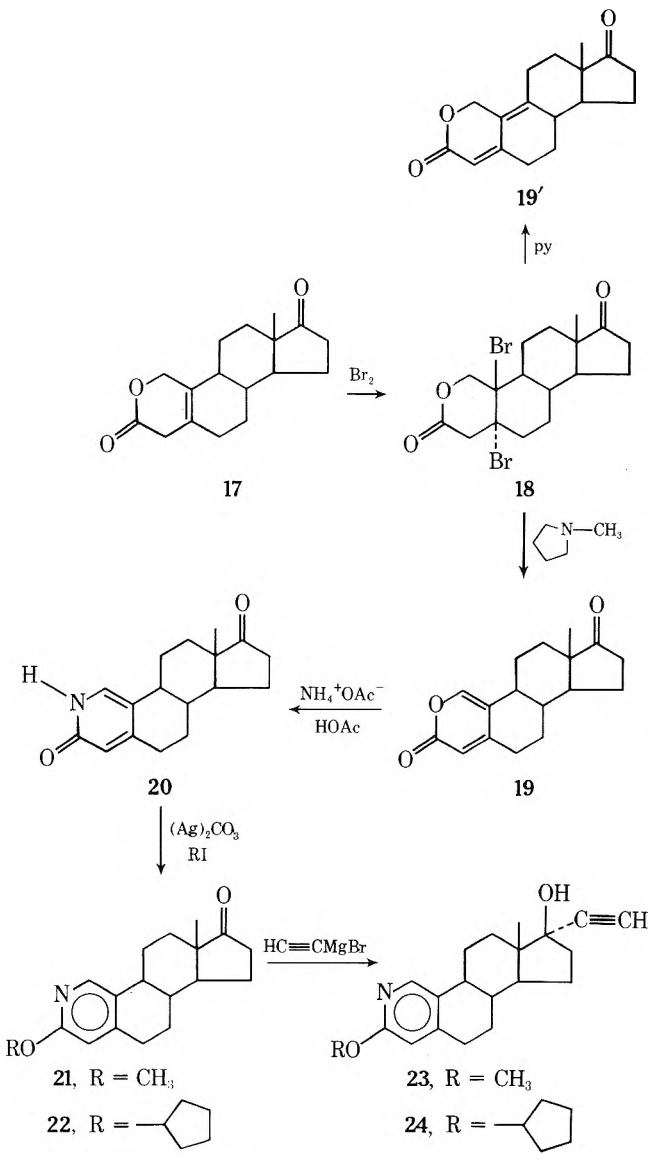
nm (ϵ 5500 and 7900),[13] and the NMR spectrum of **14** exhibited the aromatic protons of the C-1 and C-4 carbon atoms at 8.00 and 7.13 ppm. This compound was of particular interest since its tautomeric form **14′** is the aza analogue of estradiol 17-acetate. However, it has been established that the pyridone form predominates over the pyridinol form by several orders of magnitude[14] and it is perhaps for this reason these A-ring pyridones lack any estrogen-like hormonal activity.

O-Alkylation of the silver salt of **14** with methyl iodide in benzene[15] afforded 2-azaestradiol-3-methyl ether 17-acetate (**15**) in a good yield. The *N*-methyl analogue **16**, which was also formed but to a much lesser degree under these conditions, could be synthesized in high yield by alkylation of **14** with methyl iodide in dimethylformamide in the presence of potassium carbonate.[15] These isomers are readily distinguished

by the position of their A-ring methyl group resonances in their NMR spectrum (O isomer, δ 3.88 ppm; N isomer, δ 3.52 ppm).

Since the 17α-ethynyl-17β-hydroxyl derivatives of 19-nor steroids have been found to possess the greatest amount of oral estrogenic activity,[16] this derivative of the above series as well as that of 2-azaestradiol-3-cyclopentyl ether was synthesized. To obtain the necessary 17-keto-A-ring pyridone precursor **20**, an alternate synthesis was employed utilizing an intermediate available from our previous work on the synthesis of 2-oxa steroids[1d] (Scheme III).

Scheme III



Bromination of 2-oxaestra-5(10)-ene-3,17-dione (**17**) in chloroform at ca. −25 °C afforded the dibromolactone 18[12] which was not purified but rather treated with *N*-methylpyrrolidine in benzene to yield the α-pyrone **19** in ca. 65% yield from **17**. The generation of the A-ring pyrone from the 5,10-dibromolactone **18** with tertiary amine contrasted with our earlier work in this series. We had previously found that the $\Delta^{9(10)}$ isomer **19′** was the major elimination product when **18** was dehydrohalogenated with pyridine as the base. This type of dienone was also the reported product in the carbocyclic series when the $\Delta^{5(10)}$ ketone was brominated in pyridine.[17] It is conceivable that the preponderant product in each of these reactions is a reflection of different elimination mechanisms (E_1 vs. E_2)[18] and of the different steric requirements of the bases used. However, we have not studied this elimination in any detail to be more definitive about these observations.

Subsequent treatment of **19** with ammonium acetate in acetic acid gave the 17-keto-α-pyridone steroid **20** in moderate yield. Alkylation of the silver salt of **20** with either methyl iodide or cyclopentyl iodide, as previously described, afforded the 3-methoxy or 3-cyclopentoxy steroidal pyridines, **21** and **22**, respectively. Reaction of these compounds with ethynylmagnesium bromide, generated from acetylene and ethyl Grignard, yielded the 17α-ethynyl-17β-hydroxy derivatives **23** and **24**, respectively.[19]

In an effort to determine the effect an additional methoxyl group at the 1 position would have on biological activity, the 1,3-dimethoxy-2-azaestratrienes were also prepared (Scheme IV). Thus, again utilizing the bridge lactol **6** as our key intermediate, oxidation with Jones reagent[5] provided the 17-keto-A-ring anhydride **25**. Ammonium acetate–acetic acid treatment gave the A-ring unsaturated imide **26** which was more resistant to hydrogenolysis of the bridging ether by the zinc–copper couple than in the previous series. However, use of the more powerful zinc–silver couple provided the Δ^5 imide **27** in moderate yield. Oxidation of this material with Jones reagent[5] afforded what appeared to be, by thin layer chromatography, a mixture of oxidized components **28a** and **28b**. This mixture was treated without purification with hot aqueous alcoholic hydroxide solution, followed by acidification affording the A-ring glutaconimide **29** in 53% from **27**. This compound, whose NMR spectrum indicated a mixture of Δ^4 and Δ^5 isomers, did not readily crystallize. Moreover, the silver salt of **29** did not cleanly O-alkylate under the conditions previously utilized. However, treatment with diazomethane yielded, in approximately equal amounts, two dialkylated isomers which were readily separated by column chromatography. The desired bis O-alkylated compound **30** was treated as in the previous cases with ethynylmagnesium bromide to provide 17α-ethynyl-2-azaestra-1,3,5(10)-triene-1,3,17-triol 1,3-dimethyl ether (**31**) in ca. 50% yield.[19]

The other isomer formed in the alkylation reaction (**32**) has been assigned the N-methylated structure with the methoxyl group at the 3 position rather than at the 1 position (**32′**). Sterically, it would appear that the 3-carbonyl is much less hindered than that at the 1 position and should be kinetically favored during the alkylation. Moreover, a nuclear Overhauser effect (NOE)[20] has been observed for the 4 proton of **30** which was comparable to the NOE of the 4 proton of **32**.[21] Since the environment of the 4 proton of our assigned structure is similar to that of the 4 proton of **30** a similar response would be expected upon irradiation of the 3-carbon *O*-methyl groups in the two molecules.[22]

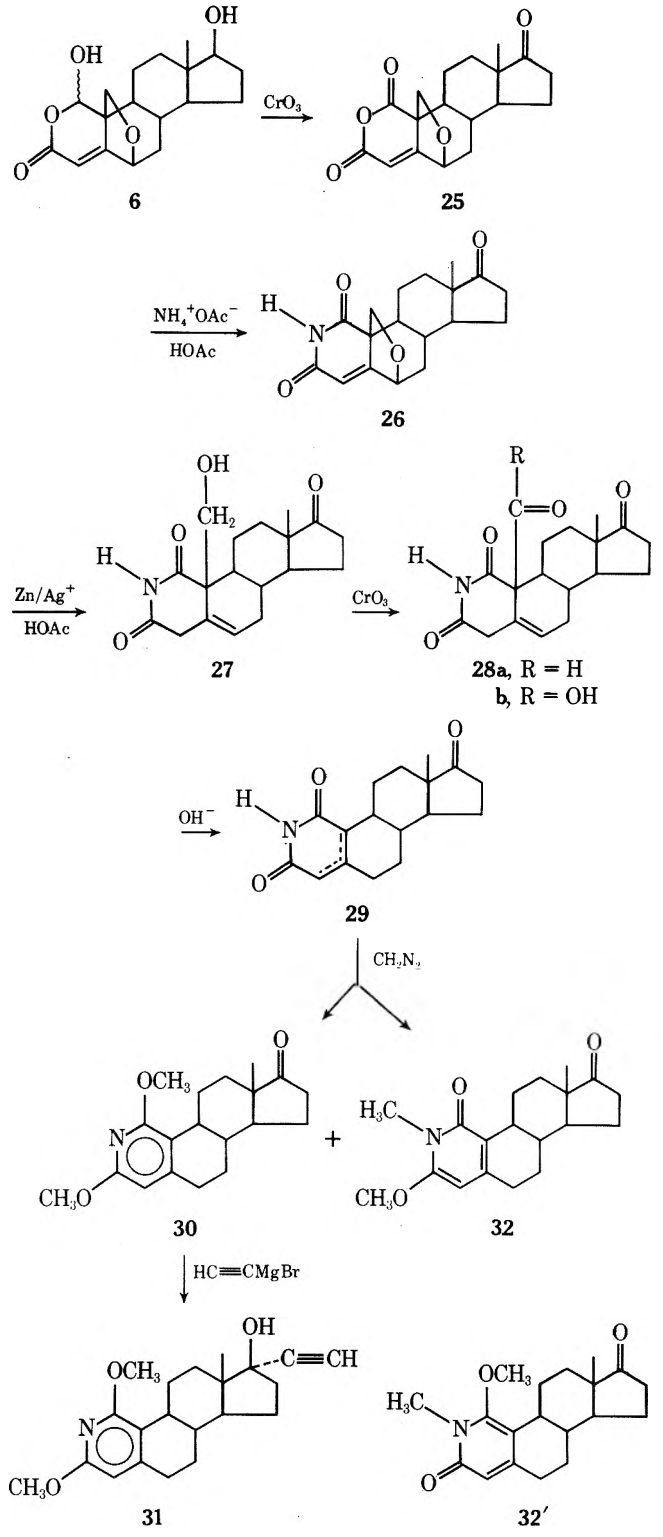
Each of the aforementioned series of 2-azaestratrienes has been tested for biological activity in our laboratories.[23] In addition **15** has been evaluated for anticancer activity when tested under the auspices of the National Cancer Institute.[24] Additional modifications of the 2-azaestratrienes are in progress.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were taken on a Varian A-60A, XL-100-15, or T-60 spectrometer using tetramethylsilane as an internal standard. Uv spectra were obtained in MeOH on a Beckman DK-2A. Infrared spectra were obtained on a Beckman IR-12. TLC runs were on 7.6-cm microscope slides covered with 0.25-mm thickness Woelm F silica with a magnesium silicate binder. Solvents were EtOAc–C_6H_6 combinations (alkoxypyridines) or MeOH–EtOAc combinations (lactams, pyridones). Visualization of spots was by 5% phosphomolybdic acid–EtOH (w/v) followed by heat.

6β,19-Oxidonandrostane-3β,5α,17-triol 17-Benzoate 3,5-Diacetate (2). To 100 g (0.248 mol) of 3β,5α-dihydroxy-6β,19-oxi-

Scheme IV



doandrostan-17-one 3,5-diacetate in 1 l. of methanol cooled to ca. 0 °C was added 6.0 g (0.158 mol) of sodium borohydride in portions over a 10-min period. The reaction mixture was stirred at 0–5 °C for 1.5 h. A sufficient volume of glacial acetic acid was then added to destroy the excess reducing agent before concentrating the solution to about 400 ml in vacuo. Addition of 600 ml of water caused formation of 95.3 g of product (95%). The dried crude material was taken up into 900 ml of pyridine and to this solution was added 60 g (0.43 mol) of benzoyl chloride. After stirring the reaction mixture overnight at room temperature it was diluted with 1.2 l. of water. The resulting oil which solidified upon continued stirring was isolated by filtration to give 113 g (94%) of crude product. Recrystallization from methanol gave **2**: mp 162–165 °C; NMR ($CDCl_3$) δ 1.00 (3 H, s, 18-CH_3), 2.05 (3 H, s, 3-OAc), 2.08 (3 H, s, 5-OAc), 3.87 (2 H, broad s, 19-CH_2), 7.40–8.35 (5 H, aromatic protons).

Anal. Calcd for $C_{30}H_{38}O_7$: C, 70.56; H, 7.50. Found: C, 70.70; H, 7.54.

6β,19-Oxidoandrostane-3β,5α,17-triol 5-Acetate 17-Benzoate (3). To 1 l. of methanol containing 5 g of anhydrous hydrogen chloride was added 55 g (0.108 mol) of the triester (**2**) and the reaction mixture was stirred at room temperature for 4 h. Neutralization of the acid with triethylamine was followed by addition of 1 l. of water which caused formation of 48.0 g (95%) of precipitate which was collected. Recrystallization from methanol resulted in pure **3**: mp 212–214 °C; NMR ($CDCl_3$) δ 0.99 (3 H, s, 18-CH_3), 2.12 (3 H, s, 5-OAc), 3.77 (2 H, broad s, 19-CH_2), 7.25–8.20 (5 H, aromatic protons).

Anal. Calcd for $C_{28}H_{36}O_6$: C, 71.77; H, 7.74. Found: C, 71.67; H, 7.75.

5α,17-Dihydroxy-6β,19-oxidoandrostan-3-one 5-Acetate 17-Benzoate (4). To 49 g (0.121 mol) of the alcohol **3** in 1 l. of acetone at room temperature was added 31 ml of Jones reagent[5] in portions over a 10-min period. After the reaction mixture was stirred for an additional 15 min, the solution was decanted from the inorganic precipitate now present and an equivalent volume of water was added. The resultant precipitate was collected and provided 46.6 g (95%) of analytically pure **4** after drying: mp 218–219 °C; NMR ($CDCl_3$) δ 1.00 (3 H, s, 19-CH_3), 2.10 (3 H, s, 5-OAc), 3.99 (2 H, broad s, 19-CH_2), 7.15–8.18 (5 H, aromatic protons).

Anal. Calcd for $C_{28}H_{34}O_6$: C, 72.08; H, 7.35. Found: C, 72.22; H, 7.36.

2,17-Dihydroxy-6β,19-oxidoandrosta-1,4-dien-3-one (5). To 44.4 g (0.0954 mol) of bridged keto diester **4** in 530 ml of *tert*-butyl alcohol containing 2.7 ml of hexamethylphosphoramide in a 1-l. Parr shaker bottle was added 48.2 g (0.43 mol) of potassium *tert*-butoxide and the reaction mixture was allowed to stand at room temperature for 1 h. Following the in situ elimination of the 5-acetate group, several atmospheres of oxygen were admitted to the reaction vessel which was then shaken under pressure for 1 h after which time 1 equiv of the gas had been absorbed by the reaction mixture. To the reaction vessel was then added 150 ml of water and the aqueous solution was allowed to stand at room temperature overnight. Neutralization of the basic solution with dilute hydrochloric acid solution was followed by addition of a sufficient volume of chloroform to cause formation of two layers after shaking. After separating, the aqueous phase was extracted with two additional portions of chloroform and the combined extracts were washed with water and dried over sodium sulfate. Solvent removal in vacuo gave an oil which was redissolved into benzene. The organic phase was extracted three times with 5% sodium bicarbonate solution prior to extraction of the desired product into 5% sodium hydroxide solution. The combined hydroxide extracts (three) were backwashed twice with chloroform before acidifying the basic solution with dilute hydrochloric acid solution. The resultant acidic solution was extracted with chloroform three times and the combined extracts were washed with water and dried over sodium sulfate. Solvent removal in vacuo gave 20.2 g (67%) of solid product. Recrystallization from methanol resulted in the pure α-diketone **5**: mp 199–201 °C; NMR ($CDCl_3$) δ 0.83 (3 H, s, 18-CH_3), 3.60, 4.43 (2 H, dd, J = 7 Hz, 19-CH_2), 6.23 (1 H, s, vinyl proton), 6.27 (1 H, s, vinyl proton); uv (MeOH) 254 nm (ϵ 9500).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.18; H, 7.84.

1,17-Dihydroxy-6β,19-oxido-2-oxaandrost-4-en-3-one (6). Ozone was passed through a solution of 1.9 l. of ethyl acetate containing 20.0 g (0.063 mol) of the α-diketone **5** cooled to −70 °C until a faint blue color was perceptible. The ozonolysis was then terminated, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature overnight. After solvent removal in vacuo the oily residue was dissolved into 450 ml of 5% sodium bicarbonate solution and this was washed twice with chloroform. The aqueous solution was then acidified with 6 N hydrochloric acid solution which caused formation of 11.8 g of product, isolated by filtration. Addition of sodium chloride to the aqueous filtrate caused formation of an additional 0.8 g of **6** (59% total). This material was generally utilized in the subsequent reactions without further purification. Recrystallization of the crude material from aqueous ethanol provided **6** as the hydrate: mp 142–147 °C; uv (MeOH) 226 nm (ϵ8800); NMR (C_5D_5N) δ 0.98 (3 H, s, 18-CH_3), 4.25 (2 H, dd, J = 8 Hz, 19-CH_2), 5.00 (1 H, broad d, 6-H), 6.14 (1 H, s, 4-H), 6.42 (1 H, broad s, 1-H).

Anal. Calcd for $C_{18}H_{24}O_5 \cdot H_2O$: C, 63.88; H, 7.74. Found: C, 63.79; H, 7.63.

17-Hydroxy-6β,19-oxido-2-azaandrost-4-en-3-one (7). To 400 ml of 98% formic acid was added 350 g (5.55 mol) of ammonium formate and the reaction mixture was heated to homogeneity before addition of 36.5 g (0.11 mol) of bridged lactol **6** and then refluxed for 23 h. Following the addition of 1 l. of water, a precipitate formed which

was collected, affording 14.5 g of product partially formylated at the 17 position. The aqueous filtrate was then extracted three times with chloroform and the combined extracts were washed with water, dried over sodium sulfate, and filtered. Solvent removal in vacuo gave an oil which was combined with the above precipitate in 100 ml of methanol containing 50 ml of 4 N sodium hydroxide solution. The solution was refluxed for 1 h before concentrating to 100 ml. The addition of ca. 300 ml of water caused formation of 10.7 g of product, isolated by filtration. The aqueous filtrate was acidified with dilute hydrochloric acid and extracted three times with chloroform. The extracts were washed with water, dried over sodium sulfate, and filtered. Solvent removal in vacuo gave an oil which upon trituration with ether provided an additional 7.35 g of product of purity comparable to the above (52% total).

The crude product was recrystallized from ethanol: mp 247–250 °C; ir ($CHCl_3$) 2.93, 5.90, 6.03 μ; uv (MeOH) 220 nm (ϵ11 200); NMR ($CDCl_3$) δ 0.84 (3, H, s, 18-CH_3), 3.46 (2 H, broad s, 1-CH_2), 3.58, 4.18 (2 H, dd, J = 7 Hz, 19-CH_2), 4.75 (1 H, broad d, J = 5 Hz, 6-H), 5.67 (1 H, broad s, 4-H).

Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.08; H, 8.04; N, 4.74.

17-Hydroxy-6β,19-oxido-2-azaandrost-4-en-3-one 17-Acetate (8). To 4.75 g (0.016 mol) of the bridged lactam **7** in 20 ml of pyridine was added 10 ml of acetic anhydride and the reaction mixture was allowed to stand at room temperature overnight. Upon addition of 200 ml of water 4.8 g (89%) of product resulted which was collected by filtration. Recrystallization from ethanol gave the pure compound: mp 299–302 °C dec; NMR ($CDCl_3$) δ 0.87 (3 H, s, 18-CH_3), 2.05 (3 H, s, –OAc), 3.45 (2 H, broad s, 1-CH_2), 3.60, 4.18 (2 H, dd, J = 8 Hz, 19-CH_2), 4.75 (1 H, broad d, J = 5 Hz, 6-H), 5.85 (1 H, broad s, 4-H).

Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.33; H, 7.97; N, 4.08.

17,19-Dihydroxy-2-azaandrost-5-en-3-one 17-Acetate (9). To 4.8 g (0.014 mol) of the bridged lactam acetate **8** in 250 ml of ethanol containing 75 ml of glacial acetic acid and 75 ml of water was added 52.5 g (0.80 mol) of Zn dust and 10.5 g (0.165 mol) of copper acetate. The mechanically stirred reaction mixture was refluxed overnight, then filtered through diatomaceous earth. The filtrate was reduced to ca. one-third of its original volume in vacuo and to the resultant solution was added 250 ml of water. The precipitate which formed was collected affording 4.25 g of product. Additional water and cooling of the aqueous filtrate afforded another 0.2 g of product (93%). Recrystallization from ethanol provided **9**: mp 271–273 °C; ir ($CHCl_3$) 2.93, 5.79, 6.02, 7.90 μ; NMR ($CDCl_3$ + CF_3CO_2D) δ 0.87 (3 H, s, 18-CH_3), 2.15 (3 H, s, –OAc), 3.89 (2 H, broad s, 19-CH_2), 5.85 (1 H, broad m, 5-H).

Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.13; H, 8.41; N, 4.03. Found: C, 69.11; H, 8.48; N, 4.01.

17,19-Dihydroxy-2-azaandrost-4-en-3-one 17-Acetate (10). To 14.0 g (0.040 mol) of Δ^5-lactam **9** in 120 ml of piperidine was cautiously added 40 ml of glacial acetic acid at room temperature and the reaction mixture was refluxed for 2 h. After cooling 500 ml of water was added to the solution and the precipitate (11.0 g) was collected. The aqueous filtrate was extracted with chloroform and the combined extracts were washed with dilute hydrochloric acid solution, then water and dried over sodium sulfate. Solvent removal gave a residue which upon trituration with ether yielded another 0.5 g of product (82% total). Recrystallization from acetonitrile containing a small amount of acetic acid afforded **10**: mp 265–275 °C; uv (MeOH) 220 nm (ϵ 13 200); NMR ($CDCl_3$ + CF_3CO_2D) δ 0.87 (3 H, s, 18-CH_3), 2.13 (3 H, s, –OAc), 3.40, 3.87 (2 H, dd, J = 14 Hz, 1-CH_2), 4.04 (2 H, broad s, 19-CH_2), 5.95 (1 H, broad s, 4-H).

Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.13; H, 8.41; N, 4.03. Found: C, 69.18; H, 8.35; N, 3.95.

17-Hydroxy-3-oxo-2-azaestr-4-ene-10-carboxylic Acid 17-Acetate (11). To 4.5 g (0.013 mol) of the conjugated lactam **10** in 300 ml of acetone containing 60 ml of acetic acid cooled to ca. 0 °C was added 12 ml of Jones reagent[5] in portions over a 15-min period with the temperature of the solution maintained below 5 °C during the addition. After the reaction mixture was stirred for 1 h at 0–5 °C a few milliliters of 2-propanol were added to destroy the excess oxidizing agent. Prior to concentrating the solution to ca. 75 ml in vacuo, 50 ml of water was added to aid in solubilizing the inorganic salts present. After addition of 200 ml of water to the concentrated solution, it was extracted with chloroform and the combined extracts were washed with saturated salt solution, dried over sodium sulfate, and filtered through diatomaceous earth. Upon solvent removal in vacuo an oil remained which upon trituration with ether gave 3.1 g of product. Concentrating the ethereal filtrate afforded another 0.6 g of product whose purity was poorer than the above. This material was taken up into 5% sodium bicarbonate solution and this solution was extracted with chloroform prior to acidification with dilute hydrochloric acid providing an additional 0.3 g of product whose purity was comparable to that originally isolated (73% total). The combined material was used without purification in the subsequent step: NMR ($CDCl_3$) δ 0.78 (3 H, s, 18-CH_3), 2.05 (3 H, s, –OAc), 5.69 (1 H, narrow m, 4-H).

17-Hydroxy-2-azaestr-5(10)-en-3-one 17-Acetate (12). To 6.6 g (0.018 mol) of the crude acid **11** in 35 ml of pyridine was added 7 ml of glacial acetic acid and the reaction mixture was refluxed for 2 h under a nitrogen atmosphere. After cooling 250 ml of water was added and 5.0 g (86%) of **12** was collected. Recrystallization from aqueous acetic acid afforded the pure compound: mp >325 °C; ir ($CHCl_3$) 2.93, 5.79, 6.00, 7.90 μ; NMR ($CDCl_3$ + CF_3CO_2D) δ 0.83 (3 H, s, 18-CH_3), 2.07 (3 H, s, –OAc), 2.90 (2 H, broad m, 4-CH_2), 3.95 (2 H, broad m, 1-CH_2).

Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.82; H, 8.65; N, 4.31.

5,10-Dibromo-17-hydroxy-2-azaestran-3-one 17-Acetate (13). To 2.2 g (0.007 mol) of $\Delta^{5(10)}$-lactam **12** in 75 ml of chloroform at room temperature was added dropwise over a 10-min period 15 ml of a carbon tetrachloride solution containing 85 mg of bromine/ml of solution (0.008 mol). The reaction mixture was stirred in the presence of the excess bromine for 30 min before solvent removal in vacuo. The resultant oil was triturated with pentane and the precipitate which formed was isolated by filtration affording 3.15 g of product. This material was used without purification for the dehydrohalogenation reaction: NMR ($CDCl_3$) δ 0.85 (3 H, s, 18-CH_3), 2.05 (3 H, s, –OAc), 3.05, 3.48 (2 H, dd, J = 19 Hz, 4-CH_2), 3.82 (2 H, broad m, 1-CH_2).

17-Hydroxy-2-azaestra-1(10),4-dien-3-one 17-Acetate (14). To 1.4 g (0.003 mol) of the dibromo lactam **13** suspended in 20 ml of pyridine was added dropwise over a 5-min period 5 ml of piperidine at room temperature. After addition the reaction mixture became homogeneous prior to the formation of a precipitate. After stirring at room temperature for 3 h 200 ml of chloroform was added to the reaction mixture and the organic phase was washed with several portions of 1 N hydrochloric acid solution (until the aqueous wash remained acidic), then saturated salt solution and dried over sodium sulfate. The solvent was reduced in volume to afford in two crops (0.77 g) of **14** (83%). Recrystallization from aqueous acetic acid provided the pure compound: mp >330 °C; uv (MeOH) 231 nm (ϵ 7900), 306 (5500); ir ($CHCl_3$) 2.93, 5.78, 6.01, 6.16, 7.90 μ; NMR (CF_3CO_2D) δ 1.02 (3 H, s, 18-CH_3), 2.27 (3 H, s, –OAc), 7.13 (1 H, broad m, 4-H), 8.00 (1 H, broad m, 1-H).

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.22; H, 7.94; N, 4.35.

2-Azaestradiol 3-Methyl Ether 17-Acetate (15). To 2.0 g (0.006 mol) of the steroidal α-pyridone **14** suspended in 150 ml of benzene containing 1.2 ml (0.019 mol) of methyl iodide was added 1.0 g (0.0036 mol) of silver carbonate and the heterogeneous reaction mixture was refluxed in the dark for 22 h. After cooling, the reaction mixture was filtered through diatomaceous earth and the solvent was removed from the filtrate in vacuo to afford an oil. The oil was taken up into methanol and upon cooling afforded 1.17 g (56%) of **14** in two crops: mp 102–104 °C; uv (MeOH) 277 nm (ϵ 3700); ir ($CHCl_3$) 5.80, 6.22, 6.70, 7.30, 7.90μ; NMR ($CDCl_3$) δ 0.83 (3 H, s, 18-CH_3), 2.05 (3 H, s, –OAc), 3.88 (3 H, s, –OCH_3), 6.44 (1 H, broad s, 4-H), 8.00 (1 H, broad s, 1-H).

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.05; H, 8.29; N, 4.09.

17-Hydroxy-2-methyl-2-azaestra-1(10),4-dien-3-one 17-Acetate (16). To 1.95 g (0.006 mol) of **14** in 200 ml of dimethylformamide containing 6 ml (0.096 mol) of methyl iodide was added 0.8 g (0.006 mol) of anhydrous potassium carbonate and the reaction mixture was heated at 70 °C for 18 h. The solvent was then removed in vacuo and 300 ml of water was added to the oily residue which caused formation of a precipitate which was collected. Recrystallization of the crude product from aqueous acetic acid afforded 1.8 g (84%) of **16**: mp 222–226 °C dec; uv (MeOH) 308 nm (ϵ 4850), 231 (5550); NMR ($CDCl_3$) δ 0.83 (3 H, s, 18-CH_3), 2.05 (3 H, s, –OAc), 3.52 (3 H, s, N-CH_3), 6.34 (1 H, broad s, 4-H), 7.10 (1 H, s, 1-H).

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.79; H, 8.29; N, 4.08.

5,10-Dibromo-2-oxaestrane-3,17-dione (18). To 15 g (0.055 mol) of 2-oxaestra-5(10)-ene-3,17-dione (**17**) in 500 ml of chloroform cooled to −30 °C was added 30.5 ml (0.059 mol) of carbon tetrachloride solution containing 310 mg of bromine per ml of solution over a 7–8-min period. The reaction mixture was stirred at ca. −20 °C for another 20 min before addition of 100 ml of a 5% sodium sulfite solution. After shaking, the two layers were separated and the aqueous phase was

extracted with an additional portion of chloroform. The combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal in vacuo (heating bath temperature <30 °C) afforded an oil which upon trituration with ether afforded 22 g of product. This material was used without purification in the subsequent reaction: NMR ($CDCl_3$) δ 0.92 (3 H, s, 18-CH_3), 3.35, 3.69 (2 H, dd, J = 16 Hz, 4-CH_2), 4.69, 4.92 (2 H, dd, J = 13 Hz, 1-CH_2).

2-Oxaestra-1(10),4-diene-3,17-dione (19). To 22 g (0.051 mol) of the crude lactone **18** in 150 ml of benzene was added 150 ml of *N*-methylpyrrolidine and the reaction mixture was refluxed for 20 min. After cooling, additional benzene was added and the solution was extracted with dilute hydrochloric acid solution until the aqueous extracts remained acidic. The organic phase was then washed with two portions of saturated salt solution and dried over sodium sulfate, and upon solvent removal in vacuo 11.55 g of solid product remained whose NMR spectrum indicated 80–85% of desired pyrone (~65% from **17**). Recrystallization from ethanol afforded **19:** mp 215.5–217.5 °C dec; uv (MeOH) 300 nm (ϵ 6000); ir ($CHCl_3$) 5.76, 6.10, 6.50 μ; NMR ($CDCl_3$) δ 0.95 (3 H, s, 18-CH_3), 6.10 (1 H, broad s, 4-H), 7.33 (1 H, broad s, 1-H).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.66; H, 7.61.

2-Oxaestra-4,9-diene-3,17-dione (19′). To 0.5 g (0.0012 mol) of **18** in 3 ml of benzene was added 3 ml of pyridine and the reaction mixture was refluxed for 20 min. Workup as in the previous experiment afforded 0.3 g of crystalline solid whose NMR spectrum indicated ca. 75% of $\Delta^{4,9}$-dienone (**19′**). Recrystallization from ethanol provided material which was ca. 90% **19′**. An additional recrystallization from ethanol afforded material which appeared to be >95% of **19′** by NMR spectroscopy: mp 202.5–204 °C; uv (MeOH) 285 nm (ϵ 17 000); NMR ($CDCl_3$) δ 1.00 (3 H, s, 18-CH_3), 4.92, 5.18 (2 H, 2 broad d, J = 15 Hz, 1-CH_2).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.71; H, 7.24.

2-Azaestra-1(10),4-diene-3,17-dione (20). To 25 ml of glacial acetic acid containing 37.5 g of ammonium acetate heated to homogeneity was added 5.2 g (0.019 mol) of the α-pyrone **19** and the reaction mixture was refluxed for 4 h. After cooling 150 ml of water was added and the precipitate which formed was isolated by filtration affording 3.45 g of crude product. Upon standing overnight at room temperature, the filtrate gave another 0.2 g of precipitate. The initial precipitate was taken up into 40 ml of ether, stirred for 10 min, and filtered giving back 3.25 g of tan solid of comparable purity (TLC) to the second precipitate above (66%). Recrystallization from aqueous acetic acid gave **20** after drying: mp >325 °C; uv (MeOH) 306 nm (ϵ 5250); NMR ($CDCl_3$ + CF_3CO_2D) δ 1.00 (3 H, s, 18-CH_3), 6.97 (1 H, broad s, 4-H), 7.93 (1 H, broad s, 1-H).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.25; H, 7.61; N, 5.16.

O-Alkylation of 20 with Methyl Iodide and Cyclopentyl Iodide. In a typical experiment, to 2.5 g (0.009 mol) of α-pyridone **20** suspended in 250 ml of benzene was added 1.6 g (0.0058 mol) of silver carbonate and 1.8 ml (0.029 mol) of methyl iodide [8 g (0.041 mol) of cyclopentyl iodide] and the reaction mixture was refluxed overnight in the dark. After cooling, the reaction mixture was filtered through diatomaceous earth and the solvent was removed from the filtrate in vacuo. The reaction from methyl iodide afforded an oil which was taken up into ethanol containing a slight amount of water and upon cooling gave **21** (60%): mp 139.5–140.5 °C; uv (MeOH) 276 nm (ϵ 3850); ir ($CHCl_3$) 5.73, 6.22, 6.70, 7.18 μ; NMR ($CDCl_3$) δ 0.92 (3 H, s, 18-CH_3), 3.90 (3 H, s, -OCH_3), 6.45 (1 H, broad s, 4-H), 8.07 (1 H, broad s, 1-H).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.77; H, 8.08; N, 4.81.

The reaction with cyclopentyl iodide gave an oily solid which upon washing with pentane gave 87% of crude **22**. Recrystallization from acetone gave the pure compound: mp 182–183 °C; uv (MeOH) 279 nm (ϵ 3730); NMR ($CDCl_3$) δ 0.92 (3 H, s, 18-CH_3), 6.40 (1 H, broad s, 4-H), 8.02 (1 H, broad s, 1-H).

Anal. Calcd for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13. Found: C, 77.78; H, 8.76; N, 4.15.

Ethynylation of 21 and 22 with Ethynylmagnesium Bromide. In a typical experiment, 50 ml of freshly distilled tetrahydrofuran was cooled to −70 °C before 1–2 g of acetylene gas was added to the solution after it had been passed through a scrubber filled with water and two scrubbers filled with concentrated sulfuric acid. To this solution was added 8.5 ml of 3 M ethylmagnesium bromide in ether and the reaction mixture was allowed to come to room temperature before the addition of 1.4 g (0.0049 mol, R = CH_3) of steroid in 10 ml of tetrahydrofuran. The reaction mixture was stirred at room temperature for 3–4 h before cooling (ice bath) and the addition of ca. 35 ml of 1 N hydrochloric acid solution followed by ether and additional water to form two layers. After separating, the aqueous phase was extracted with two additional portions of ether and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal in vacuo gave an oil. In the case of the 3-methoxy derivative, the oil was taken up into acetone and Skelly B was added until the solution became turbid. Activated charcoal was added and the solution was filtered through diatomaceous earth. The volume of this filtrate was reduced slightly and Skelly B again added and the above process was repeated to give a crystal clear solution which upon reduction of the volume of the solution and cooling afforded 57% of analytically pure product in three crops: mp 146–147.5 °C; uv (MeOH), 277 nm (ϵ 3700); NMR ($CDCl_3$) δ 0.88 (3 H, s, 18-CH_3), 2.60 (1 H, s, -C≡CH), 3.89 (3 H, s, -OCH_3), 6.45 (1 H, broad s, 4-H), 8.07 (1 H, broad s, 1-H).

Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09; N, 4.50. Found: C, 77.06; H, 8.09; N, 4.61.

In the case of the 3-cyclopentoxy derivative, the oil from the reaction mixture was taken up into ether–Skelly B and treated as above to afford an oil (74%). Though this oil would not crystallize its analytical and spectral data indicated desired product: uv (MeOH) 279 nm (ϵ 3100); NMR ($CDCl_3$) δ 0.90 (3 H, s, 18-CH_3), 2.60 (1 H, s, -C≡CH), 5.34 (1 H, broad m, -OCH), 6.44 (1 H, broad s, 4-H), 8.08 (1 H, broad s, 1-H).

Anal. Calcd for $C_{24}H_{31}NO_2$: C, 78.86; H, 8.55; N, 3.84. Found: C, 78.93; H, 8.89; N, 3.53.

6β,19-Oxido-2-oxaandrost-4-ene-1,3,17-trione (25). To 4.85 g (0.014 mol) of bridged lactol **6** in 200 ml of acetone cooled to −15 °C was added 10 ml of Jones reagent[5] at a rate so as to maintain a temperature below −5 °C during the addition. The reaction mixture was allowed to stand at 0 °C overnight before the excess oxidizing agent was destroyed with 2-propanol. The cold solution was filtered from the precipitated inorganic salts and the volume of the filtrate was reduced to 50 ml in vacuo. Addition of 100 ml of water afforded 3.25 g of crude anhydride which was isolated by filtration. The aqueous filtrate was extracted three times with chloroform and the combined extracts were washed with 5% sodium bicarbonate solution before drying over sodium sulfate. Solvent removal afforded an additional 0.33 g of **25** (74% total). Recrystallization from acetone gave the pure compound: mp 263–264 °C; uv (MeOH) 223 nm (ϵ 8550); ir ($CHCl_3$) 5.56, 5.70, 5.73 μ; NMR ($CDCl_3$) δ 0.98 (3 H, s, 18-CH_3), 4.00, 4.36 (2 H, dd, J = 9 Hz, 19-CH_2), 4.93 (1 H, broad d, J = 5 Hz, 6-H), 6.03 (1 H, broad s, 4-H).

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.45; H, 6.49.

6β,19-Oxido-2-azaandrosta-4-ene-1,3,17-trione (26). To 150 ml of glacial acetic acid containing 125 g of ammonium acetate heated to homogeneity was added 17.1 g (0.054 mol) of the bridged anhydride **25** and the reaction mixture was refluxed for 90 min. After cooling 500 ml of water was added and 9.55 g of product was collected. Concentration of the aqueous filtrate and cooling afforded another 3.75 g of product as precipitate (78% total). Recrystallization from aqueous acetic acid gave pure **26:** mp 290–292 °C dec; uv (MeOH) end absorption 220 nm; ir ($CHCl_3$) 2.96, 5.80 μ; NMR ($CDCl_3$ + CF_3CO_2D) δ 1.00 (3 H, s, 18-CH_3), 3.93, 4.35 (2 H, dd, J = 8 Hz, 19-CH_2), 4.94 (1 H, broad d, J = 5 Hz, 6-H), 5.85 (1 H, broad s, 4-H).

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.84; H, 6.85; N, 4.43.

19-Hydroxy-2-azaandrost-5-ene-1,3,17-trione (27). To 13.3 g (0.042 mol) of the bridged imide **26** in 600 ml of ethanol containing 400 ml of glacial acetic acid and 200 ml of water were added 38 g (0.226 mol) of silver acetate and 260 g (3.98 mol) of zinc dust. The reaction mixture was mechanically stirred while refluxing under an atmosphere of nitrogen for 2 h. The hot reaction mixture was then filtered through diatomaceous earth and the volume of the filtrate was reduced in volume by ca. 300 ml of solvent before addition of 1 l. of water. The turbid solution was extracted with chloroform and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal gave an oil which upon trituration with ether yielded a solid. Recrystallization from aqueous ethanol gave 6.75 g (51%) of product in three crops: mp 231–236 °C dec; ir ($CHCl_3$) 2.97, 5.75, 5.85 μ; NMR (C_5D_5N) δ 0.97 (3 H, s, 18-CH_3), 3.42 (1 H, broad d, J = 19 Hz, 4-H), 3.72 (1 H, broad d, 4-H), 3.97, 5.43 (2 H, dd, J = 10 Hz, 19-CH_2).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.23; H, 7.68; N, 4.37.

2-Azaestrene-1,3,17-trione (29). To 8.15 g (0.026 mol) of **27** in 300 ml of acetone cooled to −10 °C was added 15 ml of Jones reagent[5] in

portions so as to maintain a temperature below −5 °C during the addition. After the reaction mixture was stirred at ca. 0 °C for 1 h, the excess oxidizing agent was destroyed with 2-propanol and the solution was filtered. The solvent was removed from the filtrate and the residue was taken up into a solution containing 50 ml of methanol and 50 ml of 5% aqueous sodium hydroxide solution. After refluxing for 30 min the cooled solution was acidified with acetic acid and extracted with several portions of chloroform. The combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal in vacuo gave an oily residue which upon trituration with acetone afforded 3.9 g (53%) of amorphous solid. The NMR spectrum ($CDCl_3$) indicated a mixture of Δ^4 and $\Delta^{5(10)}$ isomers by the appearance of a broad singlet at 6.00 ppm (4-H) and a broad multiplet at 3.32 ppm (4-CH_2) with the latter [$\Delta^{5(10)}$] isomer in predominance. This material was used without purification for the subsequent alkylation: uv (MeOH) 236 nm (ϵ 2900), 244 (5800).

1,3-Dihydroxy-2-azaestra-1,3,5(10)-trien-17-one 1,3-Dimethyl Ether (30) and 3-Hydroxy-2-methyl-2-azaestra-3,5(10)-diene-1,17-dione 3-Methyl Ether (32). To a slurry of 3.75 g (0.013 mol) of crude **29** in 75 ml of methanol containing 75 ml of ether cooled to −5 °C was added a freshly prepared ethereal solution of diazomethane so as to maintain a temperature below 0 °C during addition. Soon after addition of the diazomethane solution the reaction mixture became homogeneous. When excess diazomethane was present as indicated by its yellow color, the addition was terminated and the reaction mixture was allowed to warm to room temperature. After standing at room temperature for 2 h, the solvents were removed in vacuo to give an oil consisting of a 1:1 mixture of the two isomers. The mixture was chromatographed on 75 g of SilicAR CC-7 using benzene and ethyl acetate as eluents. Compound **30** (1.3 g, 30%) was obtained when eluting with 10% ethyl acetate–90% benzene. Compound **32** (1.1 g, 26%) was obtained when eluting with 50% ethyl acetate–50% benzene. Recrystallization of **30** from Skelly B gave the analytical sample: mp 125.5–127.5 °C; uv (MeOH) 281 nm (ϵ 7000), 230 (8800); NMR ($CDCl_3$) δ 0.95 (3 H, s, 18-CH_3), 3.88 (3 H, s, -OCH_3), 3.93 (3 H, s, -OCH_3), 6.07 (1 H, broad s, 4-H).

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; H, 4.44. Found: C, 72.67; H, 8.27; N, 4.04.

The *N*-methyl isomer (**32**) was recrystallized from acetone to afford the analytical sample: mp 219–222 °C; uv (MeOH) 305 nm (ϵ 10 100), 235 (5200); NMR ($CDCl_3$) δ 0.94 (3 H, s, 18-CH_3), 3.40 (3 H, s, NCH_3), 3.85 (3 H, s, -OCH_3), 5.30 (1 H, broad s, 4-H).

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.14; H, 8.14; N, 4.48.

17α-Ethynyl-2-azaestra-1,3,5(10)-triene-1,3,17-triol 1,3-Dimethyl Ether (31). A 1.05-g (0.0033 mol) sample of **30** was treated as was described above for the preparation of **23** and **24.** The crude oil was taken up in ether and Skelly B was added until the solution became turbid, then activated charcoal was added and the solution was filtered through diatomaceous earth. This procedure was repeated two additional times before solvent removal afforded an oil which crystallized upon standing at room temperature. A small amount of pentane was added and the solid was isolated by filtration to give 553 mg of **31:** mp 101–105 °C; uv (MeOH) 281 nm (ϵ 7350), 230 (9200); NMR ($CDCl_3$) δ 0.92 (3 H, s, 18-CH_3), 2.60 (1 H, s, -C≡CH), 3.88 (3 H, s, -OCH_3), 3.92 (3 H, s, -OCH_3), 6.03 (1 H, broad s, 4-H).

Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.45; H, 7.90; N, 3.97.

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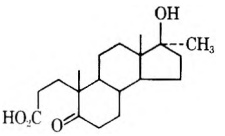
Registry No.—**1,** 807-09-0; **2,** 36334-58-4; **3,** 36405-41-1; **4,** 36334-59-5; **5,** 36334-60-8; **6,** 37147-40-3; **7,** 37147-41-4; **8,** 57178-17-3; **9,** 37147-42-5; **10,** 37147-43-6; **11,** 37147-44-7; **12,** 37147-45-8; **13,** 57178-18-4; **14,** 37147-47-0; **15,** 37147-48-1; **16,** 59433-87-3; **17,** 4623-00-1; **18,** 59433-88-4; **19,** 37695-36-6; **19′,** 21210-47-9; **20,** 57178-20-8; **21,** 57178-21-9; **22,** 57178-25-3; **23,** 57178-22-0; **24,** 57178-26-4; **25,** 53864-77-0; **26,** 53864-78-1; **27,** 53864-82-7; **Δ⁴-29,** 53864-85-0; **Δ⁵(¹⁰)-29,** 53864-84-9; **30,** 53864-72-5; **31,** 53864-73-6; **32,** 53913-59-0; benzoyl chloride, 98-88-4; methyl iodide, 74-88-4; cyclopentyl iodide, 1556-18-9; ethynyl bromide, 593-61-3.

References and Notes

(1) R. Pappo and R. J. Chorvat, *Tetrahedron Lett.*, 3237 (1972).
(2) (a) R. Pappo and C. J. Jung, *Tetrahedron Lett.*, 365 (1962); (b) R. Pappo, Abstracts, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., 1964, p 17M; (c) R. Pappo and C. J. Jung, Abstracts, 5th International Symposium on the Chemistry of Natural Products, London, 1968, p F50; (d) R. Pappo, *Intra-Sci. Chem. Rep.* **3,** 105 (1969).
(3) R. Pappo and L. N. Nysted, U.S. Patent 3 176 014 (1965). This material was provided by Searle de Mexico, Mexico 1, D. F.
(4) The β geometry of the 17-hydroxyl group was deduced from inspection of the NMR spectrum of the 17-hydroxy compound which demonstrated a sharp 18-methyl resonance at 0.79 ppm. Since the β-hydroxyl group has been determined to be the preponderant product of the borohydride reduction of 17-ketones (cf. J. Fried and J. A. Edwards, Ed., "Organic Reactions in Steroid Chemistry", Vol. I, Van Nostrand-Reinhold, Princeton, N.J., 1972, Chapter 2) and the 18-methyl resonance of the 17α-hydroxy compound would appear upfield from that of the 17β-hydroxy compound [cf. J. E. Bridgeman, P. C. Cherry, A. S. Clegg, J. M. Evans, E. R. H. Jones, A. Kasai, V. Kumar, G. D. Meakins, Y. Morisawa, E. E. Richards, and P. D. Woodgalt, *J. Chem. Soc. C,* 250 (1970)], this reduction appears to proceed with a high degree of stereoselectivity.
(5) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(6) R. Hanna and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1945 (1961).
(7) These oxygenations were performed by Mr. M. G. Scaros and his group, to whom we are grateful.
(8) L. N. Nysted and R. Pappo, U.S. Patent 3 109 016 (1963). As an additional application of this observation, we have found that ozonolysis of 17α-methyltestosterone in methylene chloride–methanol at −70 °C followed by treatment with 2 equiv of aqueous sodium hydroxide afforded 17α-



methyl-5-oxo-3,4-seco-*A*-norandrostan-3-oic acid in high yield. This method is superior to the generally utilized peroxide treatment of the ozonide product of conjugated ketones (cf. C. Djerassi, Ed., "Steroid Reactions", Holden-Day, San Francisco, Calif., 1963, Chapter 12) and appears to have general applicability.
(9) E. Caspi, B. Taqui Khan, and S. N. Balasubrahmanyam, *Tetrahedron,* **18,** 1013 (1962).
(10) R. Pappo and L. N. Nysted, these laboratories, private communication.
(11) While formic acid is not generally associated with the hydrogenation of double bonds [cf. H. W. Gibson, *Chem. Rev.,* **69,** 673 (1969)], saturation of conjugated double bonds by formate has been reported [cf. M. Sekiya and C, Yanaihara, *Chem. Pharm. Bull.,* **17,** 738 (1969); M. Sekiya and K. Suzuki, *ibid.,* **19,** 531 (1971)].
(12) The assigned trans geometry of the dibromo adduct (5α,10β) is the only reasonable isomer since the alternate dibromide (5β,10α) forces the B ring into an unfavorable boat conformation.
(13) See, for example, A. i. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products", Macmillan, New York, N.Y., 1964, Chapter 5.
(14) For a discussion of evidence supporting this fact see E. Klingsberg, Ed., "The Chemistry of Heterocyclic Compounds", Part 3, Interscience, New York, N.Y., 1972, Chapters IX–XII, p 619 ff.
(15) G. C. Hopkins, J. P. Jonak, H. J. Minnemeyer, and H. Tiekelmann, *J. Org. Chem.,* **32,** 4040 (1967).
(16) See, for example, D. A. McGinty and C. Djerassi, *Ann. N.Y. Acad. Sci.,* **71,** 500 (1958).
(17) M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay, and R. T. Rapala, *J. Am. Chem. Soc.,* **82,** 2402 (1960).
(18) See J. Hine, "Physical Organic Chemistry", 2d ed, McGraw-Hill, New York, N.Y., 1962, Chapter 8.
(19) L. F. Fieser and M. Fieser, *Experientia,* **4,** 285 (1948); H. H. Inhoffen, W. Logemann, W. Hohlweg, and A. Serini, *Chem. Ber.,* **71,** 1024 (1938).
(20) For a comprehensive discussion of NOE, see J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect", Academic Press, New York, N.Y., 1971.
(21) These experiments were performed using the pulsed Fourier transform technique described by L. F. Johnson, Abstracts, 14th Experimental NMR Conference, Boulder, Colo., April 15–18, 1973, p 31.
(22) We would like to thank Elisabeth Hajdu for performing the NOE experiments as well as Dr. Roy Bible and Lydia Swenton for assistance in interpretation of these results.
(23) The 3-methyl ether series was devoid of anabolic, androgenic, progestational, estrogenic, and antifertility activity as well as hormonal antagonist properties. However, this series did manifest moderate hypocholesterolemic activity in vivo as well as anti-influenza activity in vitro. Members of the 3-cyclopentoxy series have failed to demonstrate any biological activity. While the 1,3-dimethoxy series was devoid of hormonal and antiviral properties, compound **31** did show lipid mobilization activity.
(24) This compound was active in the L1210 assay (mouse leukemia) at 100 mg/kg when administered at 4-day intervals.

Preparation and Oxidation of 1-Hydroxypyrazoles and 1-Hydroxypyrazole 2-Oxides

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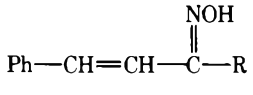
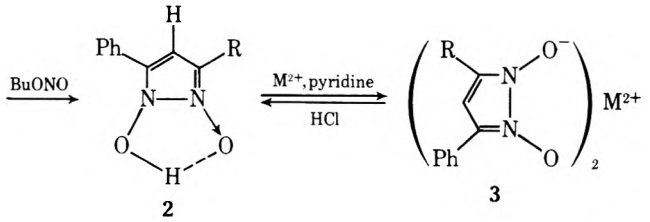
Nitrosation of α,β-unsaturated oximes in the presence of appropriate metal ions permits the isolation as their metal complexes of two new 1-hydroxypyrazole 2-oxides **2** which are unsubstituted at C-4. Reduction of **2** gives the corresponding 1-hydroxypyrazoles **7**. Both **2** and **7** may be oxidized with Fremy's salt to give 3,4-diazacyclopentadienone derivatives.

The nitrosation of benzalacetone oxime (**1a**) using butyl nitrite gives the 1-hydroxypyrazole 2-oxide **2a** which may be isolated as the insoluble metal complex **3a** when the reaction is carried out under mildly basic conditions in the presence of an appropriate metal ion.[1] We wish to report the further investigation of this reaction, its extension to the preparation of **2b** from chalcone oxime (**1b**), the reduction of **2** to 1-hydroxypyrazoles, and the behavior of 1-hydroxypyrazoles and 1-hydroxypyrazole 2-oxides under oxidizing conditions.



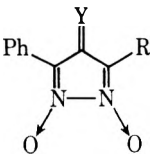
1



2 **3**

a, R = Me
b, R = Ph

Treatment of **1a** in aqueous ethanol containing 1 equiv of pyridine and an excess of an appropriate metal ion with butyl nitrite leads to the formation of **2a.** Consistent with the behavior of the known 1-hydroxypyrazole 2-oxides,[2,3] pyridine converts **2a** into its conjugate base which precipitates as an insoluble complex with the metal ion. By removing **2a** as its complex it is possible to avoid the facile reactions of **2a** under nitrosation conditions which preclude its isolation in the absence of the metal.[1,4-6] Initial studies of this novel complexation method involved the use of cobaltous chloride, but subsequent investigation shows that the divalent ions of zinc, nickel, and manganese behave in a manner similar to cobalt, giving the corresponding complexes **3a,** which can be converted to **2a** by treatment with hydrochloric acid. In each case, however, some quantities of by-products identified as the known 3,4-diazacyclopentadienone 3,4-dioxide derivatives **4** and **5** were obtained. Since **4** and **5** are the usual products



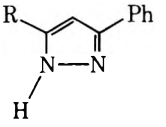
4, Y = O
5, Y = NOH

obtained when the nitrosation is carried out in the absence of the metal ion, it would appear that with these ions, the formation of the complex is not rapid enough to remove **2a** completely before further reaction occurs or else complexation is sufficiently reversible to provide some concentration of **2a** in equilibrium. Our experience suggests that both of these factors may be involved.

Copper(II) was found to be superior in effecting the isolation of **2a.** While the reactions run with the other metals typically gave yields of 25–40%, a yield of about 70% of **2a** was realized when copper sulfate was used. In addition to the higher yield obtained in this instance, the crude product was essentially free of the by-products observed in the other reactions. The advantage of copper over the other metals in this case would appear to be due to its superior ability to complex with the conjugate base of **2a.**

The synthetic procedure was extended to the nitrosation of chalcone oxime (**1b**), once again using a variety of metal ions. In this instance the most satisfactory results were obtained using cobalt(II), with which yields of about 40% of **2b** could be isolated. When copper(II) was used in this case, nitrosation was very sluggish, and low yields of the metal complex were observed. Since a marked color change from blue to dark green occurs when solutions of the unsaturated oximes are mixed with aqueous solutions of copper sulfate and pyridine, it seems likely that a copper complex with **1b** is formed which may explain the decreased reactivity. There is a considerable body of chemical literature describing the formation of complexes between oximes and metals, and it is certainly not surprising to observe such behavior in this instance. The choice of the best metal ion for the isolation of **2** would seem to be dictated by several factors, only one of which is the ability of the metal to complex with the pyrazole. Thus far attempts to extend this method to the isolation of the 3,5-dimethyl analogue of **2** have been unsuccessful. Studies of the complexation of **1** and **2** with metal ions are in progress which may help to elucidate the exact role of the metal in the reaction and to reveal the factors which determine the best choice of metal for a given case.

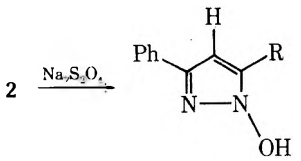
The identification of **2a** has been discussed in an earlier communication, and similar evidence is invoked in the assignment of the structure of **2b.** In addition to its chemical behavior (acidity, formation of metal complexes), **2b** gave a satisfactory elemental analysis. The infrared spectrum of **2b** closely resembled those of known 1-hydroxypyrazole 2-oxides,[2] and the NMR spectrum was completely consistent with the assigned structure. Finally, the parent 3,5-diphenylpyrazole **6b** could be obtained by reduction of **2b** with zinc in acetic acid.



6

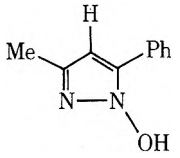
The reduction of 1-hydroxypyrazole 2-oxides with sodium dithionite is reported to yield 1-hydroxypyrazoles,[2] and the compounds **2a** and **2b** were reduced in this way to **7a** and **7b.** It is of interest that only one of the two possible isomeric 1-

hydroxypyrazoles, **7a**, is obtained when **2a** is reduced. Even though the yield of **7a** is rather low, careful investigation of



7

the crude product reveals none of the isomeric **8**, at least within the limits of detection by NMR analysis. The identification of **7a** and **7b** followed from their elemental analyses, spectra, and reduction with zinc in acetic acid to the parent pyrazoles, **6**. The oxidation of **7** to known compounds which will be discussed below not only provides further evidence for the assigned structures, but also allows the unambiguous assignment of **7a** rather than **8**. The regiospecificity of the di-



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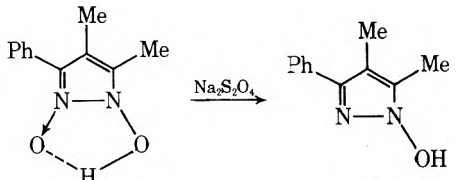
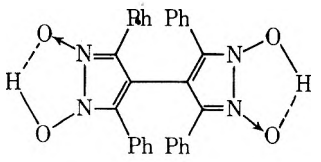
thionite reduction of 1-hydroxypyrazole 2-oxides is not without precedent, since Freeman and Gannon have reported that the reduction of **9** yields only a single product assigned as **10**.[2]



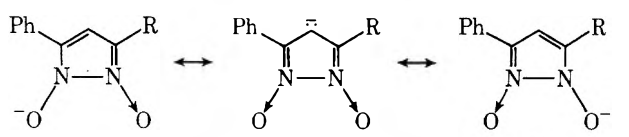
9 **10**

A principal consideration in undertaking the synthesis of **2a** and **2b** was an interest in the effect of the oxygen functions on the reactivity of the pyrazole ring. This effect includes an apparently enhanced susceptibility of the ring to electrophilic substitution and also toward free-radical oxidation as suggested by the interesting products, **4** and **5**, formed when **1** is nitrosated in aqueous acetic acid, and also by the novel dimer, **11**, which is formed when **1b** is treated with amyl nitrite in



11

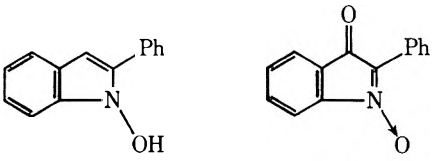
methanol.[6] All of these reactions suggest that the 1-hydroxyl group exerts an activating effect on the pyrazole ring which is analogous to the effect of the hydroxyl group on the reactivity of aromatic rings in phenols. This effect might be expected to be even more important for the conjugate base of **2**, for which contributing structures **12**, **13**, and **14** are possible.



12 **13** **14**

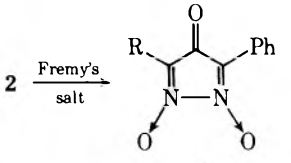
These structures suggest a particularly high electron density and potential reactivity at C-4, which is precisely the site available for study in **2**.

Precedent for the activating effect of an *N*-hydroxyl group in azole oxidation may be seen in the conversion of the 1-hydroxyindole **15** to phenylisatogen (**16**) in low yield by amyl



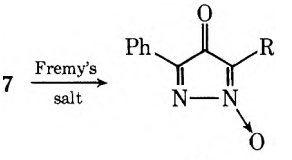
15 **16**

nitrite,[7] lead(IV) acetate,[8] and air,[9] and in nearly quantitative yield by *p*-nitroperbenzoic acid.[10] A similar oxidation has been proposed as the origin of the ketone **4** when the nitrosation of **1** is carried out in aqueous acid. In order to investigate the ease of oxidation of **2**, Fremy's salt (potassium nitrosodisulfonate) was chosen as a very mild free-radical oxidizing agent which has been widely applied for the selective oxidation of phenols to quinones.[11,12] It was observed that treatment of buffered aqueous solutions of **2a** and **2b** with Fremy's salt did, indeed, give the corresponding 3,4-diazacyclopentadienone 3,4-dioxides, **4**.



4

The 1-hydroxypyrazoles, **7**, also react readily with Fremy's salt, giving the respective 3,4-diazacyclopentadienone 3-oxides, **17**. Both **17a** and **17b** are known compounds which were



17

identified by independent synthesis. The structure of **17a** is of particular interest, since it has been demonstrated unequivocally that the methyl group is located on the carbon atom of the nitrone function as shown.[13] This serves to establish the location of the methyl group at C-5 in the 1-hydroxypyrazole **7a**.

The above results establish that the 1-hydroxypyrazoles are appreciably activated toward oxidation under free-radical conditions as has been predicted. With the ready availability of substantial quantities of **2a** and **2b** and also of **7a** and **7b**, we are pursuing further investigations into the effect of N-oxygenation on the reactivity of the pyrazole ring.

Experimental Section

The NMR spectra were obtained using a Hitachi Perkin-Elmer R20 60-MHz spectrometer, and chemical shifts are reported as δ in parts per million relative to tetramethylsilane as an internal standard. Melting points were taken in open capillaries using the Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Clark, Means, and Perkins Microanalytical Laboratory, Urbana, Ill.

5-Methyl-3-phenyl-1-hydroxypyrazole 2-Oxide (2a). A solution of 125 g (0.5 mol) of $CuSO_4 \cdot 5H_2O$ in 500 ml of water and 40 g (0.5 mol) of pyridine was added to a solution of 80.5 g (0.5 mol) of 4-phenyl-3-buten-2-one oxime (**1a**) in 1000 ml of 95% ethanol. The temperature was adjusted to about 35 °C and 56.7 g (0.55 mol) of butyl nitrite was added in one portion. The resulting solution was stirred at 35–40 °C for 2 h, cooled in ice, and the brown copper complex was filtered off and washed with 150 ml of cold ethanol–water (2:1) and then with water until the wash was colorless. The solid was added in portions to a stirred beaker of 1000 ml of warm HCl (concentrated), and when nearly all of the solid had dissolved the solution was filtered and the

filtrate was diluted with 2000 ml of water and cooled. The precipitate was collected, pressed dry, and washed under suction with water until the wash was colorless. The moist solid was dissolved with warming in a solution of 20 g of NaOH in 500 ml of 80% ethanol. The solution was treated with 5 g of activated charcoal, heated for 10 min, and filtered through Celite. The filtrate was acidified with 35 ml of acetic acid, cooled overnight, and the product was collected and washed with ethanol, then repeatedly with water, and again with ethanol. Concentration of the filtrate and dilution with water gave a small second crop. After drying in vacuo over P_2O_5, the yield was 69.7 g (73%) of white solid: mp 181–182 °C dec; NMR (CF_3CO_2H) δ 7.80–8.90 (m, 5 H, C_6H_5), 6.47 (s, 1 H, pyrazole C-4 proton), 2.52 (s, 3 H, CH_3).

An analytical sample was prepared by careful precipitation from the potassium salt in ethanol solution upon acidification with acetic acid.

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.88; H, 5.35; N, 14.54.

The potassium salt of **2a** was generated with an ethanolic solution of KOH and was recrystallized from tetrahydrofuran–ether as white needles, mp 182–186 °C. This material picked up water of hydration on standing and was dried just prior to analysis at 80 °C under vacuum.

Anal. Calcd for $C_{10}H_9N_2O_2K$: C, 52.61; H, 3.98; N, 12.26. Found: C, 52.80; H, 4.16; N, 12.08.

The cobalt complex of **2a** was prepared by treating an aqueous solution of the potassium salt with a slight excess of an aqueous solution of cobaltous chloride. The violet solid was collected by filtration and washed with water, methanol, and acetone to give **3a** (M = Co), mp 228 °C dec.

Anal. Calcd for $C_{20}H_{18}N_4O_4Co$: C, 54.92; H, 4.16; N, 12.81. Found: C, 54.56; H, 4.14; N, 13.06.

3,5-Diphenyl-1-hydroxypyrazole 2-Oxide (2b). A solution of 11.15 g (0.05 mol) of chalcone oxime in 100 ml of 95% ethanol was treated with a solution of 12 g (0.05 mol) of $CoCl_2 \cdot 6H_2O$ in 20 ml of water and 4.0 g (0.05 mol) of pyridine. The temperature was adjusted between 35 and 40 °C and 5.5 g (0.055 mol) of butyl nitrite was added over 30 min to the stirred solution. After stirring for 5 h at 35–40 °C an additional 2 g of butyl nitrite was added, and stirring was continued for 2 h. The solid was filtered off and the filtrate was diluted to 400 ml with water and treated with 200 ml of ether. The insoluble material was filtered off and added to the original solid, and the combined solids were stirred for 3 h with 150 ml of 4 N HCl. The product was filtered off and washed with water and with ethanol and dried to yield 4.88 g (39%) of tan solid. The material could be purified by reprecipitation from aqueous base. An analytical sample was prepared by careful precipitation from the recrystallized potassium salt (mp 280–282 °C) and had mp 199–200 °C dec; NMR (CF_3CO_2H) δ 7.20–8.20 (m, 10 H, C_6H_5), 6.85 (s, 1 H, pyrazole C-4 proton).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.59; H, 4.94; N, 11.01.

5-Methyl-3-phenyl-1-hydroxypyrazole (7a). To a solution of 9 g of sodium dithionite in 150 ml of water was added 2.2 g (10 mmol) of the potassium salt of **2a**. The mixture was warmed on a steam bath overnight, cooled in ice, and filtered. The white solid was recrystallized to yield 0.3 g (17.4%) of **7a**: mp 198–199 °C dec; NMR (CF_3CO_2H) δ 7.40–7.70 (m, 5 H, C_6H_5), 6.62 (s, 1 H, pyrazole C-4 proton), 2.51 (s, 3 H, CH_3).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.07. Found: C, 69.38; H, 6.08; N, 15.73.

3,5-Diphenyl-1-hydroxypyrazole (7b). A solution of 0.90 g (3 mmol) of the potassium salt of **2b** in 25 ml of water was added to a solution of 6.0 g of sodium dithionite in 100 ml of water and the mixture was warmed on a steam bath for 18 h. After cooling, the solid was filtered off and recrystallized from 2-propanol–water to give white crystals: mp 170–171 °C; NMR ($CDCl_3$) δ 11.35 (s, 1 H, OH), 7.0–8.0 (m, 10 H C_6H_5), 6.50 (s, 1 H, pyrazole C-4 proton).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.27; H, 5.13; N, 11.85. Found: C, 76.27; H, 5.10; N, 11.78.

Reduction of 2 and 7 with Zinc. In a typical reaction, 1.0 g of the oxygenated pyrazole and 5 g of zinc powder were stirred under reflux in acetic acid for 30 min. The mixture was filtered, and the filter cake was washed with methanol. The filtrate was evaporated under reduced pressure, and the residue was washed with water, recrystallized from ethanol, and sublimed. Reduction of **2a** and **7a** gave 3(5)-methyl-5(3)-phenylpyrazole (**6a**), identical with an authentic sample,[14] while **2b** and **7b** yielded 3,5-diphenylpyrazole (**6b**), which was also compared with an authentic sample.[15]

Oxidation of 2a and 2b with Fremy's Salt. A solution of 1.0 mmol of the potassium salt of the 1-hydroxypyrazole 2-oxide in 25 ml of water was added at room temperature to a stirred solution of 0.8 g of Fremy's salt[12] in 50 ml of water buffered with 1.14 g of $K_2HPO_4 \cdot 3H_2O$ and stirred. When the purple color was discharged, additional portions of Fremy's salt were added until the color persisted. The mixtures were cooled, and the products recovered by filtration. The yield of **4a**, mp 164–165 °C, was 60%, while that of **4b**, mp 192–194 °C, was 64%. The products were identified by comparison with authentic samples.[5]

Oxidation of 7a and 7b with Fremy's Salt. A solution of 0.5 g of the 1-hydroxypyrazole in 50 ml of CH_2Cl_2 was treated with 50 ml of a 5% solution of $K_2HPO_4 \cdot 3H_2O$ and stirred at room temperature while 2.5 g of Fremy's salt was added. Stirring was continued until reaction was complete (TLC), and then the organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated. The residual solid was washed with petroleum ether and recrystallized. The yield of **17a** was 41%, while that of **17b** was 90%. The products were identified by comparison with authentic samples.[5]

Acknowledgment. This research was supported by a grant from the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—**1a,** 2887-98-1; **1b,** 6502-38-1; **2a,** 55026-66-9; **2a** K salt, 59434-81-0; **2b,** 59434-82-1; **2b** K salt, 59434-83-2; **3a,** 59448-48-5; **4a,** 16901-38-5; **4b,** 17952-96-4; **7a,** 59434-84-3; **7b,** 59434-85-4; cobaltous chloride, 7646-79-9.

References and Notes

(1) J. F. Hansen and D. E Vietti, *J. Org. Chem.*, **40,** 816 (1975).
(2) J. P. Freeman and J. J. Gannon, *J. Org. Chem.*, **34,** 194 (1969).
(3) J. P. Freeman and J. J. Gannon, *J. Heterocycl. Chem.*, **3,** 544 (1966).
(4) J. P. Freeman and D. L. Surbey, *Tetrahedron Lett.*, 4917 (1967).
(5) J. P. Freeman, J. J. Gannon, and D. L. Surbey, *J. Org. Chem.*, **34,** 187 (1969).
(6) J. P. Freeman and J. F. Hansen, *J. Chem. Soc., Chem. Commun.*, 961 (1972).
(7) T. Ajello, *Gazz. Chim. Ital.*, **69,** 646 (1939).
(8) M. Colonn, and P. Bruni, *Gazz. Chim. Ital.*, **95,** 1172 (1965).
(9) L. Marchetti and V. Passalacqua, *Ann. Chim. (Rome)*, **57,** 1251 (1967).
(10) C. C. Bond and M. Hooper, *Synthesis*, 443 (1974).
(11) H. Zimmer, *Chem. Rev.*, **71,** 229 (1971).
(12) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, p 940.
(13) J. P. Freeman and M. J. Hoare, *J. Org. Chem.*, **36,** 19 (1971).
(14) B. Sjollema, *Justus Liebigs Ann. Chem.*, **279,** 248 (1894).
(15) L. Knorr and P. Duden, *Ber.*, **26,** 111 (1893).

Reactions of Methoxyvinyllithium. Synthesis and Rearrangement of 4-Hydroxyisopyrazoles

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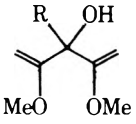
Reaction of methoxyvinyllithium (MVL) with aliphatic and aromatic esters gives, via an isolable divinyl ether intermediate, 3-hydroxy-2,4-pentanediones, which with hydrazine yield the previously unknown 4-hydroxyisopyrazoles. The stereochemistry of their facile thermal rearrangement to 2-pyrazolin-4-ones has been studied.

Recently we described the convenient acyl anion equivalent methoxyvinyllithium (MVL) and some of its reactions.[1-3] In the course of a study of the reactions of MVL with esters we hydrolyzed the initial adducts 1 to the hydroxy diones, as 2,[1] and then treated these substances with hydrazine in alcohol



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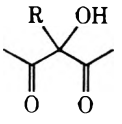

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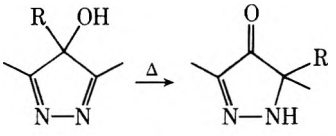
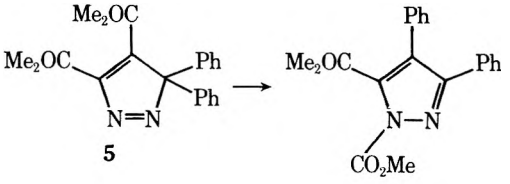
to furnish the previously unknown 4-hydroxyisopyrazoles **3**. These isopyrazoles **3** were thermally unstable, undergoing a smooth conversion to the 2-pyrazolin-4-ones **4** (cf. Table I)



3 4

R = alkyl, phenyl

at relatively low temperature (ca. 100 °C). This reaction is undoubtedly related to the van Alphen–Hüttel rearrangement of geminally disubstituted pyrazolenines.[4-6] Thus van Alphen observed the conversion of the pyrazolenine **5** to a substance thought to be **6** in acetic acid at 100 °C.[4] However, it was subsequently shown that this was in fact the isopyrazole **7**



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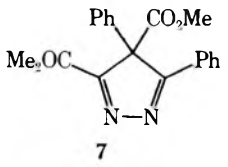

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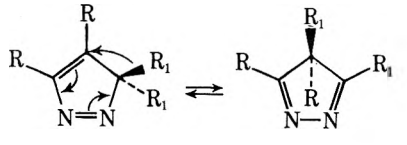
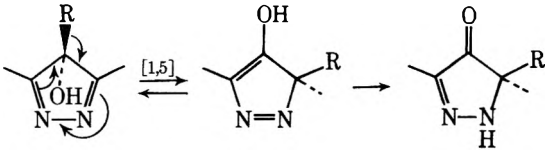
which could also be obtained by simply heating **5**.[6] These later authors[6] described this reaction as a thermal [1,5] sigmatropic change, which in the suprafacial mode should proceed with retention of configuration of the migrating group,[7] Scheme I. A similar [1,5]-sigmatropic shift is reasonable for the purely thermal rearrangement of the 4-hydroxyisopyrazoles **3**, which

Scheme I

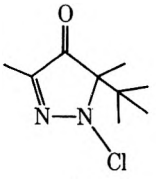


followed by a tautomerization provides the 2-pyrazolin-4-ones, Scheme II. In order to examine the stereochemistry involved

Scheme II



in this [1,5] shift we required a simple degradation of the rearrangement products and to this end examined some possible routes. An attempted ring cleavage reaction on the *N*-chloro derivative **8**, generated by reaction with *tert*-butyl hypochlorite (−78 °C), gave, by action of ethanolic sodium ethoxide, the ether **9**, presumably by way of the dehydropyrazole **10**. Lithium aluminum hydride reduction of the pyrazolone



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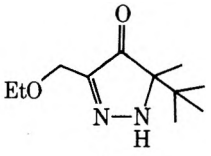

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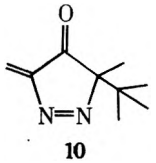

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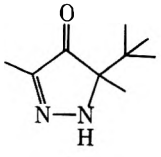
11 took an unexpected course, giving cleanly the dealkylated pyrazole **12** and presumably isobutylene. A reasonable precursor of **12** might be the deoxygenated isopyrazole **13** as its



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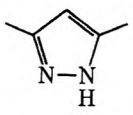

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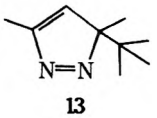

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aluminum complex. This same reductive dealkylation was observed in the *sec*-butyl substituted analogue of pyrazolone **11**. Eventually we were successful in establishing a stereochemical cycle which related the stereochemistry of the purely thermal [1,5]-sigmatropic shift to a [1,2] shift of the type characteristic of alkyl migration to an electron-deficient terminus. This is described in Scheme III. Thus the optically active isopyrazole **14**, obtained from (+)-methyl α-methylbutyrate, was thermally rearranged (110 °C, 3 min) to the pyrazolinone **15** and then converted, sequentially, by methylation and reduction to the stereoisomeric mixture of alcohols **19**, which upon treatment with mineral acid underwent a [1,2] shift to the pyrazole **18**. This same pyrazole was obtained from **14** by a reduction and methylation sequence, Scheme III. Care was taken to avoid any stereochemical fractionation at every stage in this cycle. The results are indicated in Table II.

These results prove that the stereochemistry of the thermal reaction [1,5] .s identical with that of the acid-catalyzed process [1,2]. If the reasonable assumption is made that this latter process is of the general class of [1,2] rearrangements known

Table I

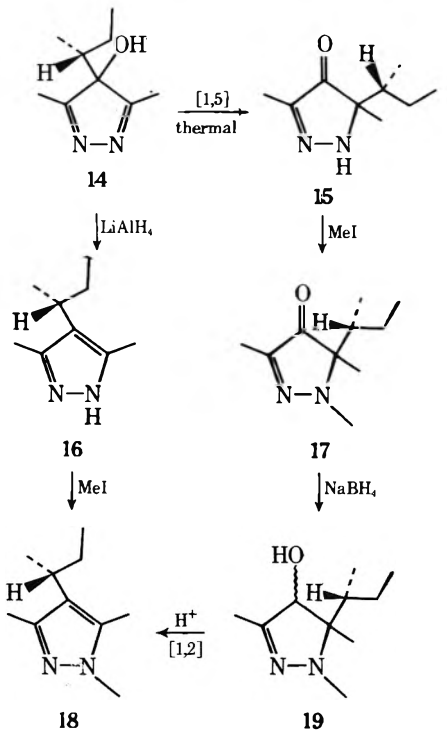
Ester	Enol ether 1 yield,[a] bp	Hydroxy dione 2 yield, bp, mp	Isopyrazole 3 yield, mp	2-Pyrazolin-4-one 4 yield, bp or mp
Methyl valerate (A)	82%, 57.5–58.0 °C (0.01 mm)	83%, 71–74.5 °C (4.5 mm)	51%, 93.5–95 °C	87%, 80 °C (0.07 mm)
(±)-Methyl α-methylbutyrate (B)	93%	62%, 93–96 °C (21 mm)	51%, 91.5–93 °C	89%, 85–86 °C (2.0 mm)
Methyl pivalate (C)	95%	52%, mp 50–52 °C	49%,[b] 83–93 °C	39%, mp 91–94 °C
Methyl benzoate (D)	75%, 82–85 °C (0.02 mm)	64%, 65–67 °C (0.17 mm)	57%, 162–163 °C	62%, mp 86–88 °C
(+)-Methyl α-methylbutyrate (E)	88%	66%, 91–92 °C (20 mm)	93%, 99–100 °C	92%, mp 61–62.5 °C

[a] All yields are for isolated purified substances. [b] The actual conversion yield in this case is low owing to loss of product by rearrangement.

Table II

1.	Pyrazole 18 from [1,5] and [1,2] pathway	$[\alpha]^{28}D$ +20.2° (c 4.35, $CHCl_3$) Picrate, mp 109.5–110.5 °C
2.	Pyrazole 18 from 14 via 16	$[\alpha]^{29}D$ +19.9° (c 6.47, $CHCl_3$) Picrate, mp 109.5–110 °C

Scheme III



to proceed with retention of the migrating group[8] then it follows that the thermal path [1,5] **14** to **15** also proceeds with retention. Furthermore, we demonstrated the essential thermal nature of this [1,5] rearrangement, **14** to **15**, by observing no change in the rate of this conversion (NMR) in pyridine upon addition of trifluoroacetic acid. An acid-catalyzed process was thereby eliminated.

In summary, we have found a convenient route to certain 4-hydroxyisopyrazoles and studied the stereochemistry of their thermal rearrangement to 2-pyrazolin-4-ones. This stereochemistry of the migrating alkyl group has been shown to be identical with that of an acid-catalyzed [1,2] shift. It follows that the thermal rearrangement of 4-hydroxyisopyrazoles to 2-pyrazolin-4-ones proceeds with retention of configuration in the migrating group.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by Midwest Microlabs Inc., Indianapolis, Ind. Ir spectra were recorded on a Perkin-Elmer Model 700 spectrophotometer. NMR spectra were recorded on a Varian Associates T-60 spectrometer or a Hitachi Perkin-Elmer R-22B instrument. Silica gel for column chromatography was Davison Chemicals grade 950 (60–200 mesh) or Merck silica gel 60, no. 7734.

3-*n*-Butyl-3-hydroxy-2,4-pentanedione (2a). Methyl valerate (9.27 g, 80 mmol) was added dropwise under nitrogen to a cold (−65 °C) solution of MVL (2 equiv) in THF–pentane. After stirring for 0.5 h at −65 °C and 1 h at room temperature, 10% aqueous ammonium chloride (50 ml) was cautiously added dropwise to the cooled (0 °C) solution. The aqueous phase was extracted with ether, and the combined organic layers washed with brine, dried ($MgSO_4$), and evaporated to leave bis enol ether **1a** (15.7 g, 98%). Distillation provided **1a** 13.2 g (82%) as a colorless liquid: bp 57.5–58.0 °C (0.01 mm); ir (film) 3700–3200, 1655, 1625 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 0.67–2.06 (m, 9 H), 2.84 (s, 1 H, exchangeable with D_2O), 3.57 (s, 6 H), 4.12 and 4.38 (AB quartet, 4 H, J_{AB} = 2.5 Hz).

Enol ether **1a** (7.0 g, 35 mmol) was stirred with methanol (40 ml) and 0.1 N HCl (20 ml) for 1.5 h, then diluted with brine (50 ml) and extracted with ether (4 × 30 ml). The combined extracts were washed with water (30 ml), dried ($MgSO_4$), and concentrated. Distillation gave **2a**, 4.97 g (83%), as a colorless liquid: bp 71–74.5 °C (4.5 mm); ir (film) 3550–3250, 1705 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 0.7–1.6 (m, 7 H), 1.8–2.2 (m, 2 H), 2.25 (s, 6 H), 4.68 (s, 1 H, exchangeable with D_2O).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.8; H, 9.37. Found: C, 63.4; H, 9.42.

4-*n*-Butyl-3,5-dimethyl-4-hydroxy-4*H*-pyrazole (3a). To a solution of **2a** (860 mg, 5 mmol) in absolute ethanol (3 ml) at 0 °C was added hydrazine hydrate (99–100%, 262 mg, 5.15 mmol) with stirring. After 0.5 h at 0 °C, the solution was concentrated at 20 °C under reduced pressure to give a clear oil. Benzene (5 ml) was added and removed under reduced pressure. Repetition of this three times gave a waxy solid, which was recrystallized from hexane–dichloromethane to provide white needles of **3a**, 392 mg (47%): mp 93.5–95 °C; NMR ($CDCl_3$) δ 0.83 (br t, 3 H), 1.0–2.0 (m, 6 H), 2.10 (s, 6 H), 6.9 (br s, 1 H). This compound obtained as described was stable in the solid state for several days when stored under nitrogen in the freezer (−20 °C); however, with traces of acid or moisture or when stored at room temperature, decomposition was rapid.

5-*n*-Butyl-3,5-dimethyl-2-pyrazolin-4-one (4a). A sample of **3a** (259 mg) was heated in the melt (bath 120 °C) under nitrogen for 10 min and then cooled. The product was transferred (in 1 ml of pentane) to a microdistillation apparatus and distilled at an oven temperature of 80 °C (0.07 mm) to give a mobile yellow liquid, 255 mg (87%), identified as **4a** by its spectral properties: ir (film) 3300, 1685 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 0.90 (br t, 3 H), 1.0–1.9 (m, 9 H, a 3 H singlet was visible at δ 1.30), 2.06 (s, 3 H), 6.55 (br s, 1 H); uv (EtOH) λ_{max} 330 nm (ε 4800) and 204 (3000), shifted to λ_{max} 357 nm (ε 7000), 335 (6640), and 211 (21 200) upon addition of base (1 N NaOH).

(±)-3-*sec*-Butyl-3-hydroxy-2,4-pentanedione (2b). The bis enol ether **1b** was prepared analogously to **1a** in 93% crude yield, using *dl*-methyl α-methylbutyrate (7.8 g, 67 mmol) as the electrophile: ir (film) 3540, 1650, 1620 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 2.0–0.65 (complex multiplet, 9 H), 2.87 (br s, 1 H), 3.50 (s, 6 H), 4.37, 4.29 (AB quartet, J = 3 Hz, 4 H).

The crude enol ether **1b** was hydrolyzed using aqueous methanolic HCl, and after normal workup gave **2b**, 9.43 g (82%). Distillation afforded 7.15 g (62% based on starting ester) as a water-white liquid: bp 93–96 °C (21 mm); ir (film) 3435, 1705 cm^{-1}; 90-MHz NMR ($CDCl_3$) δ 4.60 (s, 1 H, exchangeable with D_2O), 2.67–2.26 (m, 1 H), 2.23 (s, 6 H), 1.34–0.76 (complex m, 8 H); mass spectrum (70 eV) *m/e* 172 (parent ion).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.8; H, 9.37. Found: C, 63.1; H, 9.63.

(±)-4-*sec*-Butyl-3,5-dimethyl-4-hydroxy-4*H*-pyrazole (3b). Hydrazine hydrate (99–100%, 141 μl, 2.91 mmol) was added dropwise to a cold (−15 °C bath) solution of the hydroxy diketone (500 mg, 2.91 mmol) in absolute MeOH (~750 μl). The reaction mixture was stirred at −15 °C for 0.5 h, and then rotary evaporated (0 °C, 0.2 mm). The white solid remaining was triturated (2 × 4 ml) with pentane to leave white crystalline **3b**. Recrystallization gave white needles, 250 mg (51%): mp 91.5–93 °C; ir (film) 3370–2800, 1601 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 6.9–6.5 (br s, 1 H, exchanges with D_2O), 2.12 (s, 6 H), 1.82–1.45 (m, 1 H), 1.15–0.65 (complex m, 8 H); uv (EtOH) 232 nm (ε 1300).

(±)-5-*sec*-Butyl-3,5-dimethyl-2-pyrazolin-4-one (4b). Thermal reorganization was effected by heating under nitrogen **3b** (1.76 g, 10.5 mmol) in an oil bath at 110 °C for 3 min. Distillation through a Vigreux column (10 cm) gave **4b**, 1.57 g (89%): bp 85–86 °C (1.8–1.9 mm); ir (film) 3320, 1700, 1685 cm^{-1}. The diastereomeric relationships of **4b** may be inferred from the 90-MHz NMR ($CDCl_3$): δ 6.78–6.49 (br s, 1 H, exchangeable), 2.02 (s, 3 H), 1.86–1.45 (complex m, 1 H), 1.27, 1.24 (two singlets diastereomerically related, 3 H total), 1.24–0.73 (complex m, 5 H), 1.01 (d, 3 H, J = 7 Hz); uv (EtOH) λ_{max} 330 nm (ε 3960), 202 (ε 2080), shifted to 356 (5140), 212 (>20 000) upon addition of OH; mass spectrum m/e 168 (parent ion).

3-*tert*-Butyl-3-hydroxy-2,4-pentanedione (2c). The bis enol ether **1c** was obtained crude (20.3 g, 100%) in greater than 95% purity, using methyl pivalate (13.05 ml, 100 mmol) as the electrophile. Hydrolysis was effected with 0.02 N aqueous methanolic HCl to leave after normal workup yellow, crystalline diketone, which was recrystallized from methanol to afford colorless needles of **2c**, 7.93 g. Concentration and cooling of the mother liquors gave additional needles, 1.05 g (total 8.98 g, 52%, based on starting ester): mp 50–52 °C; ir ($CHCl_3$) 3420, 1705 cm^{-1}; 90-MHz NMR ($CDCl_3$) δ 4.78 (s, 1 H, exchanges with D_2O), 2.32 (s, 6 H), 1.07 (s, 9 H); mass spectrum m/e 172 (parent ion). The analytical sample was prepared by two consecutive sublimations at ambient temperature (0.5 mm).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.8; H. 9.37. Found: C, 62.9; H, 9.72.

4-*tert*-Butyl-3,5-dimethyl-4-hydroxy-4*H*-pyrazole (3c). Hydrazine hydrate (99–100% 432 μl, 8.90 mmol) was added dropwise to a cold (0 °C bath) solution of the diketone **2c** (1.53 g, 8.90 mmol) in absolute MeOH (18 ml). The mixture was stirred at 0 °C for 15 min, and 25 °C for 0.5 h, followed by evaporation at 25 °C (2 mm) to leave a waxy yellow solid. Trituration with pentane left **3c**, 740 mg (49%), as white plates: mp 83–93 °C; 90-MHz NMR ($CDCl_3$) δ 6.89–6.67 (br s, 1 H, exchangeable with D_2O), 2.14 (s, 6 H), 1.00 (s, 9 H). A low yield for **3c** results from facile rearrangement to **4c** during isolation.

5-*tert*-Butyl-3,5-dimethyl-2-pyrazolin-4-one (4c). Hydrazine hydrate (99–100%, 288 mg, 5.76 mmol) in MeOH (1 ml) was added dropwise to a cold (0 °C bath) solution of the diketone **2c** (992 mg, 5.76 mmol) in MeOH (8 ml). The solution was stirred at 0 °C for 15 min and 0.5 h at room temperature. Evaporation left a waxy solid which by NMR was partially rearranged material. Thermal reorganization was accomplished upon heating under nitrogen (120 °C bath) for 2 min. On cooling crystalline **4c** (880 mg) separated. **4c** was obtained as beautiful needles, mp 91–94 °C, 457 mg (39%), after three sublimations (100 °C, 760 mm). Starting diketone **2c** tends to cosublime with **4c** leading to difficulty in purification: ir ($CHCl_3$) 3380, 1705, 1685 cm^{-1}; 90-MHz NMR ($CDCl_3$) δ 6.70–6.39 (br s, 1 H, exchanges with D_2O), 2.03 (s, 3 H), 1.26 (s, 3 H), 1.00 (s, 9 H); uv (EtOH) λ_{max} 330 nm (ε 3970).

3-Hydroxy-3-phenylpentane-2,4-dione (2d). The bis enol ether **1d** was obtained from methyl benzoate (6.8 g, 50 mmol) as a colorless oil, 8.2 g (74.5%), after distillation (bp 82–85 °C, 0.02 mm) of the crude material. Enol ether **1d** formed colorless prisms on standing: mp 55.5–59.5 °C; ir ($CHCl_3$) 3550, 1665, 1635 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 3.77 (s, 1 H, exchanges with D_2O), 3.60 (s, 6 H), 4.25 [s, 4 H, the vinyl protons appeared as an AB quartet (4 H), J_{AB} = 2.5 Hz at 4.12, 4.27 when the spectrum was determined in CCl_4], 7.24–7.70 (m, 4 H).

An analytical sample was prepared by recrystallization from hexane, mp 60.5–61 °C.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.32. Found: C, 71.0; H, 7.41.

Hydroxy dione **2d** was obtained in 64% (overall from methyl benzoate) isolated yield by direct hydrolysis (methanol, 0.1 N HCl, 3:1) of crude enol ether **1d**. Alternatively hydrolysis under the same conditions of purified **1d** gave **2d** in 80–85% yield: bp 65–67 °C (0.17 mm); ir (film) 3400, 1710 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 2.30 (s, 6 H), 5.30 (s, 1 H, exchangeable with D_2O), 7.27–7.64 (m, 5 H).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.7; H, 6.29. Found: C, 69.3; H, 6.60.

This compound was a colorless liquid when freshly distilled, but rapidly developed a yellow color on storage with no change in spectral properties.

3,5-Dimethyl-4-hydroxy-4-phenyl-4*H*-pyrazole (3d). To a cold (10 °C) solution of **2d** (9.60 g, 50 mmol) in absolute ethanol (65 ml) was added dropwise hydrazine hydrate (99–100%, 2.5 g, 50 mmol) with stirring. A white precipitate appeared which after 0.5 h at 0 °C was collected and washed with a little cold ethanol to give crude **3d**, 8.35 g, mp 158–159 °C. Recrystallization from benzene containing a trace of ethanol (2%, 120 ml) provided colorless needles, 5.35 g (57%), of **3d**: mp 162–163 °C; ir ($CHCl_3$) 3500–2900, 1603 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 2.03 (s, 6 H), 7.33 (br s, 5 H), 7.73 (br s, 1 H, exchangeable); NMR (Me_2SO-d_6) δ 1.83 (s, 6 H), 6.80 (br s, 1 H), 6.95–7.50 (m, 5 H); mass spectrum (70 eV) m/e 188 (parent ion); uv (EtOH) λ_{max} 212 nm (ε 4000) with broad shoulder.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.42. Found: C, 69.7; H, 6.54.

3,5-Dimethyl-5-phenyl-2-pyrazolin-4-one (4d). Isopyrazole **3d** (1.1 g) was heated under nitrogen in the melt (175 °C bath) for 60 s. Upon cooling, yellow needles were obtained, mp 84–86 °. Recrystallization from hexane–dichloromethane gave **4d** as pale yellow prisms, 680 mg (62%): mp 86–88 °C; ir (film) 3300, 1710, 1690 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 1.67 (s, 3 H), 2.06 (s, 3 H), 6.9 (br s, 1 H), 7.35 (s, 5 H); uv (EtOH) λ_{max} 331 nm (ε 5100), 207 (10 100) shifted to 366 (7130), 350 (6290), and 211 (16 900) upon addition of base (1 N NaOH).

(+)-Methyl α-Methylbutyrate. Ethereal diazomethane was added in portions to (+)-methyl-α-methylbutyric acid[9] (5.23 g, 51 mmol) in Et_2O (75 ml), until the evolution of nitrogen had ceased. The ethereal solution was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated at room temperature to leave (+)-methyl α-methylbutyrate. Distillation afforded 3.43 g (58%), bp 114–117 °C, $[\alpha]^{25}D$ +21.04° (c 5.5, $CHCl_3$) [lit.[10] bp 108–109 °C (751 mm) $[\alpha]^{22}D$ +23.2° (neat)].

(+)-3-*sec*-Butyl-3-hydroxy-2,4-pentanedione (2e). The bis enol ether **1e**, 4.9 g (88% crude), was obtained from (+)-methyl α-methylbutyrate (3.24 g, 28 mmol). Hydrolysis of the enol ether was effected as above for **1b** to give **2e**, 2.68 g (66% based on starting ester), after distillation, bp 91–92 °C (20 mm), $[\alpha]^{26}D$ +16.7° (c 15.5, $CHCl_3$).

(−)-4-*sec*-Butyl-3,4-dimethyl-4-hydroxy-4*H*-pyrazole (3e). The optically active isopyrazole was prepared in the same manner as in the racemic series, using **2e** (2.44 g, 14.2 mmol) and hydrazine hydrate (689 μl, 14.2 mmol) to give **3e** upon trituration, 2.21 g (93%): mp 99–100 °C: $[\alpha]^{25}D$ −18.4° (c 31.4, $CHCl_3$); ir ($CHCl_3$) 3500–3650, 1601 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 2.12 (s, 6 H). 1.78–1.35 (complex m, 1 H), 1.12–0.58 (complex m, 8 H).

(−)-5-*sec*-Butyl-3,5-dimethyl-2-pyrazolin-4-one (4e). Rearrangement of **3e** (1.36 g, 8.1 mmol) was effected as in the racemic series to give **4e**, 1.25 g (92%), as a yellow liquid after distillation. The pyrazolin-4-one solidifies on standing and may be sublimed at room temperature (0.1 mm), giving white needles, mp 61–62.5 °C, $[\alpha]^{25}D$ −38.5° (c 79.4, $CHCl_3$).

5-*tert*-Butyl-3-ethoxymethyl-5-methyl-2-pyrazolin-4-one (9). *tert*-Butyl hypochlorite (228 μl, 1.9 mmol) was added to a cold (−78 °C bath) solution of the pyrazolone **4c** (320 mg, 1.90 mmol) in anhydrous ether (20 ml). The clear solution became cloudy and was stirred for 0.5 h at −78 °C, warmed to room temperature, and stirred for 2 h. Evaporation left a yellow oil: ir (film) 1760, 1380 cm^{-1}; 60-MHz NMR ($CDCl_3$) 1.96 (s, 3 H), 1.55 (s, 3 H), 1.20 (s, 9 H).

The yellow oil was stirred at room temperature under nitrogen with excess sodium ethoxide in ethanol (50 ml) for 2 h. Acidification and extraction with Et_2O gave upon evaporation of the dried solution a yellow oil, 80 mg.

Preparative TLC (elution with 30% EtOAc in hexane) gave a fluorescent band. Extraction with chloroform and evaporation gave yellow crystalline **9**: mp 88–89 °C; 90-MHz NMR ($CDCl_3$) δ 7.07–6.82 (br s, 1 H, exchangeable with D_2O), 4.26 (s, 2 H), 3.54 (q, 2 H, J = 7 Hz), 1.33–0.88 (complex m, 15 H with a 9 H s visible at 0.98); ir ($CHCl_3$) 3400, 1705, 1685 cm^{-1}.

3,5-Dimethylpyrazole 12 from $LiAlH_4$ Reduction. A solution of the *sec*-butylpyrazolinone **4b** (500 mg, 2.98 mmol) in THF (8 ml) was refluxed under nitrogen with excess $LiAlH_4$ (226 mg, 5.95 mmol) for 12 h and then quenched by careful sequential addition of H_2O (23 μl), 10% KOH (700 μl), and H_2O (1 ml). The white precipitated lithium salts were filtered, and the resulting organic solution washed with brine, dried (Na_2SO_4), and evaporated. The resultant yellow oil was chromatographed on silica gel [elution with PhH/EtOAc (1:1)] to give 3,5 dimethylpyrazole as white needles, 160 mg (50%), mp 100–102 °C (lit.[11] 107–108 °C). The *tert*-butylpyrazolinone **4c** similarly gave

3,5-dimethylpyrazole **12** in 60% yield, mp 99–101 °C after chromatography.

(+)-4-*sec*-Butyl-3,5-dimethylpyrazole (16). A suspension of hydroxyisopyrazole **3e** (752 mg, 4.48 mmol) and excess $LiAlH_4$ (540 mg, 14.2 mmol) in ether (100 ml) was stirred at room temperature under nitrogen for 9 h and then quenched by sequential dropwise addition of H_2O (0.5 ml), 10% aqueous sodium hydroxide (10.5 ml), and H_2O (1.5 ml). Filtration, washing the ethereal filtrate with brine, drying (Na_2SO_4), and evaporation left a clear, colorless liquid, 546 mg (80% crude). The compound solidified on standing to form needle clusters: mp 38–39 °C; ir (film) 3600–2800, 1585, 1465, 1390 cm^{-1}; uv (EtOH) λ_{max} 224 nm (ϵ 3410); 90-MHz NMR ($CDCl_3$) δ 7.28–6.93 (br s, 1 H, exchanges), 2.76–2.27 (complex m, 1 H), 2.21 (s, 6 H), 1.78–1.33 (m, 2 H), 1.23 (d, 3 H, J = 7 Hz), 0.82 (t, 3 H, J = 7 Hz); $[\alpha]^{25}D$ +19.80° (c 4.21, $CHCl_3$); mol wt 152.13163 (calcd for $C_9H_{16}N_2$, 152.13134).

(+)-4-*sec*-Butyl-1,3,5-trimethylpyrazole (18). Washed NaH (86 mg, 3.59 mmol, prepared by repeated washing and centrifugation of a mineral oil suspension with ether) suspended in THF (20 ml) was added via syringe to a solution of the optically active pyrazole **16** (546 mg, 3.59 mmol) in THF (15 ml). The mixture was refluxed under nitrogen overnight, cooled to room temperature, and treated with MeI (223 μl, 3.59 mmol) with stirring at room temperature for 4 h. The precipitated NaI was filtered; the filtrate washed with ether, and the combined organics were diluted with chloroform, washed with brine, dried (Na_2SO_4), and evaporated to leave 349 mg of crude **18**.

Preparative TLC elution with chloroform gave a yellow band at R_f ~0.5. Extraction with chloroform and evaporation gave **18**, 321 mg (54%), as a pale yellow liquid: ir (film) 1570, 1470, 1390, 1310, 1010 cm^{-1}; 90-MHz NMR ($CDCl_3$) δ 3.67 (s, 3 H), 2.71–2.27 (m, 1 H), 1.77–1.40 (m, 2 H), 1.20 (d, 3 H, J = 7 Hz), 0.82 (t, 3 H, J = 7 Hz); uv (EtOH) λ_{max} 230 nm (ϵ 4360); $[\alpha]^{29}D$ + 19.9° (c 64.7, $CHCl_3$); mcl wt 166.14557 (calcd for $C_{10}H_{18}N_2$, 166.14699).

18 also forms a picrate as beautiful yellow needles from ethanol, mp 109.5–110 °C.

(−)-5-*sec*-Butyl-1,3,5-trimethyl-2-pyrazolin-4-one (17). A suspension of washed KH (289 mg, 7.23 mmol, prepared by repeated washing and centrifugation of KH in oil suspension with ether) in THF (23 ml) was added via syringe under nitrogen to a solution of the pyrazolin-4-one **1e** (1.17 g, 6.96 mmol) in THF (25 ml) at room temperature. When the visible hydrogen evolution had ceased, the reaction mixture was brought to reflux for 20 min, cooled to room temperature, and treated with excess MeI (1.73 ml, 27.8 mmol) for 4 h. Filtration of the potassium iodide and evaporation left a yellow oil (1.22 g) which showed 60% starting material by NMR. The mixture was refluxed further with additional KH (263 mg, 6.6 mmol) for 1 h, treated with MeI (1.64 ml, 21 mmol), and stirred for 5 h at room temperature. Filtration of the precipitated potassium iodide and evaporation left 1.18 g of crude **17**. A solution of crude **17** in dichloromethane was washed with brine, dried ($MgSO_4$), and evaporated.

Distillation gave a fraction, 897 mg, bp 84–97 °C (2.2 mm), which was redistilled to give **17**, 403 mg (32%): bp 81–84 °C (2.1–2.4 mm); ir (film) 1700, 1682 cm^{-1}; 90-MHz NMR ($CDCl_3$) δ 3.23 (s, 3 H), 1.98 (s, 3 H), 1.23 (s, 3 H), 1.86–0.82 (complex m, 9 H); uv (EtOH) λ_{max} 367 nm (ϵ 5740) with large end absorption ~200 nm; $[\alpha]^{25}D$ −16.6° (c 4.40, $CHCl_3$). Racemic **17** was prepared similarly in 51% yield: bp 78–79.5 °C (2.5 mm); mass spectrum *m/e* 182 (parent ion).

(+)-5-*sec*-Butyl-4-hydroxy-1,3,5-trimethylpyrazoline (19). The methylated pyrazolin-4-one **17** (403 mg, 2.21 mmol) and sodium borohydride (85 mg, 2.21 mmol) were refluxed in ethanol (15 ml) for 2 h. Evaporation of the ethanol left a white solid which was partitioned between H_2O and ether. The aqueous phase was extracted with ether, and the combined ether extracts washed with brine, dried (Na_2SO_4), and evaporated to leave 326 mg of a colorless liquid. Preparative thin layer chromatography (elution with ethyl acetate) gave **19** as a clear oil, 245 mg (60%): $[\alpha]^{28}D$ +5.14° (c 6.17 $CHCl_3$); ir (film) 3650–2800, 1625, 1475, 1385, 1139, 1078 cm^{-1}. The presence of a stereoisomeric mixture resulting from reduction at either face of the molecule may be inferred from the NMR spectrum: 90-MHz NMR ($CDCl_3$) δ 4.56, 4.06 (two broad singlets, 1 H total), 2.72, 2.67 (two singlets, 3 H total, the signal at 2.72 show a 2-Hz long-range coupling to the carbinol proton), 2.40 (br s, exchangeable), 2.01, 1.91 (two singlets, 3 H total, the signal at 1.91 shows a long-range 2-Hz coupling to the carbinol proton), 1.91–0.81 (complex multiplet, 12 H).

(+)-4-*sec*-Butyl-1,3,5-trimethylpyrazole (18). Optically active **19** (190 mg, 1.03 mmol) in EtOH (5 ml) was refluxed with 6 drops of concentrated hydrochloric acid for 0.75 h. The cooled reaction mixture was diluted with H_2O (20 ml), neutralized with sodium bicarbonate to pH 7, extracted with chloroform, dried (Na_2SO_4), and evaporated to leave crude **18**, 144 mg (84%), $[\alpha]^{28}D$ +20.2° (c 4.35, $CHCl_3$). The ir and NMR spectra were superimposable upon the spectra of **1E** obtained via path B.

Tetrasubstituted **18** gave a yellow crystalline picrate as needles from ethanol, mp 109.5–110.5 °C. An admixture with the picrate derived via **16** melted at 109–109.8 °C.

An analytical sample was prepared by repeated recrystallization from ethanol, mp 109.5–109.8 °C.

Anal. Calcd for $C_{16}H_{21}N_5O_7$: C, 48.6; H, 5.35; N, 17.7. Found: C, 48.3; H, 5.47; N, 17.6.

NMR Kinetics. An approximate assessment of the rate of the thermal rearrangement was determined in pyridine d_5 on **3b** at 89 °C. The extent of rearrangement was determined by integration of the C-5 methyl group.

3b (38 mg) in pyridine-d_5 (450 μl) was heated at 89 °C in the probe of a 90-MHz spectrometer. After 60 min integration showed 87% rearrangement to the pyrazolin-4-one **4b**.

3b (37 mg) in pyridine-d_5 (450 μl) containing CF_3CO_2H (5 μl) was heated at the same temperature as before. After 26 min integration showed 50% rearrangement and after 65 min the compound appeared 91% rearranged to pyrazolin-4-one **4b**.

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Registry No.—**1a**, 54123-69-2; **1b**, 59434-24-1; **1c**, 59434-25-2; **1d**, 54123-68-1; **1e**, 59434-26-3; **2a**, 54123-79-4; **2b**, 59434-27-4; **2c**, 59434-28-5; **2d**, 54123-78-3; **2e**, 59434-29-6; **3a**, 59434-30-9; **3b**, 59434-31-0; **3c**, 59434-32-1; **3d**, 59434-33-2; **3e**, 59434-34-3; **4a**, 59434-35-4; **4b**, 59434-36-5; **4c**, 59434-37-6; **4d**, 59434-38-7; **9**, 59448-78-1; **12**, 67-51-6; **16**, 59434-39-8; **17**, 59434-40-1; **18**, 59434-41-2; **18** picrate, 59434-42-3; **19**, 59434-43-4; methyl valerate, 624-24-8; MVL, 42722-80-5; hydrazine hydrate, 10217-52-4; *dl*-methyl α-methylbutyrate, 53955-81-0; methyl pivalate, 598-98-1; methyl benzoate, 93-58-3; (+)-methyl α-methylbutyrate, 10307-60-5.

References and Notes

(1) J. E. Baldwin, G. A. Höfle, and O. W. Lever, Jr., *J. Am. Chem. Soc.*, **96**, 7125 (1974).
(2) J. E. Baldwin, R. K. Boeckman, Jr., K. J. Bruza, and O. W. Lever, Jr., *J. Chem. Soc., Chem. Commun.*, 519 (1975).
(3) C. Heathcock and C. G. Chavdarian, *J. Am. Chem. Soc.*, **97**, 3822 (1975).
(4) J. van Alphen, *Recl. Trav. Chim. Pays-Bas.*, **62**, 485 (1943).
(5) R. Huttel, K. Franke, H. Martin, and J. Riedl, *Chem. Ber.*, 93, 1433 (1960).
(6) R. Bauwers, J. Elguero, R. Jaquier, and G. Tarrago, *Tetrahedron Lett.*, 3781 (1973).
(7) R. B. Woodward and R. Hoffman, "The Conservation of Orbital Symmetry", Academic Press, New York, N.Y., 1970.
(8) (a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", 2d ed, Cornell University Press, Ithaca, N.Y., 1969; (b) P. de Mayo, Ed., "Molecular Rearrangements", Part 1, Interscience, New York, N.Y., 1967; (c) J. Lane and E. Wallis, *J. Org. Chem.*, **6**, 443 (1941); (d) J. Lane and E. Wallis, *J. Am. Chem. Soc.*, **63**, 1674 (1941); (e) C. Arcus and J. Kenyan, *J. Chem. Soc.*, 916 (1939); (f) A. Campbell and J. Kenyan, *ibid.*, 25 (1946).
(9) L. Listowsky, G. Avigad, and S. Englard, *J. Org. Chem.*, **35**, 1080 (1970).
(10) G. Odham, *Ark. Kemi*, **20**, 507 (1962).
(11) I. Heilbron, Ed., "Dictionary of Organic Compounds", Vol. 2, Oxford University Press, London, 1965.

Acylation of Vicinal Dianions. Further Observations Concerning Proton Transfer and Rearrangements during Reaction

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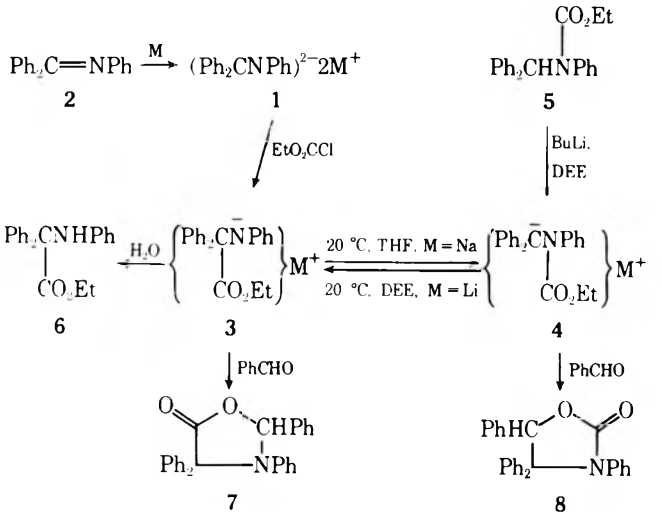
The dianion **1** formed by reducing benzophenone anil with alkali metals is used as a model compound in examining reactions involving acyl chlorides and a series of aliphatic chloro esters. The previously reported C → N rearrangement of an ethoxycarbonyl group derived from ethyl chloroformate is shown to be reversible and dependent on the cation involved. A similar behavior of 2-chloroethyl chloroformate is also described. Successful alkylations of the dianion by ethyl chloroacetate and ethyl 3-chloropropionate are obtained. However, with ethyl 4-chlorobutyrate and with propionyl chloride, enolate anion formation becomes a serious side reaction forming, in the case of the chloro ester, a complex series of products.

The dianionic species, **1**, formed by the reductive metalation of benzophenone anil (**2**) with alkali metals has served as a model compound in studying the chemical behavior of such anions. Recently, it was reported[1] that preferential acylation occurred at the benzhydrylic carbon of **1** to produce the functionalized monoanion **3** (Scheme I). This anion was also

Scheme I. Formation and Reactions of the Ethoxycarbonyl Monoanions



observed[1] to rearrange rapidly in tetrahydrofuran (THF) to the isomeric anion **4** with sodium or potassium as counterion. In contrast, with lithium as counterion and diethyl ether as solvent, no rearrangement of **3** was detected. In the present report further observations on the acylation of **1** with acid chlorides and with esters are described.

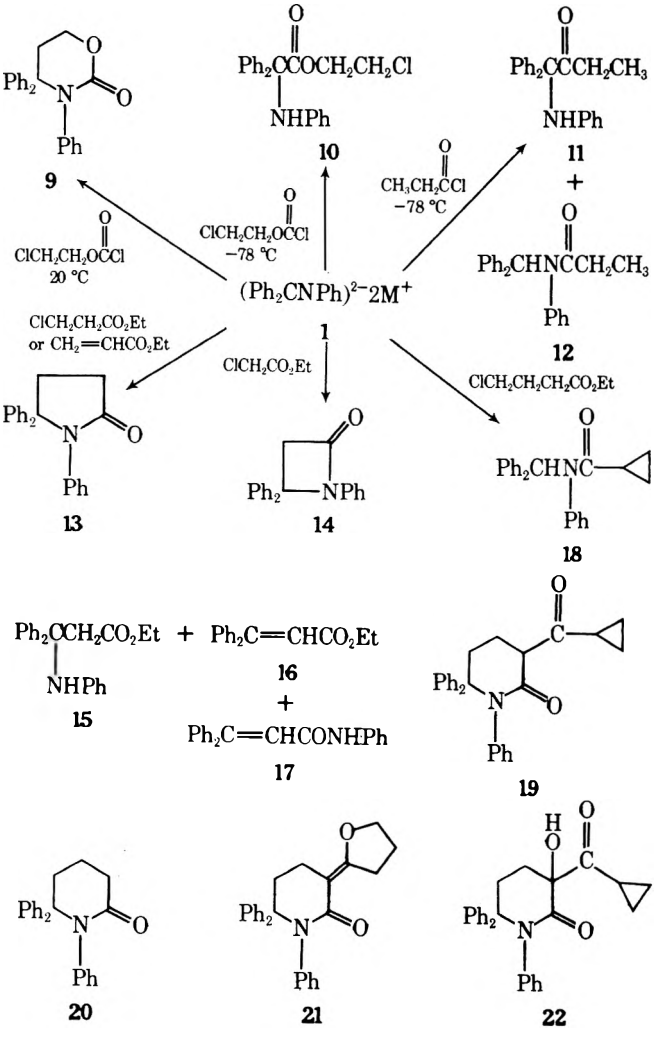
Results and Discussion

The stability of anion **3** (M = Li) in diethyl ether[1] prompted the synthesis of its isomer **4** (M = Li) by deprotonation of ethyl *N*-benzhydryl-*N*-phenylcarbamate (**5**) with *n*-butyllithium. Reaction of the anionic product so formed with benzaldehyde produced **7** rather than the expected cyclic urethane, **8**, which was obtained from benzaldehyde and **4** (M = Na) in THF. The structure **7** was assigned on the basis of an ester carbonyl absorption band in the infrared spectrum and on the hydrolysis of **7** in the presence of 2,4-dinitrophenylhydrazine which produced benzaldehyde 2,4-dinitrophenylhydrazone and α-anilinodiphenylacetic acid. The rearrangement of anion **4** (M = Li) to **3** (M = Li) prior to its reaction with benzaldehyde was confirmed by repeating the reaction of **5** and *n*-butyllithium and protonating the anionic product to give **6**, the rearranged *C*-ethoxycarbonyl compound.

This interesting interconversion of anions **3** and **4**, seemingly dependent on the associated alkali metal cations, prompted an examination of the reactivity of **1** toward bifunctional reagents in which one functional group served as the acylating agent.

With 2-chloroethyl chloroformate it was expected that the cation effect just described might lead to different products. However, with either lithium or sodium as the cation, the same product, 3,4,4-triphenylperhydro-1,3-oxazin-2-one (**9**), (Scheme II) was formed. By quenching the reaction at −78 °C

Scheme II. Reactions with Bifunctional Reagents



after a few minutes, a good yield of 2-chloroethyl α-anilinodiphenylacetate (**10**) was obtained, establishing again that the initial stage of the reaction was acylation at the benzhydrylic carbon.

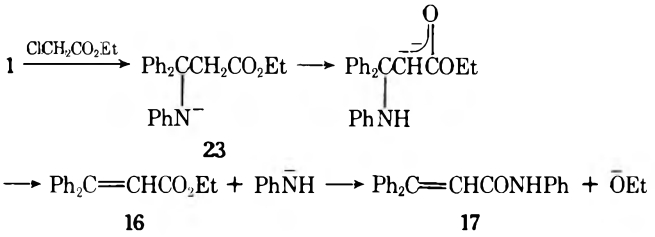
Evidently anions of the type **3** and **4** are in equilibrium. In the case of the reaction with 2-chloroethyl chloroformate, the monoanion analogous to **4** is intramolecularly alkylated by the 2-chloroethyl group forming **9** and is thus removed from the equilibrium. However, the monoanion analogous to **3** undergoes rearrangement faster than it is alkylated.

The successful C-acylation of dianion **1** by 2-chloroethyl chloroformate prompted a similar experiment with propionyl chloride. While a small yield of the C-acylated product **11** was isolated, the chief product was *N*-benzhydryl-*N*-phenylpropionamide (**12**). Evidently the basicity of the dianion **1** resulted chiefly in proton abstraction from the propionyl chloride by the carbanionic site of **1** forming methylketene.[2] Subsequent reaction of the methylketene produced the observed propionamide.

The ethyl esters of chloroacetic, 3-chloropropionic, and 4-chlorobutyric acid were examined to assess the relative amounts of acylation vs. alkylation. Generally, these reactions were accompanied by enolate anion formation as a complicating side reaction.

The dianion **1** (M = Li) reacted smoothly with ethyl chloroacetate to produce 1,4,4-triphenyl-2-azetidinone (**14**) in good yield. However, with sodium or potassium as counterions, the reaction was much more complex and proved to be time dependent. At short reaction times and low temperatures, both the β-lactam **14** and the alkylation product **13** were isolated. At longer reaction times, substantial amounts of ethyl 3,3-diphenylacrylate (**16**) were detected and at still longer reaction times the amount of **16** decreased while *N*,3,3-triphenylacrylamide (**17**) was isolated.

On the basis of this time-dependent sequence of products, it is suggested that the reactive[3] α-chloro ester rapidly alkylates dianion **1** to produce **23** which is converted to its enolate



anion when sodium or potassium are present as counterions. Cyclization to the β-lactam is prevented and a slow reverse Michael reaction occurs to produce the acrylic ester **16** and, by a slower aminolysis reaction with aniline, the anilide **17** is formed. The success of the reaction with lithium as counterion in forming the β-lactam **14** reflects a slower rate of enolate anion formation relative to acylation at the amine anionic site.

The complete disappearance of the β-lactam **14** which was formed concomitantly with **15** in experiments of short duration is due to base-induced ring opening of **14** to the anilide **17**. This reaction was demonstrated to occur with *n*-butyllithium as the base.

Ethyl 3-chloropropionate reacted rapidly with **1** at −78 °C to produce 1,5,5-triphenyl-2-pyrrolidone (**13**). Dehydrohalogenation followed by a Michael addition to the ethyl acrylate so formed cannot explain the rapidity of the reaction since such a dehydrohalogenation would result in protonation of the benzhydrylic carbon of **1** and prevent formation of the observed product. However, ethyl acrylate did react with the dianion **1** to produce the pyrrolidone **13** showing that Michael addition reactions are possible with such anionic species as **1**.

Ethyl 4-chlorobutyrate produced two compounds **18** and **19** in addition to a considerable quantity of *N*-benzhydrylaniline. Identification of **18** was based on its NMR spectrum and by synthesis of an authentic sample. The second compound was assigned structure **19** on the basis of its ir, NMR, and mass spectra. Both the keto and enol forms of **19** were detected by characteristic resonances in the NMR spectrum.

The large amount of *N*-benzhydrylaniline indicated that enolate anion formation was proceeding much faster than alkylation. Intramolecular alkylation of the enolate anion formed from ethyl 4-chlorobutyrate is known to occur rapidly[4] and produce ethyl cyclopropanecarboxylate. By terminating an experiment after a few minutes reaction at −78 °C, the rapid formation of ethyl cyclopropanecarboxylate was demonstrated. In experiments of longer duration, this ester reacted with dianion **1** or its monoprotonated derivative to give **18**.

The formation of **19** demonstrated that some alkylation proceeded competitively with enolate anion formation. After cyclization to the piperidone **20** a Claisen condensation with the ethyl cyclopropanecarboxylate generates **19**.

In an attempt to reduce the extent of enolate anion formation, the dianion **1** (M = Li) was used. Indeed, the amount of *N*-benzhydrylaniline was reduced and 1,6,6-triphenyl-2-piperidone (**20**) was isolated as well as the previously isolated **18** and **19**. However, the reaction mixture was rather complex with two additional products **21** and **22** being detected. Presumably **21** arose by Claisen condensation of **20** and ethyl 4-chlorobutyrate followed by intramolecular O-alkylation of the enolate anion of this condensation product. The minor product, **22**, probably arose by oxidation[5] of the enolate anion of **19** during isolation.

In summary, the results described here indicate that those dianions formed by reductive metalation of azomethines are more versatile synthetically than their hydrocarbon analogues. With reagents containing labile protons, proton transfer is an interfering reaction but some measure of control is available. In particular, with lithium as the counterion and/or with reagents of sufficient reactivity (e.g., ethyl chloroacetate or ethyl 3-chloropropionate) successful reactions are effected. The reversible migration of ethoxycarbonyl groups which has been described earlier and is elaborated upon here is also a reaction with possibilities that bear further exploration.

Experimental Section

Melting points were measured in a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-10 spectrometer and NMR spectra were recorded on a Varian T-60 spectrometer in deuteriochloroform (unless otherwise specified) with chemical shifts reported in δ units downfield from internal tetramethylsilane. Mass spectra were determined with an AEI MS-30 double beam double focusing mass spectrometer at 70 eV with perfluorokerosene in the reference beam. Vapor phase chromatography (VPC) was performed on a Varian 1520 instrument with flame ionization detectors. Analyses were performed by MHW Laboratories, Garden City, Mich.

Unless otherwise specified, reaction products were isolated by diluting the reaction mixture with water, extracting with ether, drying the extract with magnesium sulfate, and concentrating on a rotary evaporator. Column chromatography of the crude products was accomplished on 0.05–0.20 mm silica gel (E. Merck) using hexane–25% benzene as solvent except where otherwise specified.

The preparation of dianion **1** from benzophenone anil has been described[6] elsewhere.

***N*,3,3-Triphenylacrylamide (17)** was prepared by the dehydration[7] of phenyl 3-hydroxy-3,3-diphenylpropionamide, mp 134–135 °C (reported 136–137 °C).

Preparation of 3,4,4,5-Tetraphenyl-1,3-oxazolid-2-one (8). The monoanion **4** (M = Na) was prepared as previously described[1] and treated with 1.1 g (0.01 mol) of benzaldehyde at 20 °C. After 12 h the reaction product (3.7 g) was isolated and chromatographed to give 2.7 g of crude **8** (69%), mp 210–215 °C. Recrystallization from ethanol

gave an analytical sample: mp 216–218 °C; ir (KBr) 1750 (C=O), 1370 (C–O), 1600, 1500, 760, 720, 700, 690 cm^{-1}; NMR δ 6.47 (s, 1, PhCH), 6.8–7.8 (m, 20, aromatic H).

Anal. Calcd for $C_{27}H_{21}NO_2$: C, 82.84; H, 5.41; N, 3.58. Found: C, 82.62; H, 5.32; N, 3.34.

Acylation of 4 with 1.2 g (0.01 mmol) of dimethylcarbamoyl chloride followed by 1.1 g (0.01 mol) of benzaldehyde also produced 8 although in lower yield (25%).

Preparation of 2,3,4,4-Tetraphenyl-1,3-oxazolid-5-one (7). *N*-Ethoxycarbonyl-*N*-benzhydrylaniline (**5**, 207 mg, 0.63 mmol) was dissolved in 40 ml of anhydrous diethyl ether, cooled to −78 °C, and treated with 0.32 ml of a 2 M solution of *n*-butyllithium in hexane (0.64 mmol). After 15 min the yellow solution was warmed to 20 °C whereupon it became reddish brown, and after 3 h, the solution was treated with ethanol. Analysis of the crude product (198 mg) by VPC (10 ft × 0.125 in. column of 3% SE-52 on Chromosorb W at 220 °C) showed this to consist of 7% of the starting material **5** and 93% of the rearrangement product ethyl α-anilinodiphenylacetate (**6**). Crystallization of the crude product from ethanol gave 130 mg (63%) of **6**, mp 111–114 °C, mixture melting point was undepressed.

Treatment of the anion with 75 mg (0.71 mmol) of benzaldehyde dissolved in 1 ml of ether led to slow formation of a precipitate. The crude product was recrystallized from ethanol giving 127 mg (52%) of **7**: mp 131–132 °C dec; ir (KBr) 1790 (C=O), 1610, 1500, 1310, 1200 (broad), 1060, 740, 690 cm^{-1}; NMR δ 6.4–8.0 (m, aromatic H and benzylic).

Anal. Calcd for $C_{27}H_{21}NO_2$: C, 82.83; H, 5.42; N, 3.58. Found: C, 82.71; H, 5.43; N, 3.37.

Hydrolysis of 2,3,4,4-Tetraphenyl-1,3-oxazolid-5-one (7). A solution of 200 mg (0.51 mmol) of **7** and 109 mg (0.55 mmol) of 2,4-dinitrophenylhydrazine in 20 ml of ethanol was treated with 0.5 ml of concentrated sulfuric acid and refluxed for 1 h. Within a few minutes a precipitate formed. The mixture was cooled and filtered and the solid washed with ethanol to give 132 mg (93%) of benzaldehyde 2,4-dinitrophenylhydrazone, mp 238–241 °C, mmp with an authentic sample 238–242 °C.

The ethanol filtrate was diluted with water and extracted with ether to give 173 mg of material, mp 160–165 °C. This was dissolved in the minimum amount of benzene and extracted with dilute sodium hydroxide solution; the alkaline extract was acidified and the precipitate filtered off, washed with water, and dried to give 93 mg (60%) of α-anilinodiphenylacetic acid, mp 174–178 °C dec, mmp with an authentic sample 175–177 °C dec,[8] and the ir spectra (KBr) were identical.

Reaction of Dianion 1 with Chloroethyl Chloroformate. Preparation of 3,4,4-Triphenylperhydro-1,3-oxazin-2-one (9) and 2-Chloroethyl α-Anilinodiphenylacetate (10). A solution of **1** (0.01 mol, M = Na) in THF was treated at −78 °C with 1.4 g (0.01 mol) of chloroethyl chloroformate. After warming to 20 °C, the reaction product (2.94 g) was isolated and triturated with ether to give 2.21 g (67%) of **9**, mp 228–232 °C. Recrystallization from benzene gave an analytical sample: mp 230–232 °C; ir (Nujol) 1690 (C=O), 1410, 1300 (C–O), 765, 750, 700 cm^{-1}; NMR δ 2.83 (t, J = 6 Hz, 2) and 4.10 (t, J = 6 Hz, 2) (CH_2CH_2), 6.93 (s, 5, NPh), 7.23 (s, 10, CPh_2).

Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.41; H, 5.84; N, 4.16.

A repetition of this reaction with **1** (0.01 mol, M = Li) gave 2.89 g (88%) of **9**, mp 228–231 °C.

The introduction of 2-chloroethyl chloroformate to the solution of the dianion **1** at −78 °C was accompanied by an immediate color change from opaque dark red to a translucent red orange. If the solution (0.01 mol of **1**, M = Li) after 15 min at −78 °C was treated with 2 ml of water, the crude product (3.73 g) was found to have mp 107–114 °C and differed markedly by TLC from **9**. Recrystallization from 80–100 °C petroleum ether–benzene (4:1) gave 2.62 g of **10**, mp 122–124.5 °C. Concentration of the filtrate to ⅓ volume gave an oil which slowly crystallized. Recrystallization of this from 80–100 °C petroleum ether gave an additional 0.43 g of **10**, mp 120–122 °C (combined yield 83%).

The analytical sample had mp 124–126 °C; ir (Nujol) 3420 (NH), 1740 (C=O), 1600, 1510, 1240, 1170, 750, 690 cm^{-1}; NMR δ 3.33 (t, J = 6 Hz, 2, CH_2Cl), 4.32 (t, J = 6 Hz, 2, CH_2O), 5.2 (broad s, 1, NH), 6.4–7.7 (m, 15, aromatic H); mass spectrum m/e (rel intensity) 367 (M^+, ^{37}Cl, 0.6), 365 (M^+, ^{35}Cl, 1.7), 259 (20), 258 (100), 180 (11), 165 (11).

Anal. Calcd for $C_{22}H_{20}O_2NCl$: C, 72.21; H, 5.52; N, 3.83; Cl, 9.69. Found: C, 72.08; H, 5.49; N, 3.82; Cl, 9.87.

Reaction of Dianion 1 with Propionyl Chloride. The dianion **1** (0.01 mol, M = Li) in tetrahydrofuran was treated at −78 °C with 0.93 g (0.01 mol) of propionyl chloride. After 20 min reaction, the solution was treated with 3 ml of methanol, warmed to 20 °C, and the reaction products isolated.

Chromatography of the reaction products (3.12 g) using 1:1 benzene–30–60 °C petroleum ether graded through benzene to 3:1 benzene–diethyl ether gave in order of elution 0.45 g (17%) of *N*-benzhydrylaniline, 0.24 g (8%) of 1-anilino-1,1-diphenyl-2-butanone (**11**), 0.27 g (11%) of benzophenone anil, 0.16 g of an unidentified compound, and 1.36 g (43%) of *N*-benzhydryl-*N*-phenylpropionamide (**12**).

The impure **11** was recrystallized twice from methanol to give an analytical sample: mp 112–113 °C; ir (CCl_4) 3400 (NH), 1720 (C=O), 1605, 1505, 700, 670 cm^{-1}; NMR (CCl_4) δ 0.90 (t, 3, J = 7 Hz, CH_2CH_3), 2.41 (q, 2, J = 7 Hz, CH_2CH_3), 5.78 (s, 1, NH), 6.2–7.7 (m, 15, aromatic H); mass spectrum m/e (rel intensity) 259 (20), 258 (100, $M^+ - C_3H_5O$), 180 (15), 165 (10), 77 (62).

Anal. Calcd for $C_{22}H_{21}NO$: C, 83.77; H, 6.71; N, 4.44. Found: C, 84.00; H, 6.81; N, 4.40.

The propionamide **12** was a noncrystallizable viscous oil and was identified by comparison of its spectral properties with those of an authentic sample prepared from *N*-benzhydrylaniline and propionyl chloride: ir (CCl_4) 1670 (C=O), 1600, 1500, 1380, 1250, 700 cm^{-1}; NMR (CCl_4) δ 1.05 (t, 3, J = 8 Hz, CH_2CH_3), 2.03 (q, 2, J = 8 Hz, CH_2CH_3), 6.6–7.4 (m, 16, $CHPh_2$).

Reaction of Dianion 1 with Ethyl 3-Chloropropionate and Ethyl Acrylate. Preparation of 1,5,5-Triphenyl-2-pyrrolidone (13). The dianion **1** (0.01 mol, M = Na) was treated with 1.36 g (0.01 mol) of ethyl 3-chloropropionate at −78 °C whereupon rapid decolorization occurred. The crude product was triturated with ether giving 2.3 g (73%) of the insoluble 1,5,5-triphenyl-2-pyrrolidone (**13**), mp 179–183 °C. An analytical sample, obtained by recrystallization from 80–100 °C petroleum ether, had mp 182.5–184.5 °C; ir (CCl_4) 1710 (C=O), 1500, 1340 (C–N), 690 cm^{-1}; NMR δ 2.53 and 2.77 (two t, J = 5 Hz, 4, CH_2CH_2), 7.07 (s, 5, NPh), 7.1–7.6 (m, 10, CPh_2).

Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.12; H, 6.32; N, 4.29.

A repetition of the above experiment with 1.0 g (0.01 mol) of ethyl acrylate required warming to 20 °C before decolorization was observed. The crude reaction product was thrice recrystallized from 80–100 °C petroleum ether to give 1.2 g of **13** identical with that previously isolated.

Reaction of Dianion 1 with Ethyl Chloroacetate. A. The dianion **1** (0.01 mol, M = Li) was treated with 1.2 g (0.01 mol) of ethyl chloroacetate at −78 °C. After warming to 20 °C, the reaction product (2.56 g) was isolated and chromatographed using benzene as eluent. *N*-Benzhydrylaniline and benzophenone anil eluted first and these were followed by 1.8 g of 1,3,3-triphenyl-2-azetidinone (**14**, 60%), mp 120–124 °C. Recrystallization from ethanol gave an analytical sample: mp 121.5–123 °C; ir (KBr) 1760 (C=O, β-lactam), 1350 (N–C), 1600, 1500, 750, 700, 690 cm^{-1} (aromatics); NMR δ 3.63 (s, 2, CH_2), 7.0–7.5 (m, 15, aromatic H).

Anal. Calcd for $C_{21}H_{17}NO$: C, 84.24; H, 5.73; N, 4.68. Found: C, 84.38; H, 5.86; N, 4.56.

B. The above experiment was repeated with potassium as the counterion. After addition of the ethyl chloroacetate the color of the solution became green and the reaction was immediately quenched with methanol. The crude reaction product was chromatographed to give 0.72 g of *N*-benzhydrylaniline, 1.2 g of benzophenone anil containing 20% of ethyl 3-anilino-3,3-diphenylpropionate (**15**), 0.24 g (7%) of **15**, and 0.36 g (12%) of the β-lactam **14**, mp 123–124 °C after recrystallization from ethanol.

The isolated **15** was recrystallized from ethanol: mp 90–91.5 °C; NMR δ 0.97 (t, J = 7 Hz, 3, CH_3CH_2), 3.53 (s, 2, CH_2CO), 3.87 (q, J = 7 Hz, 2, CH_3CH_2), 4.8 (broad s, 1, NH), 6.3–7.7 (m, 15, aromatic H); ir (CCl_4) 3400 (NH), 1740 (C=O), 1600, 1500, 1210, 1160, 700 cm^{-1}.

Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.96; H, 6.72; N, 4.05. Found: C, 79.78; H, 6.77; N, 4.04.

C. The above reaction was repeated with **1** (0.01 mol, M = Na) and the reaction warmed to 20 °C over a 1-h period before quenching with ethanol. Chromatography of the reaction products using benzene–hexane (10:3) as eluting solvent gave 1.0 g (39%) of *N*-benzhydrylaniline, 1.0 g (40%) of ethyl 3,3-diphenylacrylate (**16**), identified by comparison of its spectral properties with those of an authentic sample,[9] and 0.3 g (24%) of aniline.

D. When the reaction mixture stood at 20 °C for at least 12 h, chromatography gave 1.10 g (42%) of *N*-benzhydrylaniline, 0.24 g (4%) of benzophenone anil, 0.33 g (13%) of ethyl 3,3-diphenylacrylate (**16**), and 1.02 g (34%) of *N*,3,3-triphenylacrylamide (**17**). Recrystallization of the last from ethanol gave material of mp 130–134 °C identical in spectral properties with an authentic sample, mmp 133–134 °C.

Reaction of Dianion 1 with Ethyl 4-Chlorobutyrate. The dianion 1 (0.01 mol, M = Na) in THF was treated at −78 °C with 1.51 g (0.01 mol) of ethyl 4-chlorobutyrate. After 1 h at −78 °C, the mixture was allowed to warm to 20 °C for 20 h. The crude product (3.15 g) was chromatographed using benzene graded to benzene–20% ether as eluting solvent. In order of elution, there were obtained 1.64 g (63%) of *N*-benzhydrylaniline, 1.00 g (30%) of crude *N*-benzhydryl-*N*-phenylcyclopropanecarboxamide (18), and 0.51 g (12%) of crude **19.**

The crude amide 18 crystallized on warming in 30–60 °C petroleum ether to give 0.65 g (20%) of **16,** mp 74–77 and 95–97 °C.[10] Recrystallization from 30–60 °C petroleum ether gave an analytical sample: mp 75–77 °C; ir (CCl_4) 1660 (C=O), 1500, 1600, 1410, 1140, 700 cm^{-1}; NMR δ 0.4–0.8 (m, 2) and 0.9–1.3 (m, 3, cyclopropyl H), 6.8–7.4 (m, 15, aromatic H); mass spectrum *m/e* (rel intensity) 327 (11, M^+), 168 (16), 167 (100), 152 (11), 77 (13).

Anal. Calcd for $C_{23}H_{21}NO$: C, 84.36; H, 6.46; N, 4.24. Found: C, 84.18; H, 6.48; N, 4.17.

An authentic sample of 18 was prepared from *N*-benzhydrylaniline and cyclopropanecarboxylic acid chloride, mp 94–96 °C, mmp 95–97 °C with both the lower and the higher melting polymorphs. Spectral data were identical with those observed for **18.**

The crude **19** was crystallized by warming in methanol giving 0.32 g (8%), mp 196–199 °C. An analytical sample obtained by recrystallization from ethanol–25% benzene had mp 199–202 °C; ir (Nujol) 1630 (broad, C=O), 1600, 1580, 1500, 1430, 1340, 760, 730, 700 cm^{-1}; NMR δ 0.5–2.0 (m, 9, aliphatic H), 4.0 (double d, J_1 = 5, J_2 = 7 Hz, 0.3 H, exchanges with basic D_2O, COCHCO), 6.8–7.5 (m, 15, aromatic H), 15.7 (s, 0.7 H, exchanges with D_2O, enol OH); mass spectrum *m/e* (rel intensity) 395 (41, M^+), 327 (32), 326 (100), 324 (41), 180 (50), 166 (39), 93 (42).

Anal. Calcd for $C_{27}H_{25}NO_2$: C, 81.98; H, 6.38; N, 3.54. Found: C, 82.08; H, 6.57; N, 3.56.

The preceding reaction was repeated except that after 20 min reaction at −78 °C, 4 ml of ethanol was added to terminate the reaction. After diluting with water and extracting with ether, VPC analysis of the ether extract showed that no chloro ester remained; instead, a compound with a much shorter retention time was present.

The ether extract was concentrated to 25 ml by fractional distillation and the residue placed under vacuum. The volatile material, collected in a dry ice trap, was redistilled at atmospheric pressure to give 1.3 g (90%) of ethyl cyclopropanecarboxylate, bp 125–130 °C, identified by comparison of its infrared and NMR spectra with those of an authentic sample.

The nonvolatile material (2.63 g) was dissolved in ether and treated with gaseous hydrogen chloride to precipitate *N*-benzhydrylaniline hydrochloride (2.40 g, 81%) which was identified by the spectral properties of the regenerated amine.

The ether filtrate from the amine hydrochloride was washed with sodium carbonate and water, dried, and evaporated. The residue (0.42 g) was purified by preparative TLC on silica gel to give principally one product, the amide 18. After crystallization by treatment with 30–60 °C petroleum ether, 0.27 g (9%) was obtained, mp 87–91 °C, mmp 90–93 °C, identity confirmed via ir spectrum.

The preceding reaction was repeated with 1 (0.01 mol, M = Li). Chromatography of the crude product (3.41 g) using benzene graded to 1:1 benzene–ether gave in order of elution 0.73 g (28%) of *N*-benzhydrylaniline, 0.17 g of a fraction containing benzhydrylaniline and two unidentified compounds, 0.90 g of 18 (27%) which after crystallization with petroleum ether had mp 94–97 °C, 0.36 g (9%) of **19** having mp 190–193 °C after crystallization from methanol, 0.10 g of crude **22,** 0.29 g of **21,** followed by 0.22 g of a mixture containing 40 mol % of **21** together with **20,** and finally 0.45 g of 1,6,6-triphenyl-2-piperidone (**20**).

The crude **22** (2% yield) was twice recrystallized from methanol to give 32 mg: mp 183–184.5 °C; ir (CCl_4) 3500 (broad, OH), 1700 (C=O), 1650 (amide C=O), 1500, 1450, 1370, 1350, 1320, 700, 690 cm^{-1}; NMR δ 0.9–3.3 (m, 9, aliphatic H), 4.58 (s, 1, OH), 7.10 (s, 5, NPh), 7.2–7.8 (m, 10, Ph_2C); mass spectrum *m/e* (rel intensity) 411 (5, M^+), 342 (57), 221 (32), 205 (47), 193 (53), 180 (100), 179 (32), 165 (37), 115 (42).

Anal. Calcd for $C_{27}H_{25}NO_3$: C, 78.80; H, 6.14; N, 3.40. Found: C, 78.52; H, 6.12; N, 3.33.

The relatively pure fraction of **21** (total yield 10%) was crystallized with 30–60 °C petroleum ether (mp 190–192 °C), then recrystallized from methanol: mp 195.5–197.5 °C; ir (CCl_4) 1670 (C=O), 1600, 1500, 1450, 1360, 1325, 1170, 1140, 690 cm^{-1}; NMR δ 1.9–2.5 (m, 4), 2.77 (distorted t, 2, $C{=}CCH_2$), 3.23 (broad t, 2, J = 8 Hz, $C{=}CCH_2$), 4.17 (t, J = 8 Hz, 2, CH_2O), 6.80 (s, 5, PhN), 7.1–7.5 (m, 10, Ph_2C); mass spectrum *m/e* (rel intensity) 396 (34), 395 (100, M^+), 324 (29), 303 (74), 275 (29), 228 (37), 215 (58), 193 (90), 180 (47), 178 (31), 165 (37), 138 (42), 115 (47), 111 (53), 110 (63).

Anal. Calcd for $C_{27}H_{25}NO_2$: C, 81.98; H, 6.38; N, 3.54. Found: C, 82.20; H, 6.47; N, 3.35.

The fraction consisting essentially of **20** (total yield 17%), mp 165–168 °C, was recrystallized from methanol: mp 172.5–173.5 °C; ir (CCl_4) 1655 (C=O), 1500, 1450, 1360, 1330, 690 cm^{-1}; NMR δ 1.3–1.9 (m, 2, $CH_2CH_2CH_2$), 2.5–2.9 (m, 4, $CH_2CH_2CH_2$), 6.87 (s, 5, NPh), 7.0–7.4 (m, 10, CPh_2); mass spectrum *m/e* (rel intensity) 328 (24), 327 (81, M^+), 206 (31), 193 (50), 192 (44), 180 (30), 178 (33), 165 (32) 115 (44), 93 (100).

Anal. Calcd for $C_{23}H_{21}NO$: C, 84.36; H, 6.48; N, 4.28. Found: C, 84.36; H, 6.44; N, 4.09.

Ring Opening of 1,4,4-Triphenyl-2-azetidinone[11] (14). The β-lactam **14** (0.5 g, 0.0016 mol) in 10 ml of tetrahydrofuran was treated at −78 °C with 1 ml of a 2 M solution of *n*-butyllithium in hexane (Ventron). After 12 h the reaction mixture was warmed and diluted with water and the products isolated by ether extraction. The crude product was recrystallized from ethanol to give 0.4 g (80%) yield of **17,** mp 131–133 °C, undepressed on mixing with authentic material. Spectral properties were identical with those of authentic **17.**

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Registry No.—1 (M = K), 25033-92-5; 1 (M = Li), 25033-90-3; 1 (M = Na), 7765-70-0; 4 (M = Na), 42391-81-1; **5,** 7714-87-6; **6,** 33672-87-6; **7,** 59434-86-5; **8,** 59434-87-6; **9,** 59434-88-7; **10,** 59434-89-8; **11,** 59434-90-1; **12,** 59434-91-2; **13,** 59434-92-3; 14, 19340-70-6; **15,** 59434-93-4; **17,** 4226-74-8; **18,** 59434-94-5; **19,** 59434-95-6; **20,** 59434-96-7; **21,** 59434-97-8; **22,** 59434-98-9; chloroethyl chloroformate, 627-11-2; propionyl chloride, 79-03-8; ethyl 3-chloropropionate, 623-71-2; ethyl acrylate, 140-88-5; ethyl chloroacetate, 105-39-5; ethyl 4-chlorobutyrate, 3153-36-4.

References and Notes

(1) J. G. Smith, I. Ho, and G. E. F. Simpson, *J. Org. Chem.,* **40,** 495 (1975).
(2) C. A. Buehler and D. E. Pearson, "Survey of Organic Synthesis", Wiley-Interscience, New York, N.Y., 1970, pp 891–893, provide a brief review of this method of generating ketenes.
(3) J. Hine, "Physical Organic Chemistry", McGraw-Hill, New York, N.Y., 1956, p 158.
(4) H. O. House, "Modern Synthetic Reactions", 2d ed, W. A. Benjamin, New York, N.Y., 1972, p 543.
(5) Reference 4, pp 348–352.
(6) J. G. Smith and R. A. Turle, *J. Org. Chem.,* **37,** 126 (1972).
(7) R. L. Gay, S. Boatman, and C. R. Hauser, *Chem. Ind. (London),* **42,** 1789 (1965).
(8) W. Schlenk, J. Appenrodt, A. Michael, and A. Thal, *Chem. Ber.,* **47,** 473 (1914).
(9) R. Heilman and R. Glenat, *Bull. Soc. Chim. Fr.,* 1586 (1955).
(10) The lower melting form of the amide **18** was obtained in the first experiment in which it was isolated. All subsequent preparations gave the higher melting form.
(11) Reduction of the β-lactam **14** with sodium metal or sodium naphthalenide generated *N,*3,3-triphenylpropionamide.

Reaction of α,ω-Di-Grignard Reagents with Silver(I) Salts Forms Carbocyclic Rings[1]

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Reaction of α,ω-alkane di-Grignard reagents with silver(I) triflate in tetrahydrofuran solution provides a practical synthesis for representative four-, five-, and six-membered carbocyclic rings. The reaction works less well for medium-ring compounds.

The reaction of primary alkylmagnesium and -lithium reagents with silver(I) salts results in carbon–carbon bond formation by a reaction involving initial formation of an alkylsilver(I) reagent, followed by concerted carbon–silver bond breaking and carbon–carbon bond forming.[2-4] This reaction occurs under mild conditions (20 °C <5 min) in high yields. Free alkyl radicals are not intermediates. Although it is restricted to primary alkyl moieties,[5] within this class it is one of the cleanest oxidative methods for forming carbon–carbon bonds from Grignard and organolithium reagents.

This paper explores the utility of the coupling of α,ω-di-Grignard reagents using silver(I) salts as a method for preparing carbocyclic structures. We had originally hoped that the fact that the decompositions of the intermediate organosilver(I) compounds undoubtedly proceed within aggregates might permit the synthesis of medium rings. In fact, this reaction does *not* provide a practical synthesis of medium ring compounds. It does, however, provide a useful method of making four-, five-, and six-membered rings, and warrants consideration in circumstances in which the functionality introduced into the products by the standard methods of ring formation is not desirable.

Results and Discussion

The most useful precursors to the α,ω-di-Grignard reagents were α,ω-dichlorides, prepared, in turn, from α,ω-diols. We explored a number of routes for the conversion of diols to chlorides, and found the most general to be the displacement of tosylate or mesylate using lithium chloride in HMPA.[6] Occasionally direct reaction between diols and thionyl chloride was used, but this reaction produced cyclic ethers when applied to many of the substrates of interest. Grignard reagents were used as the organometallic starting materials rather than dilithium reagents because organomagnesium compounds are more easily prepared, more soluble, and more stable to storage in ethers than organolithium compounds. Two points concerning the preparation of the Grignard reagents deserve mention. First, a detailed examination of the mechanism of formation of Grignard reagents, presently in progress in our laboratory, indicates that the highest yields of these materials are obtained by reaction of alkyl chlorides with magnesium in refluxing THF, rather than by the more commonly used reaction of alkyl bromides with magnesium in diethyl ether at 0 °C. Much of the work described in this paper used the latter procedure, but we now believe yields obtained by the former to be 10–15% higher. Second, many di-Grignard reagents are either insoluble in, or form two liquid phases with, diethyl ether. They are much more soluble in THF. Thus, the most useful reagents for the ring closure procedures discussed here are solutions of alkane di(magnesium chlorides) in THF.

Ring closure reactions were carried out by adding the solution of di-Grignard reagent to a solution containing a slight excess of a soluble silver(I) salt in THF at −78 or 0 °C. Several experiments were carried out using tetrakis[iodo(tri-*n*-butylphosphine)silver(I)]; these experiments led to adequate yields of product, as assayed by GLC. For practical synthetic work, however, it is clear that silver(I) triflate is the most useful reagent. It is easily prepared and dried, stable, and soluble in THF at concentration greater than 1 M. Further, triflate ion is easily removed in workup: separation of tri-*n*-butylphosphine and its silver salts from products can prove a major nuisance.

The major experimental difficulty encountered in these reactions is avoiding adventitious hydrolysis and oxidation of the solutions of organometallic reagents during their manipulation. Loss of Grignard (or organosilver) reagent in handling proved to be the major factor in limiting the yield of the desired cyclized product, particularly in experiments designed to improve the yield of medium ring cycloalkanes by adding the Grignard reagents to the silver salts using high dilution techniques.

Table I compares the yields of cycloalkanes obtained by reaction of α,ω-alkane di-Grignard reagents with $[IAgPBu_3]_4$ in THF. These experiments were carried out by mixing the Grignard reagent and a 10% excess of silver(I) salt at −78 °C and allowing the resulting solutions of α,ω-alkanedisilver(I) reagents to decompose while warming to room temperature. The important conclusion from these data is that the yield of cycloalkane product formed on thermal decomposition of α,ω-alkanesilver(I) reagents depends strongly on ring size; yields of four- and five-membered rings are good; those for medium rings are poor. Although it is possible to obtain modest yields of cyclodecane and cyclododecane by working with dilute solutions, the experimental problems encountered in preparing, manipulating, and recovering products from solutions that originally contain air-sensitive organometallic reagents at concentrations less than 10^{-2} N are such that these procedures are not practical.

Table II gives further examples of this coupling reaction. These experiments used silver triflate as silver(I) salt under conditions considered practical for synthetic applications. The yields represent conversions from starting alkyl halide to product. These yields are sufficient to establish that the reaction provides a practical, although specialized, alternative to the more usual chemical and photochemical methods for preparing four-, five-, and six-membered rings.

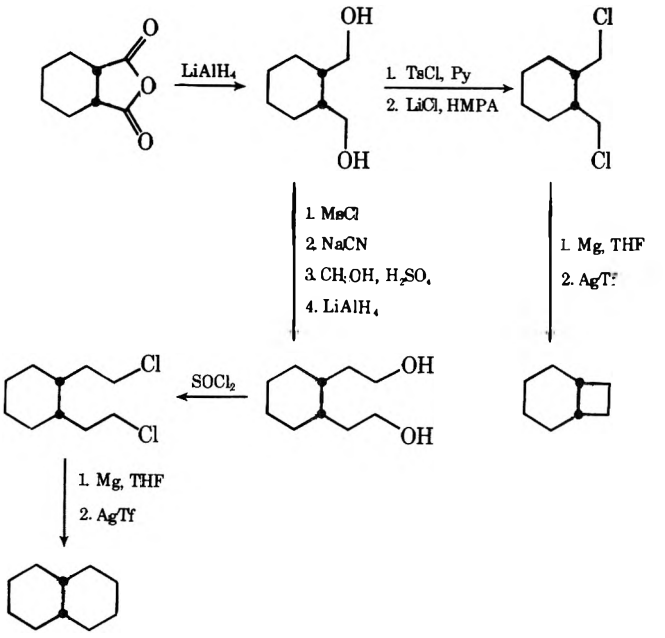
The Experimental Section of this paper contains details only for the preparations of the two alkyl halides included in the representative reaction sequences outlined by Scheme I, and for the conversion of these halides to Grignard reagents and thence to hydrocarbons by treatment with silver(I) triflate. The other transformations summarized in Scheme I are described fully in supplementary material to this paper. Details of the other procedures leading to the data in Tables I and II are sufficiently similar and repetitive that they do not warrant publication. They can, however, be found by consulting the thesis on which this work is based.[7]

Table I. Yields of Cycloalkanes by Reaction between $XMg(CH_2)_nMgX$ and $IAgPBu_3$ in THF

Registry no.	n	X	Concn, N × 10²[a]	Product	Registry no.	Yield, %[b]
23708-47-6	4	Br	5.0	Cyclobutane	287-23-0	93
23708-48-7	5	Br	2.5	Cyclopentane	287-92-3	83
59448-46-3	6	Cl	2.5	Cyclohexane	110-82-7	43
59321-71-0	7	Br	2.5	Cycloheptane	291-64-5	23
45037-87-4	8	Br	2.5	Cyclooctane	292-64-8	2
59448-47-4	9	Cl	2.5	Cyclononane	293-55-0	<1
23708-54-5	10	Br	0.77	Cyclodecane	293-96-9	10–15[c]
59434-46-7	12	Br	0.77	Cyclododecane	294-62-2	10–15[c]

[a] Concentrations are those estimated for the alkanedisilver(I) intermediates, based on the normality of the starting di-Grignard reagent and the final volume of the reaction mixture. [b] Yields are GLC determinations and are based on the normality of the starting solutions of Grignard reagents. [c] The yields of cyclodecane and cyclododecane varied, depending on the details of the experimental procedure used.

Scheme I. Representative Synthetic Procedures



Experimental Section

General Methods. Melting points and boiling points are uncorrected. All reactions involving organometallic compounds were carried out under prepurified nitrogen or argon. Solvents were reagent grade. THF was distilled from a dark purple solution of disodium benzophenone dianion under argon before use. Diethyl ether was distilled under nitrogen from lithium aluminum hydride; hexamethylphosphoramide was distilled from sodium at reduced pressure;[8] pyridine and benzene were dried over Linde 4A molecular sieves. All solvents were transferred using hypodermic syringes or stainless steel cannulas and were stored under prepurified argon or nitrogen. Alkyl halides were purified by passing through a short column of Woelm alumina (activity grade I) immediately before conversion to Grignard reagents. Grignard reagents were stored under argon in Schlenck tubes, and manipulated using standard procedures.[9] Grignard reagents were titrated using the Eastham procedure.[10] Normalities are expressed for di-Grignard reagents as equivalents of RMgX. Infrared spectra were recorded in 0.1-mm sodium chloride solution cells using carbon tetrachloride as the solvent. NMR chemical shifts are reported in parts per million downfield from tetramethylsilane. Analytical GLC analyses were carried out with Hewlett-Packard Model 810 and Perkin-Elmer Model 990 gas chromatographs equipped with flame ionization detectors.

Tetrakis[iodo(tri-*n*-butylphosphine)silver(I)] was prepared following the procedure of Mann, Wells, and Purdie.[11]

Silver trifluoromethylsulfonate was prepared according to a procedure adapted from Haszeldine and Kidd.[12] Distilled trifluoromethanesulfonic acid (60 g, 0.4 mol) was added slowly to 300 ml of water in a 500-ml flask equipped with a Teflon-coated magnetic stirring bar and cooled in an ice bath.[13] Finely powdered silver oxide (48.5 g, 0.21 mol) was added in portions; the bath was removed and stirring was continued for 25 min in the dark. The suspension was filtered through a sintered glass funnel and the filtrate was washed with 100 ml of distilled water. Water was removed under reduced pressure and the residue was dissolved in 250 ml of acetone. The acetone solution was filtered through a sintered glass funnel and the solvent was evaporated. The product was ground to a fine white powder and dried (100 °C, 0.025 Torr, 6 h), yielding 87.9 g (98%) of silver triflate. Product was stored in a desiccator with exclusion of light.

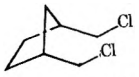
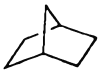
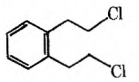
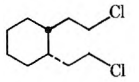
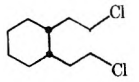
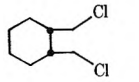
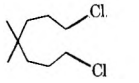
General Procedure for Preparation of Grignard Reagents. Preparation of the Grignard Reagent from *trans*-1,2-Bis(2-chloroethyl)cyclohexane. *trans*-1,2-Bis(2-chloroethyl)cyclohexane (15.7 g, 0.075 mol), which had been passed through a short column of Woelm activity grade I alumina, was transferred under argon by syringe to a 60-ml dropping funnel fitted to a dry, round-bottomed, three-necked flask equipped with a Teflon-coated magnetic stirring bar and charged with 7.3 g (0.3 g-atom) of magnesium powder. An argon bubbler was attached to the flask and 25 ml of dry THF was added, followed by 0.5 ml of dibromoethane. After the reaction with dibromoethane had ceased, the THF was removed by forced siphon and was replaced with 150 ml of fresh THF. The addition of the dichloride was made to the stirred suspension of magnesium in THF over 4 h. When all the halide had been added, the dropping funnel was rinsed with 3 ml of THF and stirring was continued overnight.

General Procedure for Preparation of Cycloalkanes with Tetrakis[iodo(tri-*n*-butylphosphine)silver(I)] at High Dilution. Synthesis of Cyclododecane. A THF solution of the di-Grignard reagent (1 ml, 0.85 N) prepared from 1,12-dibromododecane was diluted to a total volume of 75 ml with dry THF. This solution was added from a dropping funnel over 1.5 h to a magnetically stirred solution containing 0.41 g (0.935 mmol) of tetrakis[iodo(tri-*n*-butylphosphine)silver(I)] and 50 ml of THF, which was cooled in a dry ice bath and protected by a nitrogen atmosphere. When the addition was complete, the bath was removed and the solution was allowed to warm to room temperature. GLC analysis using internal standards indicated that cyclododecane had been formed in 10% yield. Dodecane was also present in 71% yield, presumably as the result of adventitious hydrolysis of the di-Grignard or alkylsilver(I) reagent during the course of the reaction. In general, yields of cyclodecane and of cyclododecane prepared by this procedure were maximized when the di-Grignard concentration was approximately 10^{-2} N. Higher concentrations resulted in less hydrolysis but lower yields of cycloalkanes, while lower concentrations were more prone toward hydrolysis.

***cis*-1,2-Bis(2-chloroethyl)cyclohexane.** Thionyl chloride (71.5 g, 0.6 mol) was added over 0.5 h to a stirred solution of 24.5 g (0.142 mol) of *cis*-1,2-bis(2-hydroxyethyl)cyclohexane and 500 ml of dry benzene which was protected with a $CaSO_4$ drying tube. The reaction mixture was stirred for 6 h at room temperature and then heated at reflux for 4 h. The cooled reaction mixture was transferred cautiously to 500 ml of water and neutralized with solid sodium bicarbonate. The organic phase was separated and was washed with two 250-ml portions of water and with 100 ml of saturated sodium chloride solution. The organic phase was dried ($MgSO_4$), filtered and concentrated, and the crude dichloride was distilled to yield 21 g (71%) of pure material (bp 69–71 °C, 0.15 Torr): ir (CCl_4) 3000 (vw), 930 (s), 2860 (w), 2670 (w), 1448 (m), 1375 (w), 1347 (w), 1323 (w), 1280 (m), 1190 (w), 1035 (w), 937 (w), 857 (w), 713 (w), 661 cm^{-1}; (m); NMR ($CDCl_3$) δ 3.50 (poorly resolved t, 2), 1.73 (poorly resolved t, 2), 1.46 (broad s, 5).

***cis*-Decalin.** A THF solution (800 ml, ca 0.2 N) of the di-Grignard reagent from *cis*-1,2-bis(2-chloroethyl)cyclohexane (16.7 g, 0.08 mol) was added in drops to 160 ml of a chilled (ice bath) THF solution of $AgOSO_2CF_3$ (45.2 g, 0.18 mol), which was vigorously stirred under

Table II. Yields of Cycloalkanes by Reaction between Di-Grignard Reagents and CF_3SO_3Ag in THF

Starting halide	Registry no.	Concn, N[a]	Product	Registry no.	Yield, %[b]
1,4-Dibromobutane	110-52-1	0.21	Cyclobutane		84
1,5-Dibromopentane	111-24-0	0.21	Cyclopentane		80
1,6-Dichlorohexane	2163-00-0	0.21	Cyclohexane		55
	59434-47-8	0.80		279-23-2	82
	59448-77-0	0.50		119-64-2	70
	59434-48-9	0.20		493-02-7	(67)
	59434-49-0	0.20		493-01-6	(57)
	38300-68-4	0.69		28282-35-1	(61)
	59434-50-3	0.22			0

[a] Concentrations are estimated based on the quantity of alkyl halide used in preparing the di-Grignard reagent, the volume of the reaction solution containing the disilver reagent, and the assumption that the overall conversion of alkane dihalide to alkanedisilver reagent occurred in 90% yield. [b] Yields not in parentheses are GLC yields; yields in parentheses are isolated yields. Both are based on starting alkyl halide.

argon with a Teflon-coated magnetic stirring bar. When the addition was completed, the reaction mixture was allowed to warm to room temperature and filtered through a pad of Celite. The solution was passed through a short alumina column and concentrated under reduced pressure at 25 °C to ca. 75 ml. Water (150 ml) and pentane (150 ml) were added and the phases were separated. The aqueous phase was extracted with three 50-ml portions of pentane and the combined organic phase was then washed with water (2 × 50 ml) and saturated aqueous sodium chloride solution (25 ml) and dried ($MgSO_4$). After filtering and concentrating, the product was distilled through a Holtzman column [bp 81–83 °C, 19 Torr (lit.[14] bp 196 °C, 760 Torr)], yield 6.3 g (57%). NMR and ir spectra were indistinguishable from those of an authentic sample of *cis*-decalin.

***cis*-1,2-Bis(hydroxymethyl)cyclohexane Ditosylate.** *cis*-1,2-Bis(hydroxymethyl)cyclohexane (44 g, 0.306 mol) and 300 ml of pyridine were cooled under argon to 0 °C. A solution of *p*-toluenesulfonyl chloride (143 g, 0.75 mol) and 400 ml of pyridine was added to the diol solution over a period of 3 h. The reaction mixture was stored at 0 °C for 12 h and was then poured into a mixture of 700 ml of concentrated HCl and 800 g of crushed ice. The mixture was extracted with three 300-ml portions of methylene chloride and the organic phase was washed with three 400-ml portions of water and 200 ml of saturated aqueous sodium chloride solution. After drying ($MgSO_4$), filtering, and evaporating the solvent, the ditosylate was recrystallized from a mixture of pentane and methylene chloride (4:1 v/v) at −78 °C: mp 83.5–84.5 °C (lit.[15] mp 84–85 °C); yield 89 g (64%); ir ($CHCl_3$) 3020 (w), 2935 (m), 2865 (w), 1600 (m), 1450 (m), 1360 (s), 1309 (w), 1290 (w), 1175 (s), 1098 (m), 955 (s), 555 cm^{-1} (m); NMR ($CDCl_3$) δ 7.53 (AB q, 4) 3.87 (d, 2), 2.47 (s, 3) 2.16–1.60 (broad m, 1), 1.37 (broad s, 4).

***cis*-1,2-Bis(chloromethyl)cyclohexane.** *cis*-1,2-Bis(hydroxymethyl)cyclohexane ditosylate (89 g, 0.192 mol), lithium chloride (68 g, 1.6 mol), and 400 ml of HMPA were heated to 100 °C and stirred under argon for 12 h. The cooled reaction mixture was added to 1.2 l of water and extracted with four 400-ml portions of pentane. The pentane extracts were combined and washed with three 800-ml portions of water and with 200 ml of saturated sodium chloride solution. The solution was dried ($MgSO_4$), filtered, and concentrated. Distillation (139–140 °C, 30 Torr) afforded 31.5 g (90%) of the dichloride: ir (CCl_4) 2985 (w), 2955 (m), 2870 (w), 1445 (m), 1322 (m), 1195 (w), 1140 (w), 1110 (w), 1060 (w), 717 cm^{-1} (m); NMR ($CDCl_3$) δ 3.50 (d, 2), 2.20 (broad s, 1), 1.53 (broad s, 8).

Bicyclo[4.2.0]octane. A THF solution (450 ml) of the di-Grignard reagent prepared from *cis*-1,2-bis(chloromethyl)cyclohexane (28 g, 0.155 mol) was added over 2 h to a vigorously stirred solution of $AgOSO_2CF_3$ (87.6 g, 0.341 mol) and THF (90 ml) cooled in an ice bath and protected by an argon atmosphere. When the addition was completed, the bath was removed, and the reaction mixture was allowed to warm to room temperature. After filtration through a pad of Celite, the solution was passed through a column containing 100 g of alumina, which was subsequently washed with 100 ml of pentane. This solution was concentrated to approximately 150 ml by distillation through a 36-cm Holtzman column. The residue was poured into 100 ml of water and the layers were separated. The aqueous phase was extracted with five 30-ml portions of pentane. The combined organic phases were washed with two 50-ml portions of water and 25 ml of saturated sodium chloride solution, dried ($MgSO_4$), and filtered. The solution was distilled through a 36-cm Holtzman column, yielding 10.4 g (61%) of bicyclo[4.2.0]octane, bp 135.5–137 °C (lit.[16] bp 136–137.5 °C). The NMR and ir spectra of this material were indistinguishable from those of a sample prepared by hydrogenation of Δ^7-bicyclo[4.2.0]-octene.[17,18]

Registry No.—1,7-Dibromoheptane, 4549-31-9; 1,8-dibromooctane, 4549-32-0; 1,9-dichlorononane, 821-99-8; 1,10-dibromodecane, 4101-68-2; 1,12-dibromododecane, 3344-70-5; α,ω-butanedisilver(I), 59434-51-4; α,ω-pentanedisilver(I), 59434-56-9; α,ω-hexanedisilver(I), 59434-53-6; α,ω-heptanedisilver(I), 59434-54-7; α,ω-octanedisilver(I), 59434-55-8; α,ω-nonanedisilver(I), 59434-56-9; α,ω-decanedisilver(I), 59434-57-0; α,ω-dodecanedisilver(I), 59434-58-1; 1,3-bis(silvermethyl)cyclopentane, 59434-59-2; 1,2-bis(2-silverethyl)benzene, 59434-60-5; *trans*-1,2-bis(2-silverethyl)cyclohexane, 59434-61-6; *cis*-1,2-bis(2-silverethyl)cyclohexane, 59434-62-7; *cis*-1,2-bis(silvermethyl)cyclohexane, 59434-63-8; 1,3-bis(chloromethyl)cyclopentane Grignard reagent, 59434-64-9; 1,2-bis(2-chloroethyl)benzene Grignard reagent, 59434-65-0; *trans*-1,2-bis(2-chloroethyl)cyclohexane Grignard reagent, 59434-66-1; *cis*-1,2-bis(2-chloroethyl)-cyclohexane Grignard reagent, 59434-67-2; *cis*-1,2-bis(chloromethyl)cyclohexane Grignard reagent, 59434-68-3; 4,4-dimethyl-1,7-dichloroheptane Grignard reagent, 59434-69-4; tetrakis[iodo-(tri-*n*-butylphosphine)silver(I)], 59448-71-4; silver triflate, 2923-28-6; *cis*-1,2-bis(2-hydroxyethyl)cyclohexane, 59434-70-7; *cis*-1,2-bis(hydroxymethyl)cyclohexane ditosylate, 59461-66-4; *cis*-1,2-bis(hydroxymethyl)cyclohexane, 15753-50-1; *p*-toluenesulfonyl chloride, 98-59-9.

Supplementary Material Available. Experimental procedures for the preparations of compounds listed in Scheme I and not de-

scribed in the Experimental Section (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Supported by the National Science Foundation, Grant MPS74-20946.
(2) M. Tamura and J. Kochi, *J. Am. Chem. Soc.*, **93**, 1483 (1971); M. Tamura and J. Kochi, *Bull. Chem. Soc. Jpn.*, **45**, 1120 (1972).
(3) G. M. Whitesides, D. E. Bergbreiter, and P. E. Kendall, *J. Am. Chem. Soc.*, **96**, 2806 (1974).
(4) The reaction of silver(I) salts with organoboranes and organolead compounds probably involves intermediate organosilver(I) reagents; cf. H. C. Brown, N. C. Herbert, and C. H. Snyder, *J. Am. Chem. Soc.*, **83**, 1001 (1961); H. C. Brown, C. Verbrugge, and C. H. Snyder, *ibid.*, **83**, 1001 (1961); R. Johnson, *J. Chem. Soc.*, 3923 (1960).
(5) Yields of coupled products from secondary alkylsilver compounds are significantly lower than those from primary alkylsilver reagents, and there is evidence that these two classes of organosilver compounds may decompose by different mechanisms.[2,3]
(6) P. Anderson, B. Stephenson, and H. S. Mosher, *J. Am. Chem. Soc.*, **96**, 3171 (1974).
(7) F. D. Gutowski, M. S. Thesis, Massachusetts Institute of Technology, Cambridge, Mass., June 1975.
(8) *Caution.* Hexamethylphosphoramide (HMPA) vapors have been reported to cause cancer in rats: J. A. Zapp, Jr., *Science*, **190**, 422 (1975). Operations with HMPA should be carried out in a good hood, and care taken to avoid breathing HMPA vapors or allowing HMPA to contact the skin.
(9) H. C. Brown, G. W. Kramer, A. B. Levy, and M. M. Midland, "Organic Syntheses *via* Boranes", Wiley, New York, N.Y., 1975; D. F. Shriver, "The Manipulation of Air-Sensitive Compounds", McGraw-Hill, New York, N.Y., 1969, Chapter 7.
(10) S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967).
(11) F. G. Mann, A. F. Wells, and D. Purdie, *J. Chem. Soc.*, 1828 (1937).
(12) R. N. Haszeldine and J. M. Kidd, *J. Chem. Soc.*, 4228 (1954).
(13) Use of undistilled trifluoromethanesulfonic acid resulted in silver triflate having a brown color. This material served as well as purer, white material in the coupling reaction.
(14) R. C. Weast, Ed., "CRC Handbook of Chemistry and Physics", 50th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1968–1970, p C-264.
(15) G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 389 (1953).
(16) A. T. Blomquist and J. Kwiatek, *J. Am. Chem. Soc.*, **73**, 2098 (1951).
(17) W. G. Dauben and R. L. Cargill, *J. Org. Chem.*, **27**, 1910 (1962).
(18) M. E. Ali and L. N. Owen, *J. Chem. Soc.*, 2111 (1958).

Linear Carboxylic Acid Esters from α Olefins. 2. Catalysis by Homogeneous Palladium Complexes

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Regioselective carbonylation of α olefins is catalyzed by a series of ligand-stabilized palladium(II)–group 4B metal halide complexes of the composition $[(p\text{-}XC_6H_4)_3P]_2PdCl_2$–$MCl_2$ (where X = H, CH_3, CH_3O, and Cl, and M = Sn or Ge) and by related complexes. For the synthesis of linear carboxylic acid esters the sensitivity of the carbonylation to palladium catalyst composition, the structure of the olefin substrate and that of the nucleophilic coreactant have been examined in relation to observed kinetics and the isolation of active intermediates.

In a previous paper[1] we described the synthesis of linear carboxylic acid esters from linear α olefins in high yields (eq 1a) catalyzed by a novel class of ligand-stabilized

$$RCH{=}CH_2 + CO + R'OH \rightarrow \begin{cases} RCH_2{-}CH_2{-}COOR' & \text{(1a)} \\ RCH(CH_3){-}COOR' & \text{(1b)} \end{cases}$$

platinum(II)–group 4B metal halide carbonylation catalysts. These highly regioselective catalysts, typified by $[(C_6H_5)_3As]_2PtCl_2$–$SnCl_2$, afford up to 98 mol % selectivity to the linear ester. We report herein the extension of that work to palladium chemistry, and the development of a series of highly active ligand-stabilized palladium(II)–group 4B metal halide catalysts. These catalysts also yield linear esters in 85–89 mol % selectivity but have the intrinsic advantages of requiring lower CO pressures, greater flexibility regarding olefin feed stock, and lower cost.

Palladium salts have, in recent years, found extensive application as carbonylation catalysts.[2-7] Where the addition is to an α olefin of three or more carbons, however, most catalysts, e.g., $PdCl_2$[8] and $PdCl_2[P(C_6H_5)_3]_2$,[5] yield a mixture of normal and iso acid derivatives and generally it is the iso ester that predominates (eq 1b).[3] The use of more selective palladium bimetallic catalysts which ensure higher selectivity to linear acid derivatives has been recognized in the patent literature.[9-12]

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Results

Effect of Palladium Catalyst Structure. By analogy with earlier studies[1] a broad range of palladium bimetallic complexes have been screened for carbonylation activity. Palladium bonded to group 5B and 6B tertiary donor ligands containing aryl, substituted aryl, alkyl, and aryloxy radicals in combination with group 4B metal halides has been considered.[11] Methyl octanoate synthesis was selected as the model reaction. Table I illustrates the importance of catalyst structure upon both activity and selectivity to linear ester. Under typical screening conditions linear ester selectivity varies from a low of 44% up to 89 mol %. Yields of methyl octanoate also vary widely, but exceed 70 mol % for at least four palladium complexes, viz., $[(C_6H_5)_3P]_2PdCl_2$–$SnCl_2$, $[(p\text{-}CH_3C_6H_4)_3P]_2PdCl_2$–$SnCl_2$, $[(p\text{-}CH_3OC_6H_4)_3P]_2PdCl_2$–$SnCl_2$, and $[(C_6H_5)_3P]_2PdCl_2$–$GeCl_2$ (expt 1–3, 10). Total ester yields, which include 10–13% methyl 2-methylheptanoate and 1–2% methyl 2-ethylhexanoate, are in excess of 85 mol % for each of these catalysts. The remaining products are isomerized heptenes, primarily *cis*- and *trans*-2-heptenes.

No simple correlations have been found between catalyst performance and either the size or electronic character of the coordinated ligands, although both properties are clearly important. For a series of substituted arylphosphine complexes, differences in the effective size of the coordinated ligands may have a critical effect upon the degree of steric crowding and consequently upon catalyst reactivity. This is illustrated by the more than 20-fold difference in ester yield between otherwise similar ortho- and para-substituted methoxyphenylphosphine complexes, viz., $[(o\text{-}CH_3OC_6H_4)_3P]_2PdCl_2$–$SnCl_2$ and $[(p\text{-}CH_3OC_6H_4)_3P]_2PdCl_2$–$SnCl_2$ (expt

Table I. 1-Heptene Carbonylation Catalyzed by Various Palladium Complexes [a]

Expt	Composition of palladium complex	1-Heptene conversion, mol %	Yield of 2-, 3-heptenes, mol %	Methyl octanoate Yield, mol %[b]	Methyl octanoate Selectivity, mol %[c]
1	$[(C_6H_5)_3P]_2PdCl_2$–$10SnCl_2$	96	4.6	76	87
2	$[(p\text{-}CH_3C_6H_4)_3P]_2PdCl_2$–$10SnCl_2$	97	4.7	78	87
3	$[(p\text{-}CH_3OC_6H_4)_3P]_2PdCl_2$–$10SnCl_2$	88	4.6	71	85
4	$[(p\text{-}ClC_6H_4)_3P]_2PdCl_2$–$10SnCl_2$	16	<1	10	89
5	$[(o\text{-}CH_3OC_6H_4)_3P]_2PdCl_2$–$10SnCl_2$	5	<1	2.9	81
6	$[C_6H_5(CH_3)_2P]_2PdCl_2$–$10SnCl_2$	65	5.8	42	88
7	$[(C_6H_5O)_3P]_2PdCl_2$–$10SnCl_2$	3.0	<1	2.8	89
8	$[(C_6H_5)_3As]_2PdCl_2$–$10SnCl_2$	2.2	<1	None	
9	$[(C_6H_5)_3As]_2PdCl_2$–$10GeCl_2$	42	2.3	23	76
10	$[(C_6H_5)_3P]_2PdCl_2$–$10GeCl_2$	96	3.7	73	88
11	$[(C_6H_5)_3P]_2PdI_2$–$10SnI_2$	4.3	<1	None	
12	$[(C_6H_5)_3P]_2PdCl_2$–$10PbCl_2$	87	<2	33	44
13	$[(C_6H_5)_3P]_2PdCl_2$–$10SnCl(Ph)_3$	7.9	<1	3.3	89
14	$[(C_6H_5)_3P]_2PdCl_2$	93	2.3	42	58

[a] Run conditions: [1-heptene], 0.52 M; [Pd]:[1-C_7H_{14}]:[CH_3OH] = $1:10^2:7.4 \times 10^2$; 240 atm; 80 °C; 360 min. [b] Methyl octanoate yield based on 1-heptene charged. [c] Selectivity calculated basis: methyl octanoate yield/total methyl C_8 acid ester.

Table II. 1-Heptene Carbonylation Catalyzed by $[(C_6H_5)_3P]_2PdCl_2$–$SnCl_2$ [a]

Expt	Mole Ratio $(C_6H_5)_3P$:Pd:$SnCl_2$			Methyl octanoate Selectivity, mole %[b]	Methyl octanoate Rate, M h^{-1} [c]
15	2	1	1	85.8	0.14
16	2	1	5	88.5	0.38
17	2	1	10	86.5	0.24
18	2	1	10[d]	87.9	0.21
19	2	1	30	88.7	0.085
20	4	1	10	88.7	0.034

[a] Run conditions: [1-heptene], 0.52 M; [Pd]:[1-C_7H_{14}]:[CH_3OH], $1:10^2:7.4 \times 10^2$; 136 atm, 70 °C, 180–360 min. [b] Selectivity calculated basis: methyl octanoate yield/total methyl C_8 acid ester. [c] Rate of methyl octanoate formation. [d] With anhydrous $SnCl_2$.

3 and 5). Likewise comparing arylarsine and phosphine complexes, the inactivity of $[(C_6H_5)_3As]_2PdCl_2$–$SnCl_2$ (expt 8) contrasts with that of the analogous $[(C_6H_5)_3P]_2PdCl_2$–$SnCl_2$ and $[(C_6H_5)_3As]_2PdCl_2$–$GeCl_2$ complexes (expt 1 and 9), and the 86 mol % yield of methyl octanoate realized under similar conditions with the platinum catalyst $[(C_6H_5)_3As]_2$-$PtCl_2$–$SnCl_2$.[1] Carbonylation is achieved in the palladium case only with the spatially smaller P vs. As atom of the tertiary donor ligands and/or Ge^{2+} vs. Sn^{2+} salts[13] of the group 4B metal halide cocatalyst.

For a series of phosphines of similar cone angle,[14] activity is maximized with arylphosphines of moderate base strength[15] (eq 2). The effect of strongly electron-withdrawing para substituents (e.g., *p*-Cl, expt 4), or the replacement of aryl by the more basic alkylphosphines (expt 6), is, in both cases, to lower the yield of ester. Likewise, although both tin(II) chloride and germanium(II) chloride proved to be excellent cocatalysts, substituted tin(II) salts, tin(II) iodide and lead chloride, which form significantly weaker bonds to palladium,[16] were less effective (expt 11–13). No ester was detected with $PdCl_2$–$SnCl_2$ alone, and bis(triphenylphosphine)palladium(II) without cocatalyst gave similar amounts of linear and branched ester (expt 14).[5]

$$(C_6H_5O)_3P < (p\text{-}ClC_6H_4)_3P < (C_6H_5)_3P \approx (p\text{-}CH_3C_6H_4)_5P > (CH_3)_2C_6H_5P \quad (2)$$

In related studies (Table II) it was further established that (a) tin to palladium mole ratios of ca. 5 produce the most rapid rates of carbonylation, lower ratios leading to catalyst instability, and additional cocatalyst only suppressing the rate; (b) excess triphenylphosphine (2 mol/g-atom of Pd, expt 20) dramatically lowers the rate of methyl octanoate formation but does not influence the normal to branched isomer ratio; (c) tin(II) chloride dihydrate replacement by anhydrous tin(II) chloride (expt 17 and 18) results in ca. 12% loss in rate (cf. Pt–Sn hydrogenation catalysis[17,18]) but overall yields of ester are within experimental error.

Effect of Olefin Structure. Palladium bimetallic catalysts, typified by $[(C_6H_5)_3P]_2PdCl_2$–$SnCl_2$, will carbonylate a variety of nonconjugated olefin types, including linear and branched α olefins, internal olefins, and cyclic olefins (see Table III). Here we chose to study the relationship between catalyst performance, as gauged by the rate and selectivity to linear ester, and the stereochemical requirements and properties of the alkene.[19] Linear α olefins generally react most readily, the rate varying by a factor of 10, however, over the carbon range C_3–C_{20} (expt 21–25), and reaching a maximum in the C_5–C_7 range. Selectivity does improve with increasing molecular weight but exceeds 90 mol % only in the case of methyl heneicosanoate synthesis from 1-eicosene.

In contrast to analogous platinum bimetallic catalysts,[1] $[(C_6H_5)_3P]_2PdCl_2$–$SnCl_2$ carbonylates at least three classes of polysubstituted olefins (expt 26–33). Sterically hindered branched α olefins in which the alkyl substituent is on the β or γ carbon provide excellent examples of regioselective carbonylation. Selectivity to linear ester exceeds 99 mol % in the case of methyl 3-methylhexanoate from 2-methyl-1-pentene (expt 28) and 98 mol % for methyl 4-methylhexanoate synthesis (expt 27). Rates of carbonylation are considerably slower, however.

Internal, disubstituted olefins also carbonylate more slowly than linear α olefins, but here the product distribution is quite different. CO addition is no longer predominantly at the terminal carbon. Some 6–10% linear methyl octanoate is formed from 2-heptenes, but the rate and selectivity are further reduced for *cis*-3-heptene, and no ester is detected with *trans*-5-decene. Of note is the significantly faster rate of *cis*- vs. *trans*-2-heptene conversion to methyl 2-methylheptanoate (the primary product in both cases).

Effect of Nucleophile Structure. Carbonylation may be effected with a range of nucleophilic coreactants having mobile hydrogen atoms, including alcohols, water, mercaptans,

Table III. Alkene Carbonylation Catalyzed by Solutions of $[(C_6H_5)_3P]_2PdCl_2$–$SnCl_2$ [a]

Expt	Alkene	Alkene conversion, mol %	Major carbonylation products: Identity	Selectivity, mol %	Rate, M h^{-1}
21	Propylene	90	Methyl butyrate	84.9	0.16
22	1-Pentene	N.D.[b]	Methyl hexanoate	89.5	0.23
23	1-Heptene	>95	Methyl octanoate	86.5	0.24
24	1-Undecene	59	Methyl dodecanoate	88.5	0.11
25	1-Eicosene	20	Methyl heneicosanoate	90.8	0.024
26	4-Methyl-1-pentene	86	Methyl 5-methylhexanoate	88.8	0.16
27	3-Methyl-1-pentene	71	Methyl 4-methylhexanoate	98.0	0.15
28	2-Methyl-1-pentene	30	Methyl 3-methylhexanoate	>99	0.021
29	Cyclooctene	36	Methyl cyclooctanecarboxylate	>99	N.D.
30	*trans*-2-Heptene	11	Methyl octanoate	10	0.004
			Methyl 2-methylheptanoate	60	0.021
			Methyl 2-ethylhexanoate[c]	30	0.012
31	*cis*-2-Heptene	54	Methyl octanoate	6.9	0.010
			Methyl 2-methylheptanoate	71	0.12
			Methyl 2-ethylhexanoate[c]	22	0.032
32	*cis*-3-Heptene	N.D.	Methyl octanoate	Trace	
			Methyl 2-methylheptanoate	22	0.018
			Methyl 2-ethylhexanoate[c]	78	0.061
33	*trans*-5-Decene	1.0	None		

[a] Run conditions: 70 °C; 136 atm; 180 min; excess CH_3OH. [b] N.D., not determined. [c] May contain some methyl 2-propylpentanoate.

Table IV. 1-Heptene Carbonylation Catalyzed by Solutions of $[(C_6H_5)_3P]_2PdCl_2$–$SnCl_2$. The Effect of Changes in Nucleophilic Coreactant [a]

Expt	Nucleophilic coreactant	Heptene conversion, mol %	Major carbonylation products: Identity	Selectivity, mol %	Rate, M h^{-1}
34	Methanol	>95	Methyl octanoate	87.8	0.26
35	1-Hexanol	>95	*n*-Hexyl octanoate	88.6	0.26
36	2-Propanol	30	Isopropyl octanoate	89.4	0.084
37	2-Chloroethanol	95	2-Chloroethyl octanoate	87	N.D.[b]
38	Phenol	59	Phenyl octanoate	84	0.022[c]
39	Water	>95	Octanoic acid[d]	86	0.21
40	Ethanethiol	25	Ethyl thioloctanoate	88	0.065[e]

[a] Run conditions: [1-heptene] = 0.49–0.59 M; [Pd]:[1-C_7H_{14}]:[ROH] = $1:10^2:3 \times 10^2$; 136 atm; 70 °C. [b] N.D., not determined. [c] 1-Heptene conversion faster by a factor ≈3; final product contains 0.04 M octanoic acid. [d] Identified as methyl octanoate by treating crude product with methanol/BF_3 reagent. [e] Thiol addition reactions predominate.

and hydrogen halides. The trends parallel those for nickel carbonyl[20] and platinum bimetallic catalysts.[1] Here the nucleophile structure has only a small effect upon catalyst selectivity, be it primary, secondary or substituted alcohol, water, or thiol (Table IV), but the catalytic effectiveness varies by a factor of at least 10. Where oxygen is the attacking atom of the nucleophile, increasing nucleophilicity[21] leads to improved rates of product formation (eq 3). Competing addition reactions are prevalent with thiols (expt 40).

$$\text{ROH} > \text{HOH} > \text{PhOH} \quad (3)$$

Attempts to prepare fatty acid amides and anilides led to the formation of intractable tars. Carboxylic acid halogenides, such as octanoyl chloride, may be synthesized in moderate yields using HCl treated solutions of the palladium salts in halogenated solvents such as methylene chloride.[22]

Kinetic Studies. As a means of establishing general trends, carbonylation activity was surveyed over a broad range of temperatures (ambient to 120 °C) and superatmospheric pressures of CO (up to 300 atm).[11] Selectivity to linear ester is not seriously affected by these changes except at low CO pressures (Table V, expt 59), where 1-heptene isomerization becomes the predominant reaction and the rates of *cis*- and *trans*-2-heptene carbonylation rival that of the 1 isomer.

Kinetic measurements, made under more selective conditions, were set to avoid induction periods prior to carbonylation by heating the catalyst solution under CO pressure before the injection of olefin (see Experimental Section). The effects of varying the tin to palladium mole ratio have already been summarized in Table II; for a constant Sn/Pd ratio of 10, the dependence of carbonylation rate upon catalyst concentration has been examined up to ca. 50 mM (data exemplified in Table V). Reproducibility is poor below 1 mM [Pd], but the rate obeys pseudo-first-order kinetics up to about 6 mM, and then reaches an asymptotic value. Similar rates at [Pd] > 6 mM might be due to the limited solubility of the active catalyst, but we see no evidence for insoluble material under these conditions. More likely it may be ascribed, as in related Pt–Sn catalysis,[18] to association of the effective catalyst, and/or inhibition of the associated complex, the palladium existing as a cluster[23] or halogen-bridged[24] species. The observed rate is also first order in CO pressure (expt 44, 45, 56–62), but independent of alcohol concentration provided at least a stoichiometric excess is present to satisfy eq 1. A zero-order de-

Table V. 1-Heptene Carbonylation Catalyzed by Solutions of $[(C_6H_5)_3P]_2PdCl_2$–$SnCl_2$. Rate Studies [a]

Expt	[Pd], mM	$[C_7H_{14}]$, M	CO, atm	$C_7H_{15}COOCH_3$ Selectivity, mol % [b]	$C_7H_{15}COOCH_3$ Rate, M h^{-1} [c]
41	25.8	0.52	136	84.4	0.32
42	20.6	0.52	136	84.6	0.30
43	10.3	0.52	136	85.6	0.29
44	5.15	0.52	136	86.5	0.25
45	3.61	0.52	136	87.6	0.17
46	2.58	0.52	136	87.5	0.13
47	2.06	0.52	136	87.5	0.095
48	1.55	0.52	136	87.3	0.078
49	5.15	1.72	136	87.8	0.23
50	5.15	0.96	136	90.9	0.24
51	5.15	0.78	136	88.1	0.22
52	5.15	0.36	136	88.1	0.23
53	5.15	0.11	136	88.9	0.12
54	5.68	0.57 [d]	136	86.5	0.23
55	5.95	0.60 [e]	136	88.6	0.13
56	5.15	0.52	102	87.8	0.17
57	5.15	0.52	68	87.0	0.13
58	5.15	0.52	34	88.0	0.060
59	5.15	0.52	8	76	<0.02
60	3.61	0.52	102	88.8	0.11
61	3.61	0.52	68	88.2	0.075
62	3.61	0.52	34	86.7	0.049

[a] Run conditions: [Sn]/[Pd] = 10; $[CH_3OH]$ = 3.82 M; 70 °C. [b] Selectivity basis: methyl octanoate/total methyl C_8 acid ester. [c] Rate of methyl octanoate formation. [d] $[CH_3OH]$ = 1.73 M. [e] $[CH_3OH]$ = 0.59 M.

pendence on olefin concentration has been confirmed at different palladium concentrations (e.g., expt 49–52) but some dropoff in rate is evident at low olefin/Pd mole ratios. Under normal operating conditions linear ester formation may be expressed in the form

$$\frac{d(\text{ester})}{dt} = \frac{k[\text{Pd}]p_{CO}}{(1 + K[\text{Pd}])} \quad (4)$$

for which the constant k has been calculated at 0.34 M^{-1} h^{-1}. An activation energy for this reaction of 31 kcal mol^{-1} was determined from Arrhenius plots over the temperature range 38–70 °C.

Nature of Palladium Catalyst. Beyond the analysis of recovered catalyst samples, other experiments were designed to isolate labile intermediates more akin to those truly responsible for carbonylation. The heating of an equimolar mixture of bis(triphenylphosphine)palladium(II) chloride (5 mmol) and tin(II) chloride dihydrate in benzene–ethanol under CO (100 atm) yielded a clear-red solution from which was isolated a green, crystalline solid (2.0 g) of the approximate composition $PdH(SnCl_3)(P(C_6H_5)_3)_2$. Anal. Calcd: Pd, 12.4; Cl, 12.4; P, 7.23. Found: Pd, 12.5; Cl, 13.0; P, 7.5; $\nu_{(Pd-H)}$ 2040 cm^{-1}, $\nu_{(Sn-Cl)}$ 315 cm^{-1}. Recycle of this material (1 mmol) in benzene with 1-octene (50 mmol) and excess ethanol gave ethyl nonanoate in 85.7 mol % selectivity. Total yield of ethyl C_9 acid ester was 92 mol %, octene conversion 94 mol %.

Palladium–trichlorotin complexes related to $PdH(SnCl_3)[P(C_6H_5)_3]_2$ have been reported previously;[25] the platinum analogue, $PtH(SnCl_3)[P(C_6H_5)_3]_2$, containing coordinated olefin, was isolated by Tayim and Bailar[26] during polyene hydrogenation catalyzed by $[(C_6H_5)_3P]_2PtCl_2$–$SnCl_2$ solutions.

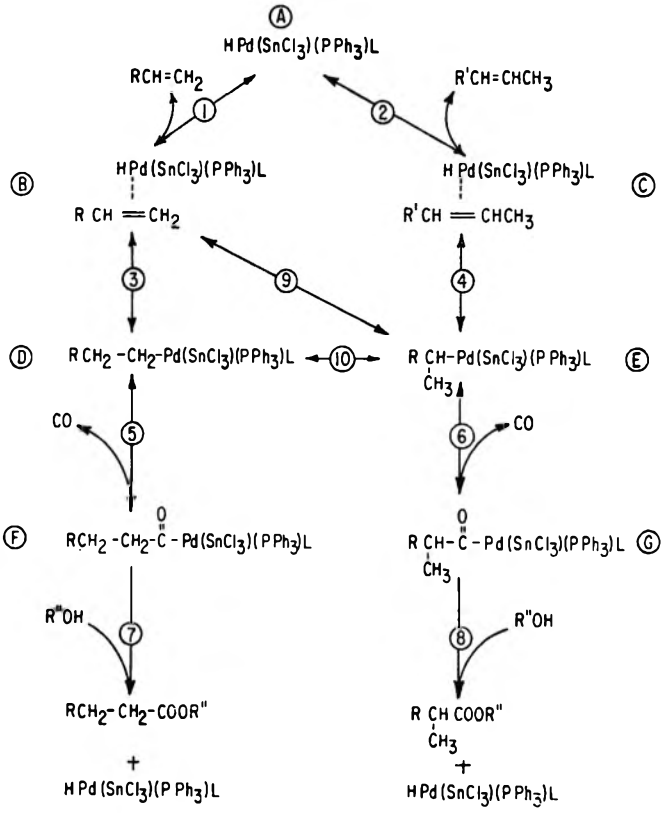
The heating of bis(triphenylphosphine)palladium(II) chloride (0.5 mmol) with additional quantities of tin(II) chloride (5.0 mmol) under CO led to the isolation of reddish-brown solids of the approximate composition $Pd(SnCl_3)_2[P(C_6H_5)_3]_2$. Similar materials were recovered from product solutions after carbonylation, but repeated studies failed to yield unequivocal evidence either for palladium carbonyl or for palladium–olefin adducts.

Discussion

The facile conversion of terminal olefins to linear, straight-chain acid esters in better than 85 mol % selectivity is the most significant feature of the stabilized palladium(II)–tin(II) chloride catalysts exemplified in Table I. This high regioselectivity is relatively insensitive to parameters such as temperature, CO pressure, solvent, and the nature of the coreactant, but is significantly influenced by the structure of the alkene and the composition of the active palladium catalyst.

The observed trends, summarized in Tables I and IV, may be rationalized in terms of the proposed reaction Scheme I.

Scheme I [a]



[a] WHERE L = $SnCl_3^-$, PPh_3, CO OR CHLORIDE ION

This scheme, similar to those for related catalyses,[1,3,27] is consistent with observed rate data, identified intermediate species, and prior studies of the integral steps of carbonylation, particularly the formation of labile palladium alkyls via olefin migration[3,6] and acyl–palladium species via CO insertion.[28-30]

The purpose of initially screening a large number of stabilized palladium–group 4B metal halide complexes was to identify ligand combinations which, through modification of the metal center, might (a) increase the selectivity to linear acid isomer, (b) accelerate the rate of carbonylation, and (c) suppress competing olefin isomerization. Although no simple correlations have been recognized between catalyst structure vs. effectiveness, a series of preferred catalysts of the composition $[(p\text{-}XC_6H_4)_3P]_2PdCl_2$–$MCl_2$ (where X = H, Cl, CH_3O, and CH_3 and M = Sn or Ge) has been identified (Table I). The moderately basic arylphosphines would be expected

to raise the hydridic nature of intermediate A, Scheme I, and thereby to promote both anti-Markownikoff Pd–H addition to the olefin substrate (step 3) and the formation of straight-chain palladium alkyls, such as D. Although this would be partly offset by the strong π-acceptor ability of coordinated $SnCl_3^-$,[16] the combined steric bulk of the phosphine and $SnCl_3^-$ ligands should provide a particularly sterically hindered catalyst in which steric constraints would act to favor both anti-Markownikoff Pd–H addition and high equilibrium concentrations of the less sterically hindered σ-alkyl and σ-acyl–Pd isomers such as D and F. Additional steric bulk serves only to block one or more of these rearrangements, as in the replacement of $(p\text{-}CH_3OC_6H_4)_3P$ by $(o\text{-}CH_3OC_6H_4)_3P$ and $(C_6H_5)_3P$ by $(C_6H_5)_3As$ (Table I).

The maximum catalytic activity realized at Sn:Pd mole ratios of ca. 5 (Table II) is in contrast to the isolation of the reactive intermediate $PdH(SnCl_3)(PPh_3)_2$, analogous to A in Scheme I, and to the fact that no palladium–tin(II) chloride complexes with group 5B donor ligands have been reported containing more than two $SnCl_3^-$ coordinated to each palladium.[31] Although unequivocal identification of the active catalyst has not been possible, evidence, such as the suppression of the rate by excess triphenylphosphine, and additional tin(II) chloride, suggests several interdependent equilibria existing in these tin-rich solutions (eq 5) prior to carbonylation, and the formation of inactive species with excess ligand. A platinum hydrocarbonyl species analogous possibly to the known[32] hydroformylation catalyst $[PtH(SnCl_3)(CO)(PPh_3)_2]$ has been isolated[33] from solutions of the related platinum carbonylation catalyst $[(C_6H_5)_3As]PtCl_2$–$SnCl_2$.[1] However, in line with the well-recognized lability of palladium carbonyls bonded to arylphosphines[29] no palladium hydrocarbonyl could be detected in this work.

$$[PdHCl(PPh_3)_2] + SnCl_2 \rightleftharpoons [PdH(SnCl_3)(PPh_3)_2] \begin{cases} \rightleftharpoons PdH(SnCl_3)(PPh_3) + PPh_3 \\ \overset{SnCl_3^-}{\rightleftharpoons} [PdH(SnCl_3)_2(PPh_3)]^- \end{cases} \quad (5)$$

Olefin structure plays a critical role in carbonylations catalyzed by $[(C_6H_5)_3P]_2PdCl_2$–$SnCl_2$. Of particular note (Table III) is (a) the reduced rate of carbonylation with increase in polysubstitution about the double bond, in the order linear α olefin > branched α olefin > internal olefin, (b) the variation in regioselectivity with α olefin structure, from a low of 84.9% for the least hindered homologue, propylene, to near 100% for certain β-substituted isomers such as 2-methyl-1-pentene, and (c) the markedly different product distributions for terminal and nonterminal olefins.

The selectivity trends outlined above will depend primarily upon how olefin structure influences initial Pd–H addition, subsequent skeletal rearrangement of the σ-alkyl- and, to a lesser extent, σ-acylpalladium transition states, and the relative rates of CO insertion.[34] The latter is most likely to be product controlling in view of the derived rate expression (eq 4). Regioselective carbonylation will be maximized where steric factors dictate an equilibrium dominance of least hindered palladium–alkyl (e.g., D vs. E) and comparatively faster rates of CO insertion for the least hindered isomer ($k_5 > k_6$). This condition is realized in the case of 2-methyl-1-pentene conversion to methyl 3-methylhexanoate (expt 28). Differences in the ease of carbonylation of *cis*- and *trans*-2-heptenes (expt 30 and 31) are consistent with the well-established[34] initial cis addition of olefin to the $[(C_6H_5)_3P]_2PdCl_2$–$SnCl_2$ catalyst, but suggest, at least for internal monoene carbonylation, that initial π complexation is a slow step.[35]

Competing double bond migration, which likely proceeds via π ⇌ σ interconversions similar to those depicted in Scheme I, competes successfully with olefin carbonylation only at low CO pressures (Table V). A relatively slow rate of alkylpalladium isomerization vs. CO insertion at higher CO pressures (>30 atm) is consistent with the relative yield data in Table I, the low selectivity to methyl octanoate realized with 2- and 3-heptenes, and the negligible changes in isomer distribution when carbonylating 1-heptene over the pressure range 34–240 atm. This latter result also implies no change in active catalyst composition at higher CO pressures, i.e., coordinated organophosphine is not displaced by additional CO.[34]

The observed minimal variation in linear ester selectivity with change in alkanol structure (Table IV), be it primary, secondary, or substituted alcohol, water, or phenol, militates against their involvement in the regioselective steps of the carbonylation (Scheme I). Rates of ester formation are affected by coreactant structure, but such variations are pronounced only where the coreactant is a poor nucleophile (e.g., phenol) or competing reactions become important as in the case of thiols. There is little evidence for the intermediate formation of palladium alkoxycarbonyl species,[6] similar to those recently synthesized in the presence of tertiary amine,[36] being of importance here.

Finally, regarding the source of hydrogen in Scheme I, the carbonylation of 1-heptene in the presence of methanol-d_1 yields linear ester of which >80% is methyl octanoate-3-d_1 (eq 6). These syntheses were run in carbon tetrachloride solutions of $[(C_6H_5)_3P]_2PdCl_2$–$SnCl_2$ (experimental conditions specified in Table II). Similar studies in methyl isobutyl ketone were less definitive, but for carbonylations in $^3H_2$-treated MIBK both the methyl octanoate product and unreacted heptene showed only a low level of tritium incorporation (see Table VI[37]). Furthermore, there were insignificant concentrations of ^3H in samples of recovered palladium catalyst. It would appear that solvent exchange is not important to the carbonylation sequence (Scheme I). Equation 6 is in agreement, however, with the work of Itatani and Bailar,[35] who found $[(C_6H_5)_3]_2PdCl_2$–$SnCl_2$ to be an adequate hydrogen transfer catalyst where methanol is the hydrogen donor.

$$C_5H_{11}CH{=}CH_2 + CO + CH_3OD \rightarrow C_5H_{11}CHDCH_2COOCH_3 \quad (6)$$

Experimental Section

Materials. Carbon monoxide was CP grade. Reagents and solvents were commercial grade; olefins were generally of high purity, and were freed of peroxide prior to use by passage through a column of neutral alumina. The palladium complexes $PdCl_2[P(C_6H_5)_3]_2$[35] and $PdCl_2[As(C_6H_5)_3]_2$[35] were prepared by published methods. Similar techniques were used to prepare $PdCl_2[P(p\text{-}CH_3C_6H_4)_3]_2$, $PdCl_2[P(o\text{-}CH_3OC_6H_4)_3]_2$, $PdCl_2[P(CH_3)_2C_6H_5]_2$, and $PdCl_2[P(C_6H_{11})_3]_2$. Hydrated tin(II) chloride, $SnCl_2{\cdot}2H_2O$, was used throughout as the cocatalyst except where specified.

General Procedures. The extent of carbonylation and the distribution of products were estimated by GLC. Olefin and ester analyses were both carried out with 4–10-ft columns of 10–20% polyphenyl ether (five rings, Analabs Inc. GP77) on 60/80 mesh Chromosorb G. High molecular weight fractions were also analyzed with the aid of a 4-ft column of 7% SE-30 on Chromosorb G. The esters were isolated by preparative GLC and by distillation, and identified by a combination of GLC, ir, NMR, mass spectrometric, and elemental analyses techniques.

After some preliminary experiments to establish suitable carbonylation conditions, most catalyst screening was carried out in a 600-ml glass-lined rocking autoclave under the conditions specified in Tables I–IV. Rates of carbonylation were measured using a 300-ml capacity, glass-lined autoclave equipped with Magnadrive stirrer and sampling valve.

Synthesis of Methyl Octanoate. Bis(triphenylphosphine)palladium(II) chloride (0.5–20 mmol) and tin(II) chloride dihydrate (2.5–20 mmol) were added to a N_2-saturated mixture of methyl isobutyl ketone (75 ml), methanol (5–15 ml), and 1-heptene (50–200 mmol). The mixture was stirred for 2–5 min to partially dissolve the solid catalyst, and the loaded liner containing the deep red liquid charge was

transferred to the autoclave. The autoclave was sealed, deoxygenated with a purge of N_2, and heated to 80 °C under 240 atm of carbon monoxide. After rocking the reactor at temperature for 3–6 h, the apparatus was allowed to cool, and the clear reddish-brown, liquid product recovered. Typical analyses data are as follows: 1-heptene conversion 95%, yield of methyl C_8 acid ester 88 mol %, selectivity to linear methyl octanoate 88 mol %, material balance, 97%.

The methyl C_8 acid esters may be recovered from the crude product liquid by fractional distillation in vacuo. Anal. Calcd for $C_7H_{15}COOCH_3$: C, 68.3; H, 11.4. Found: C, 68.4; H, 11.6.

Kinetic Measurements. Degassed solvent (70 ml) and methanol (15 ml) containing a weighed quantity of palladium complex (0.5–1.0 mmol) and tin(II) chloride dihydrate (2.5–20 mmol) were introduced into the glass-lined autoclave, and flushed with N_2. The clear, red solution was heated to temperature under a small pressure of carbon monoxide (5–10 atm), a mixture of olefin (50–200 mmol) and solvent (5 ml) injected from a side ampule, and the pressure adjusted with CO. The rate of carbonylation was monitored by withdrawing liquid samples (0.5 ml) at regular time periods. The samples were rapidly cooled and analyzed by GLC for olefin and methyl ester content with the aid of standard calibration curves.

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Supplementary Material Available. Table VI describing 1-heptene carbonylation in tritiated methyl isobutyl ketone (1 page). Ordering information is given on any current masthead page.

Registry No.—$[(C_6H_5)_3P]_2PdCl_2$, 13965-03-2; $[(p\text{-}CH_3C_6H_4)_3P]_2PdCl_2$, 31173-63-4; $[(p\text{-}CH_3OC_6H_4)_3P]_2PdCl_2$, 56781-20-5; $[(p\text{-}ClC_6H_4)_3P]_2PdCl_2$, 57457-62-2; $[(o\text{-}CH_3OC_6H_4)_3P]_2PdCl_2$, 57512-77-3; $[C_6H_5(CH_3)_2P]_2PdCl_2$, 15616-85-0; $[(C_6H_5O)_3P]_2PdCl_2$, 29891-44-9; $[(C_6H_5)_3As]_2PdCl_2$, 14126-26-2; $[(C_6H_5)_3P]_2PdI_2$, 23523-32-2; $SnCl_2$, 7772-99-8; $GeCl_2$, 10060-11-4; SnI_2, 10294-70-9; $PbCl_2$, 7758-95-4; $SnCl(Ph)_3$, 639-58-7; propylene, 115-07-1; 1-pentene, 109-67-1; 1-heptene, 592-76-7; 1-undecene, 821-95-4; 1-eicosene, 3452-07-1; 4-methyl-1-pentene, 691-37-2; 3-methyl-1-pentene, 760-20-3; 2-methyl-1-pentene, 763-29-1; cyclooctene, 931-88-4; *trans*-2-heptene, 14686-13-6; *cis*-2-heptene, 6443-92-1; *cis*-3-heptene, 7642-10-6; *trans*-5-decene, 14686-14-7; methanol, 67-56-1; 1-hexanol, 111-27-3; 2-propanol, 67-63-0; 2-chloroethanol, 107-07-3; phenol, 108-95-2; ethanethiol, 75-08-1.

References and Notes

(1) J. F. Knifton, *J. Org. Chem.*, **41**, 793 (1976).
(2) F. R. Hartley, *Chem. Rev.*, **69**, 799 (1969).
(3) J. Tsuji, *Acc. Chem. Res.*, **2**, 144 (1969).
(4) P. M. Maitlis, "The Organic Chemistry of Palladium", Vol. II, Academic Press, New York, N.Y., 1971, p 18.
(5) K. Bittler, N. V. Kutepow, D. Neubaver, and H. Reis, *Angew. Chem., Int. Ed. Engl.*, **7**, 329 (1968).
(6) D. M. Fenton, *J. Org. Chem.*, **38**, 3192 (1973).
(7) P. M. Henry, *Tetrahedron Lett.*, 2285 (1968).
(8) J. Tsuji, M. Morikawa, and J. Kiji, *Tetrahedron Lett.*, 1437 (1963).
(9) S. A. Butter, U.S. Patent 3 700 706 (1972).
(10) J. F. Knifton, German Patent 2 303 118 (1973).
(11) J. F. Knifton, U.S. Patent 3 919 272 (1975).
(12) J. J. Mrowca, U.S. Patent 3 859 319 (1975).
(13) L. Pauling, "Nature of the Chemical Bond", Cornell University Press, Ithaca, N.Y., 1960, p 518.
(14) C. A. Tolman, *J. Am. Chem. Soc.*, **92**, 2956 (1970).
(15) J. Halpern and P. F. Phelan, *J. Am. Chem. Soc.*, **94**, 181 (1972).
(16) J. F. Young, *Adv. Inorg. Chem. Radiochem.*, **11**, 91 (1968).
(17) H. A. Tayim and J. C. Bailar, *J. Am. Chem. Soc.*, **89**, 3420 (1967).
(18) I. Yasumori and K. Hirabayashi, *Trans. Faraday Soc.*, **67**, 3283 (1971).
(19) The carbonylation of more strongly polarized double bonds will be considered elsewhere.
(20) J. Falbe, "Carbon Monoxide in Organic Synthesis", Springer-Verlag New York, New York, N.Y., 1970, Chapter II.
(21) E. S. Gould, "Mechanism and Structure in Organic Chemistry", Holt, Rinehart and Winston, New York, N.Y., 1959, p 258.
(22) J. F. Knifton, U.S. Patent 3 880 898 (1975).
(23) K. Kudd, M. Hidai, and Y. Uchida, *J. Organomet. Chem.*, 33, 393 (1971).
(24) K. R. Dixon and D. J. Hawke, *Can. J. Chem.*, **49**, 3252 (1971).
(25) J. V. Kingston and G. R. Scollary, *J. Chem. Soc. A*, 3765 (1971).
(26) H. A. Tayim and J. C. Bailar, *J. Am. Chem. Soc.*, **89**, 4330 (1967).
(27) R. F. Heck, *J. Am. Chem. Soc.*, **85**, 2013 (1963).
(28) A. Wojcicki, *Adv. Organomet. Chem.*, **11**, 138 (1973).
(29) G. Booth and J. Chatt, *J. Chem. Soc. A*, 634 (1966).
(30) L. S. Hegedus and K. Siirala-Hansen, *J. Am. Chem. Soc.*, **97**, 1184 (1975).
(31) E. Maslowsky, *Chem. Rev.*, **71**, 507 (1971).
(32) C. Hsu and M. Orchin, *J. Am. Chem. Soc.*, 97, 3553 (1975).
(33) J. F. Knifton, unpublished results.
(34) M. Orchin and W. Rupilius, *Catal. Rev.*, **6**, 85 (1972).
(35) H. Itatani and J. C. Bailar, *J. Am. Oil Chem. Soc.*, **44**, 147 (1967).
(36) M. Hidai, M. Kokura and Y. Uchida, *J. Organomet. Chem.*, **52**, 431 (1973).
(37) See paragraph at end of paper regarding supplementary material.

Stereochemistry of Reduction of Ketones by Simple and Complex Metal Hydrides of the Main Group Elements

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The stereochemistry of reduction of selected ketones by a variety of simple and complex main group metal hydrides, both old and new, has been investigated under identical conditions of solvent, concentration, stoichiometry, temperature, and reaction time for comparison purposes. The stereochemical results of these studies are discussed in terms of steric approach control, torsional strain, compression effect, change in conformation of the ketone, and orbital distortion theory. The stereochemistry of reduction of complex aluminohydrides is shown to be dependent on the nature of the cation. Comparison of $LiAlH_4$ and $LiBH_4$ as reducing agents toward ketones shows $LiBH_4$ to be less sensitive to steric interactions. Reduction of 2-methylcyclohexanone with $ClMgAlH_4$ and $Mg(AlH_4)_2$ gave results best explained by assuming complexation of the carbonyl oxygen by magnesium followed by a change in the conformation of the ketone (methyl group equatorial to axial). Results obtained from reduction studies of substituted cyclopentanones and *cis*-2-methyl-4-*tert*-butylcyclohexanone do not suggest the presence of a compression effect in metal hydride reductions. A study of the reduction of ketones by $LiAl(OR)_3H$ compounds shows the stereochemistry to be independent of concentration. The stereochemistry of reduction of ketones by $LiAlH_4$ and $LiAlD_4$ is similar.

In recent years the area of stereoselective reduction of ketones by AlH_3, $LiAlH_4$, and their alkoxy derivatives has been investigated by several workers.[1,2]

Stereochemical results were first explained by Dauben, who suggested the concepts of "product development and steric approach control".[3] While "steric approach control" appears

to be an unquestionably valid concept, the concept of product development control has been questioned. In this connection Cherest and Felkin have introduced the concept of torsional strain[4-7] as an alternative to "product development control." Other alternatives to the concept of "product development control" have been suggested;[8,9] however, the concept of torsional strain seems to be the concept best accepted at the present time.[10,11] However, recently orbital symmetry arguments[12] and unequal distortion of electron density[13] about the carbonyl group have been advanced as possible factors in stereochemical control of metal hydride reduction of ketones. Thus factors, other than "steric approach control", that determine the stereochemistry of metal hydride reduction of ketones remain an area of great interest and controversy.

The importance of the cation in ketone reductions has been investigated for complex metal borohydrides. The borohydride ion was found to require a protic solvent or the presence of lithium or magnesium ions in order to be effective in the reduction of esters[14] and ketones.[15] The lithium ion may catalyze the reduction by polarizing the B–H bond or the C=O bond. On the other hand, $NaAlH_4$[16] and its alkoxy derivatives[17] as well as NR_4AlH_4 compounds[18] are known to reduce ketones; therefore, the lithium ion is not necessary for the reduction of ketones by complex aluminohydrides. It has been suggested[1] that reduction of ketones by $LiAlH_4$ may involve a prior or synchronous association of the carbonyl oxygen atom with the lithium cation which assists the hydrogen transfer.

If complexation of the carbonyl group is rate determining, then reaction rates should reflect the rate of complexation of the ketone by the hydride. However, because of the large difference in the rate of reduction of a series of cyclohexanones with $LiAl(OBu\text{-}t)_3H$,[11] it was concluded that complexation of the ketone by the hydride was not rate determining as the rate of complexation should be about equal for the series. It was pointed out, however, that the importance of complexation of the carbonyl group by the hydride on the stereochemistry of such reductions is not known.

Reduction of 3,3,5-trimethylcyclohexanone by $LiAlH_4$ in diethyl ether and tetrahydrofuran (THF) gives different results, namely, 55 and 75% equatorial attack, respectively.[19] Therefore, solvation of the $LiAlH_4$ appears to be important in determining the stereochemistry of reduction of ketones. Recently we have determined that $LiAlH_4$ has a much higher molar conductance in THF than in diethyl ether.[20] This observation suggests that $LiAlH_4$ in THF is more selective than in diethyl ether because $LiAlH_4$ is a solvent separated ion pair in THF while it is best described as a contact ion pair in diethyl ether. It has also been suggested[21] that the greater stereoselectivity of $LiAl(OCH_3)_3H$ compared to $LiAl(OBu\text{-}t)_3H$ could be ascribed to the higher degree of association of $LiAl(OCH_3)_3H$ and hence its greater steric requirement.

Unfortunately, the value of the literature for comparing one hydride reduction to another is often diminished significantly because of the wide variation in experimental conditions used. The purpose of this work was to evaluate complex aluminohydrides as stereoselective reducing agents toward model ketones under identical conditions with the hope that emerging patterns might appear. Reactant concentration, temperature, cation, solvent, stoichiometry, and order of addition of reactant were held constant for each study. For example, it was thought that if the nature of the cation was important it would be reflected in the stereochemical results provided that all the data was collected at the same temperature, solvent, concentration, etc. Other studies carried out involve an evaluation of a large number of simple and complex metal hydrides (other than aluminohydrides) as stereoselective reducing agents and the effect of concentration and hence association on stereoselectivity.

Results and Discussion

A variety of complex metal hydrides were allowed to reduce several ketones which had the possibility of giving, on hydrolysis, isomeric alcohols. The ketones employed reflect different degrees of steric hindrance at the carbonyl group and ranged from relatively flexible cyclic ketones, e.g., 2-methylcyclohexanone, to rigid bicyclic ketones, e.g., norcamphor. The homogeneous reductions were carried out at 0 °C for 2 h in THF using two ratios of hydride to ketone (H^-/ketone = 6 and H^-/ketone = 1). The heterogeneous reductions were carried out at room temperature in the presence of excess hydride. The ketones used in this study are 4-*tert*-butylcyclohexanone (I), 2-methylcyclohexanone (II), 3,3,5-trimethylcyclohexanone (III), norcamphor (IV), and camphor (V). The results of the reductions of the above ketones with $LiAlH_4$, $NaAlH_4$, NR_4AlH_4 (NR_4 = tri-*n*-octyl-*n*-propylammonium ion), $Mg(AlH_4)_2$, and $ClMgAlH_4$ are given in Table I. The reactions were carried out under identical conditions except in those cases where the hydride had limited solubility [$Mg(AlH_4)_2$ and $ClMgAlH_4$].

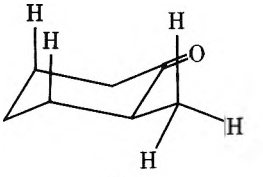
Reduction of 4-*tert*-Butylcyclohexanone (I). All the hydrides in Table I behave similarly toward I, although a trend may be suggested involving $LiAlH_4$, $NaAlH_4$, and NR_4AlH_4. The 10% equatorial attack observed for $LiAlH_4$ represents a 1.0:9.0 ratio of products while the 15% equatorial attack for NR_4AlH_4 represents a 1.0:5.7 ratio of products. In spite of the limitations of GLC analysis to determine absolute yield data, the results were entirely reproducible.

In the case of I, steric hindrance and torsional strain favor different directions of attack. Torsional strain appears to be the dominant factor (Table I) in that predominant axial attack is observed. Why $LiAlH_4$ and $ClMgAlH_4$ might experience torsional strain more than other hydrides is not readily apparent, but it is clear that the difference is not great. It is also clear from Table I that the hydride:ketone ratio is of little importance with all the hydrides studied.

4-*tert*-Butylcyclohexanone should be a good model for the chair form of cyclohexanone. The *tert*-butyl group is locked in an equatorial position and is removed from the reaction center. Its inductive, steric, and field effects on the reaction center should be minimal. Therefore, the data in Table I for ketone I should represent accurately the ratio of axial:equatorial attack on the chair conformation of cyclohexanone.

Reduction of 2-Methylcyclohexanone (II). The hydrides in Table I are less similar in their selectivity toward II compared to I. Magnesium aluminum hydride and $ClMgAlH_4$ give 12–24% more apparent equatorial attack than $LiAlH_4$ toward II, whereas little difference (0–3%) was observed in the reaction of I. The other hydrides ($NaAlH_4$ and NR_4AlH_4) are similar to $LiAlH_4$ and give about 25% apparent equatorial attack.

All of the hydrides studied should give more equatorial attack on II than I, if the reactive conformation is considered to be IIe. It has been suggested[22] that the hydrogen atoms of



IIe

the methyl group introduce a third, 1,3-diaxial interaction with respect to the incoming nucleophile. This effect will, of course, retard axial attack. Reaction of II through the flexible forms (the various boat and twist-boat conformations) has also been suggested[23] to explain the increase in equatorial attack on II over I. This increase in apparent equatorial attack has

Table I. Reductions of Some Representative Ketones with a Series of Complex Aluminohydrides ($MAlH_4$) in THF

Ketone[a]	Hydride[a]	H^-/ketone = 6		H^-/ketone = 1	
		% equatorial or exo Attack	Yield[b]	% equatorial or exo Attack	Yield[b]
4-*tert*-Butylcyclohexanone (I)	$LiAlH_4$	10	103	8	94 (2)
	$NaAlH_4$	13	104	12	98
	NR_4AlH_4	15	99	14	80 (12)
	$Mg(AlH_4)_2$[c]	13	99 (2)	14	75 (14)
	$ClMgAlH_4$[d]	10	86 (2)	10	85 (18)
2-Methylcyclohexanone (II)	$LiAlH_4$	24	96	25	96
	$NaAlH_4$	29	91	28	96
	NR_4AlH_4	26	84	27	77 (11)
	$Mg(AlH_4)_2$[c]	48	90	49	81 (10)
	$Mg(AlH_4)_2$[e]	48	96		
	$ClMgAlH_4$[d]	36	94	43	83 (14)
3,3,5-Trimethylcyclohexanone (III)	$LiAlH_4$	80	108	75	96 (6)
	$NaAlH_4$	59	100	65	102 (2)
	NR_4AlH_4	55	106 (2)	55	80 (25)
	$Mg(AlH_4)_2$[c]	61	102	56	86 (9)
	$ClMgAlH_4$[d]	71	100	61	81 (18)
Norcamphor (IV)	$LiAlH_4$	91	98	90	97 (6)
	$NaAlH_4$	83	100	82	89 (11)
	NR_4AlH_4	74	106 (2)	76	73 (20)
	$Mg(AlH_4)_2$[c]	87	102	86	94 (9)
	$ClMgAlH_4$[d]	92	98	88	83 (16)
Camphor (V)	$LiAlH_4$	9	99	10	68 (26)
	$NaAlH_4$	12	98	12	79 (25)
	NR_4AlH_4	12	82 (26)	13	46 (57)
	$Mg(AlH_4)_2$[c]	26	101	25	84 (16)
	$Mg(AlH_4)_2$[e]	25	100		
	$ClMgAlH_4$[d]	19	96	22	69 (39)

[a] The initial concentration of hydride and ketone was 0.50 M. Ketone was added to hydride when $H^-/K = 6$. Hydride was added to ketone when $H^-/K = 1$. The reaction was carried out at 0 °C and quenched after 2 h. [b] Absolute yield measured with an internal standard. The percent recovered ketone is given in parentheses. [c] 0.25 M ketone was added directly to the solid $Mg(AlH_4)_2$ in the ratios H^-/ketone = 8 and 1. The $Mg(AlH_4)_2$ contained NaCl. $Mg(AlH_4)_2$ has a small solubility in THF since it can be extracted from NaCl with THF. [d] The initial concentrations of $ClMgAlH_4$ and ketone were 0.19 and 0.25 M, respectively. [e] Same as *c* except $Mg(AlH_4)_2$ with no NaCl present.

also been attributed[3,24] to reaction of the chair conformation with the methyl group axial (IIa). Axial attack on this con-

IIa

formation would give the cis alcohol accounting for the increase in apparent equatorial attack on II over I. 2-Methylcyclohexanone is reported[25] to exist in such a conformation (IIa) to the extent of approximately 5% at ambient temperature. On the other hand, it has been reported[2] that $LiAlH_4$ gives 91% axial attack on *cis*-2-methyl-4-*tert*-butylcyclohexanone. This result shows that the introduction of an equatorial 2-methyl group on I has not increased steric hindrance to axial attack since 4-*tert*-butylcyclohexanone gives 90% axial attack with $LiAlH_4$. The implication then is that decreased axial attack on 2-methylcyclohexanone is not due to the pseudoaxial hydrogen of the 2-methyl group, but probably due to reaction via conformer IIa. Increased axial attack on conformer IIa can be explained by steric repulsion of the substituents in the 2(CH_3), 6(H) axial positions thus forcing the conformation more in the direction of a half-chair. As we shall see a little later in this paper, the above data could not be reproduced; as a matter of fact, the data obtained from the present studies indicate that indeed the pseudoaxial hydrogen of the 2-methyl group does provide steric hindrance to axial attack since reaction of $LiAlH_4$ with *cis*-2-methyl-4-*tert*-butylcyclohexanone gave twice as much equatorial attack as the reaction with 4-*tert*-butylcyclohexanone.

Magnesium aluminum hydride and $ClMgAlH_4$ give considerably more equatorial attack on II than $LiAlH_4$ while their results with I were similar to $LiAlH_4$. An explanation based on steric hindrance was considered first. If $ClMgAlH_4$ and $Mg(AlH_4)_2$ have a larger steric requirement than $LiAlH_4$, then these compounds would possibly attack conformation IIe less from the axial side due to an increase steric hindrance introduced by the quasi-axial hydrogen of the methyl group. Such an explanation based on steric hindrance should also be consistent with observed stereochemical results for reduction of other ketones by $LiAlH_4$, $ClMgAlH_4$, and $Mg(AlH_4)_2$ and not conveniently invoked to explain the results with II. Magnesium aluminum hydride and $ClMgAlH_4$ give more axial attack on 3,3,5-trimethylcyclohexanone (III) and more exo attack on camphor (V); thus, they have an apparent smaller steric requirement than $LiAlH_4$ in these two cases.

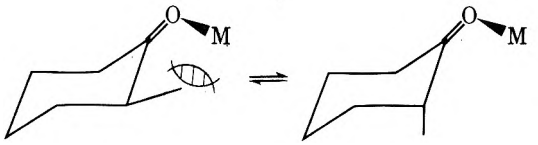
It was next considered that possibly more of conformation IIa is involved in the reaction when II is reduced by $ClMgAlH_4$ and $Mg(AlH_4)_2$ than $LiAlH_4$. Such an explanation may be made by assuming that the cation, M^+, of $MAlH_4$ associates with the carbonyl oxygen during the reduction step. If the cation complexes the carbonyl oxygen prior to or concurrent with reduction, then the $MgCl^+$ or $MgAlH_4^+$ being larger than Li^+ would interact more with the methyl group of IIe and force more of the reaction to proceed through the chair conformation IIa. Such a conformation produces less interaction be-

tween the cation as it complexes the carbonyl oxygen atom and the methyl group.

Reduction of *cis*-2-methyl-4-*tert*-butylcyclohexanone (VI) by $LiAlH_4$, $ClMgAlH_4$, and $Mg(AlH_4)$ was carried out[26] to investigate the possibility that cation complexation of the carbonyl oxygen satisfactorily explains the reduction data obtained for II. In the case of VI the methyl group is locked in an equatorial position and since a change in conformation cannot easily occur, the stereochemical outcome should be nearly the same with all three hydrides as in the case of I.

Table II shows the extent of apparent equatorial attack on I, II, and VI. The order of apparent equatorial attack on II (IIe) is $LiAlH_4 < ClMgAlH_4 < Mg(AlH_4)_2$. The hydrides show less variation in the amount of equatorial attack on I and VI than II. Each hydride gives about twice the amount of equatorial attack on VI as I. Since the results of this study show the steric requirement of each hydride to be nearly the same toward VI, the conclusion is that more of conformation IIa is involved in the reduction of II by $Mg(AlH_4)_2$ and $ClMgAlH_4$ than by $LiAlH_4$. Although the hydrides give more equatorial attack on VI than I, the important consideration is that the amount of equatorial attack is about the same for each hydride. It is clear from this work that the amount of equatorial attack on VI is too small to explain the amount of apparent equatorial attack on II as taking place only through conformation IIe.

It has been shown that lithium and magnesium salts or protic solvents catalyze[14,15] borohydride reduction of ketones and esters. These results suggest a mechanism for ketone reduction by $LiAlH_4$ involving prior or concurrent association of the carbonyl oxygen with Li^+ as the hydride is transferred. If complexation of the carbonyl group occurs during reduction, then the concentration of IIaC (and its transition state corresponding to axial attack) should increase relative to IIa since the energy difference between IIaC and IIeC is less than be-



(1)

IIeC IIaC

tween IIa and IIe. Therefore, it is not surprising that more reaction proceeds through IIaC with bulkier complexing agents such as $-MgCl^+$ and $-MgAlH_4^+$ than with a smaller complexing agent such as Li^+. We have previously shown that a ketone will associate with the lithium cation in tetrahydrofuran solution.[20]

Each hydride in Table II gives twice the amount of equatorial attack on VI as compared to I. Reduction of I, II, and VI by $LiAlH_4$ gives 10, 24, and 19% equatorial attack, respectively. If both conformations IIa (5%) and IIe (95%) have the same rate of reaction, then 19% equatorial attack on IIe by $LiAlH_4$ (since VI gives 19% equatorial attack) plus a large amount of axial attack on IIa (present in 5%) produce approximately 24% apparent equatorial attack on II which is what is experimentally observed. Thus the results indicating that the C-2 methyl group does hinder axial attack can be explained by assuming that the C-2 methyl (1) blocks the axial approach of the aluminohydride ion from a direction perpendicular to the plane of the carbonyl group; (2) blocks the hydride from moving into an axial position after complexation of the oxygen atom; and/or (3) causes steric strain involving the cation as it complexes the oxygen atom thus causing part of the reduction to occur via the flexible form.

Chloromagnesium aluminum hydride exhibits a change in selectivity when the ratio of hydride to II is varied but $Mg(AlH_4)_2$ does not show such a change. Results with II involving the other hydrides in Table I show that selectivity is insensitive to ratio of reactants. Since $Mg(AlH_4)_2$ is only slightly soluble in THF, its reactions reported in Table I are probably only occurring in solution at one ratio (H^-/ketone ≤ 1, i.e., excess ketone) even though the measured ratios are different. Since $ClMgAlH_4$ is soluble in THF, the results do indeed reflect reaction at two different ratios (H^-/ketone = 1 and 6). A change in stereochemistry for $ClMgAlH_4$ with ratio of reactants occurs not only for II but also for III, IV, and V (Table I). The effect of ratio of reactants on stereochemistry is negligible for $LiAlH_4$ and ketones I–V except maybe for III (Tables I and VI). Eliel has interpreted[19,27] such results as indicating that $LiAlH_4$ is the reducing agent at all ratios because the following disproportionation reactions are very rapid.

$$4/nLiAl(OR)_nH_{(4-n)} \rightarrow (4-n)/nLiAlH_4 + LiAl(OR)_4 \quad (2)$$

$$n = 1, 2, \text{or } 3$$

If any alkoxy intermediates were reacting one would expect the steric requirement of the intermediate to be greater than $LiAlH_4$ and hence attack on the ketone from the least hindered side should increase. However, when III, IV, and V (H^-/ketone = 1) are allowed to react with $ClMgAlH_4$ the results show increased attack from the more hindered side of the ketone than when excess hydride is used and thus resemble more the results obtained using $Mg(AlH_4)_2$. Although no explanations appear particularly convincing it is possible that the intermediates formed on reduction of $ClMgAlH_4$ with ketones ($ClMgAlH_nOR_{4-n}$) disproportionate to $Mg(AlH_4)_2$ and thus the results resemble those obtained with $Mg(AlH_4)_2$.

Table II. Percent Cis Alcohol from the Reaction of Complex Metal Hydrides with Cyclohexanones in THF

Hydride[a]	I 4-*tert*-Butylcyclohexanone	II 2-Methylcyclohexanone	VI *cis*-2-Methyl 4-*tert*-butylcyclohexanone
$LiAlH_4$[b]	10	24	19[c]
$LiAlH_4$	8	25	
$ClMgAlH_4$[b]	10	36	21[c]
$ClMgAlH_4$	10	43	21[c]
$Mg(AlH_4)_2$[b]	13	48	27,[c] 26[d]
$Mg(AlH_4)_2$	14	49	

[a] See footnotes *a*, *c*, and *d* of Table I. [b] Excess hydride [c] Ratio measured by GLC analysis [d] Ratio measured by NMR analysis.

Reduction of 3,3,5-Trimethylcyclohexanone (III). Ketone III introduces a methyl group in the C-3 axial position which severely hinders axial attack on this cyclohexanone. The largest difference in selectivity of the hydrides studied occurs with this ketone (Table I). Equatorial attack predominates for all hydrides and ratios of reactants (55–80%). Steric hindrance is experienced more by $LiAlH_4$ than the other hydrides and results in the largest amount of equatorial attack (8). The order of selectivity is $LiAlH_4 > ClMgAlH_4 > Mg(AlH_4)_2 \approx NaAlH_4 > NR_4AlH_4$.

Reduction of Norcamphor (IV). Reductions of IV show a similar trend in selectivities of the hydrides as III: $LiAlH_4 \approx ClMgAlH_4 > MgAlH_4 > NaAlH_4 > NR_4AlH_4$. Steric hindrance and torsional strain favor opposite sides of attack in I, II, III, and V but not necessarily in IV where both effects might favor exo attack. It is important to note that when a hydride attacks endo, torsional strain occurs between the C_1–C_6 bond and the newly forming C_1–H bond. Although reductions of I and II are governed largely by torsional strain

and III and V by steric hindrance, it is not so easy to decide the predominant factor that governs the reduction of IV. It is likely that both torsional strain and steric hindrance are important in the reduction of IV. Lithium aluminum hydride shows a similar degree of selectivity for IV and V (91% of the less stable isomer). If steric hindrance was the only important factor controlling the selectivity of a hydride toward IV as probably it is in V, then the other hydrides should show the same degree of selectivity for IV as they do V, just as $LiAlH_4$ does; however, this is not the case; thus factors other than steric hindrance must be important. Since I gives similar results with each hydride and torsional strain is believed to be the governing factor in the stereochemistry of reduction, it may be expected that each hydride would give about the same results with IV if torsional strain was the only important factor controlling stereochemistry, but neither is this the case. The large amount of exo attack on IV by all the hydrides can probably be best attributed to the fact that it is favored by both steric hindrance and torsional strain. The 18% spread in the selectivity of the hydrides may be attributed to how each hydride experiences the steric hindrance; thus they follow a trend similar to III.

Reduction of Camphor (V). The hydrides $LiAlH_4$, $NaAlH_4$, and NR_4AlH_4 are similar in their selectivity toward V; they give 87–91% endo attack. The syn C-7 methyl group severely blocks exo attack and the results are as expected. The hydrides $ClMgAlH_4$ and $Mg(AlH_4)_2$ give less endo attack (81 and 74%, respectively) than the other hydrides. This is unexpected since they appeared to experience steric hindrance more than $NaAlH_4$ and NR_4AlH_4 with III and IV. If torsional strain is used to explain why $ClMgAlH_4$ and $Mg(AlH_4)_2$ give more exo attack on V than the other hydrides, then it is difficult to explain why they give more equatorial attack on III than $NaAlH_4$ and NR_4AlH_4. Perhaps forces other than steric hindrance and torsional strain influence the stereochemical outcome of reductions of ketones.

General Considerations Concerning Aluminohydrides as Reducing Agents. The stereoselectivity of hydride reduction of ketones can be seen from Table I to have some dependence upon the cation present. If the hydrides containing magnesium are not considered, the smaller the cation (greater charge density) the more the hydride will attack from a particular side of I, III, and IV. Results with ketones II and V are too similar to allow any conclusions. It does appear that $LiAlH_4$ is the most selective hydride in attacking either side of the carbonyl group whether the stereochemistry is controlled by steric hindrance or torsional strain. This means that $LiAlH_4$ experiences torsional strain or steric hindrance more than the other hydrides, depending on the nature of the ketone.

The difference in selectivities may be due to two possible factors: (1) the cation participates directly in the step in which the stereochemistry is determined, or (2) the cation alters the reducing species in solution. Probably the most apparent mechanism by which the lithium ion may participate directly in the reaction would be for it to complex the ketone during reduction. Brown has shown that the lithium ion catalyzed the reduction of ketones by the borohydride ion in aprotic solvents because $LiBH_4$ reduces acetone in aprotic solvents and $NaBH_4$ does not.[14] The lithium ion may enter into catalysis by either polarizing the carbonyl bond or the B–H bond.[14] If complexation of the carbonyl oxygen by the cation were to occur, the resulting influence on the stereochemistry is not readily apparent for all ketones even though its possible importance in the reduction of II was discussed. Since $NaAlH_4$ and NR_4AlH_4 will reduce ketones, it is apparently not necessary for the reaction of the aluminohydride ion to require the presence of the lithium cation. Since the reduction of V by NR_4AlH_4 is slower than by $LiAlH_4$ (Table I), the lithium ion must catalyze the reaction in some manner. Since the lithium cation will associate with ketones in tetrahydrofuran,[20] it is not only possible but probable that the lithium cation polarizes the carbonyl group increasing the rate of reaction.

Table III. Reductions of Some Representative Ketones with $LiBH_4$ in THF

	H^-/ketone = 6		H^-/ketone = 1	
Ketone[a]	% equatorial or exo attack	% yield[b]	% equatorial or exo attack	% yield[b]
I	7	97	8	92
II	29	92	36	95 (2)
III	53	95	60	96
IV	82	103	90	88
V	31	100[c,d]	26	94 (6)[c,e]

[a] See footnote *a* Table I. [b] Absolute yield measured with an internal standard. [c] Relative yield. [d] 98% reaction in 9 days determined by uv spectroscopy. Reaction was quenched after 10 days. [e] 91% reaction in 31 days as determined by uv spectroscopy. Reaction was quenched after 31 days.

It should not be overlooked that solvation of the cation may alter the reducing species. Reduction of III by $LiAlH_4$ in diethyl ether gives only 55% equatorial attack compared to 75% in THF[15] as solvent. This difference may be attributed to solvation of the cation. Since solvation of $MAlH_4$ varies with M, the stereochemistry should also depend on M due to a change in the ion pair structure and steric requirement of the hydride. In addition, the presence of a solvated cation in the transition state may require more order in the transition state for hydride transfer, thus a greater selectivity.

The magnesium cation is about the same size[28] as the lithium cation but carried a +2 charge instead of +1. In light of the above discussion $Mg(AlH_4)_2$ and $ClMgAlH_4$ may be expected to be more selective than $LiAlH_4$ toward III, IV, and V because the magnesium cation would have a larger charge density than the lithium cation. This is not observed. It probably is unfair to try to make such a comparison between $Mg(AlH_4)_2$ and $ClMgAlH_4$, and $LiAlH_4$ because the nature of the species in solution could be quite different.

Reductions with $LiBH_4$. Ketones I–V were reduced with $LiBH_4$ under identical conditions as with $LiAlH_4$. The results are tabulated in Table III. Reductions with $LiBH_4$ were slower than with $LiAlH_4$. Reactions with III, IV, and V were followed spectrophotometrically to assure completion of reaction before quenching since considerable reduction was found to occur upon quenching.

Lithium borohydride gives results similar to $LiAlH_4$ for I and II where torsional strain is believed to be the controlling factor in determining the direction of attack. When the reduction is controlled by steric hindrance (III, IV, and V) $LiBH_4$ gives more attack than $LiAlH_4$ from the more hindered side. This is consistent with the fact that the borohydride ion is smaller[29] than the aluminohydride ion or that $LiBH_4$ is less solvated[20] than $LiAlH_4$ in THF; thus it has a smaller steric requirement. When the ratio of H^-/ketone = 1, $LiBH_4$ gives more attack from the least hindered side of the ketone in all cases than when $LiBH_4$ is used in excess. This is consistent with more of the reduction occurring via alkoxy intermediates at low hydride:ketone ratios.[30]

Reduction of Cyclopentanones. In order to compare the reduction of cyclopentanones to alkylation results using CH_3MgBr and $Al(CH_3)_3$,[31] 2-methylcyclopentanone (VII), 3-methylcyclopentanone (VIII), and *cis*-3,4-dimethylcyclopentanone (IX) were reduced with $LiAlH_4$ (Table IV).

The preferred conformation of cyclopentanone (half-chair model) has a C_2 axis of symmetry[32] which allows equal attack

Table IV. Reduction of Methyl Substituted Cyclopentanones with $LiAlH_4$, $Mg(AlH_4)_2$, and $ClMgAlH_4$ in THF

Ketone[a]	Hydride[a]	H^-/ketone = 6		H^-/ketone = 1	
		% cis attack	Yield[b]	% cis attack	Yield[b]
2-Methylcyclopentanone (VII)	$LiAlH_4$	84[c,d]	100	84[c,d]	100
	$ClMgAlH_4$	65[c]	100	58[c]	91
	$Mg(AlH_4)_2$	45[c]	99		
3-Methylcyclopentanone (VIII)	$LiAlH_4$	27[d]	100	29[d]	92
	$ClMgAlH_4$	25[d]			
	$Mg(AlH_4)_2$	20[d]			
cis-3,4-Dimethylcyclopentanone (IX)	$LiAlH_4$	10[d]	100	10[d]	90
	$ClMgAlH_4$	10[d]			
	$Mg(AlH_4)_2$	10[d]			

[a] See footnotes *a*, *c*, and *d* of Table I. [b] Relative yields based on GLC analysis. [c] Ratio of products measured by GLC analysis. [d] Ratio of products measured by NMR in Me_2SO-d_6.

from either side; however, substituents distort the symmetry causing one side to be attacked more easily than the other. Since VII is attacked 84% cis (with respect to the methyl group) by $LiAlH_4$, any steric hindrance from the C-2 methyl group seems to be minor. The methyl group is probably in a quasi-equatorial position and offers less steric hindrance than torsional strain by the quasi-axial hydrogen at C-2 on the other side of the ring.[2] Common methylating reagents [$Al(CH_3)_3$, CH_3MgBr] are slightly hindered by the methyl group and give about 40% cis attack.[31]

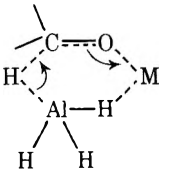
The ketone VIII is attacked 71–73% trans by $LiAlH_4$. This may at first glance be ascribed to steric hindrance of the C-3 methyl group blocking cis attack since the introduction of an axial C-3 methyl group on a cyclohexanone ring results in a large decrease in axial attack, from 90% to 20% (ketones I and III). This observation in the cyclohexanone case is clearly ascribed to steric hindrance. However, since the cyclohexanone chair conformation does not allow equal attack on both sides while the half-chair conformation of cyclopentanone does, it is important to note that the C-3 methyl group of VIII only changes the preferred direction of attack from 50% to 72%. This is less than for the C-2 methyl group of VII (50 to 84%) whose stereochemistry of reduction is not controlled by steric hindrance, but probably by torsional strain. Several methylating reagents, which usually have larger steric requirements than hydrides, give[31] only 60% trans attack on VIII. It is also reported that VIII and 3-*tert*-butylcyclopentanone are attacked the same amount trans (60%) by $LiAlH_4$[33] in diethyl ether. These results indicate that torsional strain or factors other than steric hindrance control the stereochemistry of reduction and alkylation of VIII. The C-3 methyl group is probably in a quasi-equatorial position and offers little steric hindrance to cis attack.

On the other hand, the vicinal methyl groups of IX probably twist in a manner to avoid eclipsing each other. One takes a quasi-axial position and the other a quasi-equatorial position. The quasi-axial methyl group now can hinder cis attack on the carbonyl group; thus $LiAlH_4$ attacks IX 90% from the trans side. Methylating reagents also give[31] about 90% trans attack.

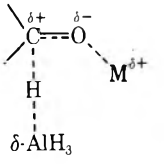
The large amount of apparent equatorial attack on II by $ClMgAlH_4$ and $Mg(AlH_4)_2$ was explained by the magnesium ion complexing the carbonyl oxygen and sterically interacting with the equatorial C-2 methyl group and forcing it into an axial position. This steric interaction is somewhat similar to the "compression effect" used[31] to explain alkylation of cyclohexanones in benzene with $Al(CH_3)_3$. The "compression effect" involves compression of the complexed carbonyl group against unequal substituents above or below the plane of the carbonyl group. The "compression effect" favors attack from the side of the carbonyl group which will relieve the compression strain. The "compression effect", however, exactly as described for alkylation, does not seem to be operating in the cases considered here. If it was, the amount of axial attack on VI by $LiAlH_4$, $ClMgAlH_4$, and $Mg(AlH_4)_2$ should be greater than on I, whereas the opposite is observed.

To investigate the "compression effect" further, VII was reduced using $ClMgAlH_4$ and $Mg(AlH_4)_2$. It has been previously pointed out[31] that VII is a good model to test for the "compression effect". Results of the reduction of VII by $ClMgAlH_4$ and $Mg(AlH_4)_2$ (Table IV) are opposite to that expected for the "compression effect", that is, more trans attack is observed than in the case of $LiAlH_4$. Thus, it is concluded that the "compression effect" is minor or inoperative in the reduction of ketones VI and VII by complex metal hydrides.

It appears that if $ClMg^+$ or AlH_4Mg^+ complex the carbonyl group of VII it pushes the methyl group from its quasi-equatorial position to a more axial position which increases steric hindrance to cis attack. It is also possible that the methyl group prevents the aluminohydride ion, via a six-center transition state, from swinging around to attack cis as the magnesium ion complexes the carbonyl oxygen.



Reduction of VIII and IX by $ClMgAlH_4$ and $Mg(AlH_4)_2$ gives results which are very similar to those with $LiAlH_4$. Chloromagnesium aluminum hydride and $Mg(AlH_4)_2$ also give results with I, III, and IV which are similar to those with $LiAlH_4$ and $NaAlH_4$. However, they give different results with II, V, and VII, where each ketone has a C-2 methyl group. A mechanism consistent with these results involves association of the carbonyl oxygen with the cation. Steric interaction between the substituent at C-2 and the complexing cation could alter the stereochemistry depending on the size of the complexing agent and how strongly it complexes the oxygen atom.



Reduction of Ketones by Insoluble Hydrides. The crystal lattice network of an insoluble hydride should present

Table V. Reduction of 4-*tert*-Butylcyclohexanone, 3,3,5-Trimethylcyclohexanone, and Camphor with Some Insoluble Complex Metal Hydrides

Hydride[a]	Solvent	H^-/ketone	Concn of ketone, M	% equatorial or endo attack	% yield[b]	Time, h
			4-*tert*-Butylcyclohexanone (I)			
MgH_2	THF	2.0	0.077	64	14 (76)	24
MgH_2	THF	0.91	0.13	65	6 (78)	24
$NaZnH_3$	THF	2.7	0.13	28	13 (50)	87
Li_2ZnH_4	THF	4.1	0.13	36	97 (trace)	87
$NaMgH_3$	THF	4.0	0.13	10	36 (39)	87
NR_4MgH_3	THF	1.4	0.13	trace	4 (72)	87
Na_3AlH_6	Benzene	10.7	0.13	30	28 (58)	87
Na_3AlH_6	THF	11.0	0.13	24	49 (42)	87
Na_3AlH_6	THF	12.3	0.13	15	25[c]	3
Na_3AlH_6	THF	12.3	0.13	16	28[c]	15
Na_3AlH_6	THF	12.3	0.13	22	39[c]	43
Na_3AlH_6	THF	12.3	0.13	25	55[c]	87
			3,3,5-Trimethylcyclohexanone (III)			
MgH_2	THF	2.0	0.046	45	23 (79)	24
MgH_2	THF	1.5[d]	0.062	20	12 (94)	24
Na_3AlH_6	THF	6.2	0.13	75	82 (17)	85
Na_3AlH_6	Benzene	6.3	0.19	65	68 (5)	85
Na_3AlH_6	THF	5.0[e]	0.42	68	25 (61)	85
Na_3AlH_6	Benzene	4.8[f]	0.33	61	37 (45)	85
			Camphor (V)			
MgH_2	THF	2.0	0.046	79	24 (74)	28
Na_3AlH_6	THF	6.7	0.13	90	64 (46)	85
Na_4AlH_6	Benzene	6.1	0.13	75	19 (85)	85

[a] Reaction mixture stirred continuously at room temperature. [b] Absolute yield measured with an internal standard. Percent recovered ketone is given in parentheses. [c] Relative yield. [d] 1.28 mmol of ketone and 1.76 mmol of alcohol (75% axial) were added to 2.28 mmol of MgH_2. [e] 3.90 mmol of ketone and 5.38 mmol of alcohol (70% axial) were added to 7.70 mmol of Na_3AlH_6. [f] 3.90 mmol of ketone and 3.16 mmol of alcohol (70% axial) were added to 5.64 mmol of Na_3AlH_6.

a large steric requirement to a ketone, and thus should provide a high degree of selectivity. Several insoluble hydrides were investigated in order to test this concept. The results are tabulated in Table V.

The most reactive hydride based on percentage of recovered I is Li_2ZnH_4 and the least reactive is NR_4MgH_3. The amount of equatorial attack on I varied from 10 to 65%. Although MgH_2 and Na_3AlH_6 give more equatorial attack on I than $LiAlH_4$, they give less equatorial and endo attack on III and V, respectively, than $LiAlH_4$. Equilibration during reduction was shown to be important for MgH_2, but not the other hydrides used in this study. The reaction of III and a mixture of 3,3,5-trimethylcyclohexanols (75% trans) with MgH_2 gave a mixture of alcohols which was 20% trans with only 12% reduction of the ketone. Equilibration is probably occurring via a Meerwein–Ponndorf process through $Mg(OR)_2$ as an intermediate. The fact that MgH_2 equilibrates a mixture of 3,3,5-trimethylcyclohexanols is indicative of cation complexation in reduction since association of $Mg(OR)_2$ with ketone in the Meerwein–Ponndorf equilibration is necessary.

The reaction of III and a mixture of its alcohols (70% trans) with Na_3AlH_6 showed little or no equilibration. The recovered ketone, at least for Na_3AlH_6, may not be attributed to enolate formation since reaction samples to which $LiAlH_4$ was added before quenching gave about 1% recovered ketone, indicating that the ketone was unreacted and not enolized. The insoluble hydrides are capable of reducing ketones, but have no advantage in terms of stereochemical selectivity over more common reducing agents.

Selectivity of $LiAl(OR)_3H$ as a Reducing Agent. It was reported that the stereoselectivity of $LiAl(OCH_3)_3H$ toward II in THF depends on the concentration of the hydride in the reaction mixture.[21] The increased steric requirement of $LiAl(OCH_3)_3H$ over $LiAl(OBu\text{-}t)_3H$ was explained by the greater association of $LiAl(OCH_3)_3H$ compared to $LiAl(OBu\text{-}t)_3H$ in THF. It was felt that these results should be checked since the previous results were obtained with only one ketone, II, which may have been a poor choice since the results of the present work show that the stereoselectivity seems to depend on which conformation reacts. The ketones I and II were examined over a 100-fold change in concentration of hydride, using $LiAlH_4$, $LiAl(OCH_3)_3H$, and $LiAl(OBu\text{-}t)_3H$. The results are given in Table VI. These data show that there is no change in selectivity with concentration of hydride although $LiAl(OCH_3)_3H$ associates appreciably with an increase in concentration whereas $LiAl(OBu\text{-}t)_3H$ is monomeric over a wide concentration range. These results suggest that in the reaction of $LiAl(OCH_3)_3H$ with I or II the same species is involved, probably the monomer; therefore the increased association of $LiAl(OCH_3)_3H$ with concentration cannot be the reason for its greater selectivity compared to $LiAl(OBu\text{-}t)_3H$.

These results leave us with no explanation for the difference in the selectivities of $LiAl(OCH_3)_3H$ and $LiAl(OBu\text{-}t)_3H$. Reaction of $LiAl(OBu\text{-}t)_3H$ via $Al(OBu\text{-}t)_2H$ as an intermediate[27,34] does not seem likely since it has been shown that $LiAl(OBu\text{-}t)_3H$ and $Al(OBu\text{-}t)_2H$ exhibit different stereoselectivities toward certain ketones.[21] Reaction of $LiAl(OBu\text{-}t)_3H$ via $LiAlH_4$ from disproportionation does not seem likely either since $LiAlH_4$ will react with certain substrates that $LiAl(OBu\text{-}t)_3H$ will not[35] and also the selectivity of $LiAlH_4$ toward II compared to $LiAl(OBu\text{-}t)_3H$ is quite different. We have found that the equivalent molar conductance[20] of $LiAl(OCH_3)_3H$ (2.32 mhos/cm^2 at 0.1 M) is much greater in THF than that of $LiAl(OBu\text{-}t)_3H$ (0.0124 mhos/cm^2 at 0.1 M) indicating that the former is considerably more solvated. Greater solvation of $LiAl(OCH_3)_3H$ and hence a

Table VI. Reduction of 4-*tert*-Butylcyclohexanone and 2-Methylcyclohexane with $LiAl(OBu\text{-}t)_3H$, $LiAl(OCH_3)_3H$, and $LiAlH_4$ at Varying Concentrations in THF

Ketone[a]	Hydride[a]	Initial concn of hydride, M	% equatorial attack	Yield
4-*tert*-Butylcyclohexanone (I)	$LiAl(OBu\text{-}t)_3H$	0.0051	10	112
		0.055	10	114 (1)
		0.51	11	113
	$LiAl(OCH_3)_3H$	0.0051	41	85 (14)
		0.055	41	119
		0.58	44	97
	$LiAlH_4$	0.0049	8	105 (1)
		0.056	9	103
		0.62	10	112
2-Methylcyclohexanone (II)	$LiAl(OBu\text{-}t)_3H$	0.0051	35	66[b]
		0.055	34	103
		0.51	36	99
	$LiAl(OCH_3)_3H$	0.0032	65 (63)[c]	40[b]
		0.0051	63[d]	76[b]
		0.0053	68 (68[c]	57[b]
		0.0080	66 (67)[c]	37[b]
		0.055	65[d]	97
		0.58	63[d]	109
	$LiAlH_4$	0.0049	19	65
		0.056	21	100
		0.62	24	109

[a] 0.5 M ketone added to hydride at 0 °C in THF. Ratio $H^-/K = 1.5$. The reaction was quenched after 2 h. [b] Reaction mixture was concentrated after quenching with an aspirator. Some of the product was probably lost under reduced pressure which accounts for the low yield. [c] The value in parentheses was obtained with a flame ionization GLC before the solution was concentrated. [d] Second preparation of $LiAl(OCH_3)_3H$.

Table VII. Reaction of 3,3,5-Trimethylcyclohexanone with $LiAlH_4$ and $NaAlH_4$ at Various Concentrations in THF

Hydride[a]	Initial concn of hydride,[a] M	Ratio H^-/ketone	% equatorial attack	Yield[b]
$LiAlH_4$[c]	0.0020	8.0	89.4	106 (3)
	0.012	6.0	82.4	105 (2)
	0.051	5.8	79.4	107
	0.11	5.8	79.9	98
	0.29	6.0	76.8	98
	0.38	6.0	75.6	102
	0.73	5.8	75.0	99
	1.0	5.8	74.6	98
$NaAlH_4$[c]	0.012	6.4	68.2	105 (2)
	0.055	5.9	60.4	108
	0.12	5.9	57.7	103
	0.39	6.2	55.5	104
	1.0	6.7	51.3	100
$LiAlH_4$[d]	0.0097	1.0	76.4	80 (8)
	0.048	1.0	75.7	96 (4)
	0.048	1.0	76.5	92 (4)
	0.12	1.0	73.6	95 (2)
	0.20	1.0	71.9	97
	0.20	1.0	70.7	99
	0.20	1.0	71.0	98
	0.50	1.0	65.5	95

[a] Reaction at 0 °C in THF for 2 h. [b] Absolute yield measured with an internal standard. The percent of recovered ketones is given in parentheses. [c] 1.0 M ketone added to hydride. [d] 1.0 M $LiAlH_4$ added to ketone. The concentration of $LiAlH_4$ reported is based on the resulting volume of reaction mixture.

higher steric requirement could be the reason for greater selectivity compared to $LiAl(OBu\text{-}t)_3H$.

The stereoselectivity of $LiAlH_4$ toward I is essentially independent of concentration. However, results with II indicate that there may be some dependence on concentration. On the other hand, when III was allowed to react with $LiAlH_4$ and $NaAlH_4$ at varying concentrations, selectivity was definitely shown to be a function of concentration (Table VII).

Both $LiAlH_4$ and $NaAlH_4$ are more selective toward III at lower concentrations, although both $LiAlH_4$ and $NaAlH_4$ have been shown to be more associated at higher concentrations.[20] It is clear from these results that the more highly associated species are not the reactive intermediates. In THF $LiAlH_4$ is best represented by solvent separated ion pairs and $NaAlH_4$ by a mixture of solvent separated and contact ion pairs. Thus $LiAlH_4$ being more solvated should have a greater steric requirement and give more equational attack on III than N_2AlH_4 as observed. Since solvation is greater at lower concentrations, both $LiAlH_4$ and N_2AlH_4 should have a higher steric requirement at lower concentrations and give more

Table VIII. Reduction of 4-*tert*-Butylcyclohexanone and 3,3,5-Trimethylcyclohexanone with Lithium Triaryloxy Aluminohydrides in THF

Aryloxy group	% equatorial attack[a]	% yield[b]
4-*tert*-Butylcyclohexanone		
4-Chlorophenoxy[c]	8	101
Phenoxy[d]	7	92
4-*tert*-Butylphenoxy[e]	7	92
3,3,5-Trimethylcyclohexanone		
4-Chlorophenoxy[c]	65	92
Phenoxy[d]	63	92
4-*tert*-Butylphenoxy[e]	61	94

[a] The ratio of H^-/ketone in all cases was 1.5. Ketone (0.50 M) was added to the hydride at 0 °C. Th reaction was quenched after 2 h. The phenol was extracted with NaOH before GLC analysis was carried out. [b] Absolute yield measured with an internal standard. [c] 0.40 M initial concentration. [d] 0.37 M initial concentration. [e] 0.39 M initial concentration.

Table IX. Reduction of 3,3,5-Trimethylcyclohexanone by $LiAlH_4$ and $NaAlH_4$ and Tri-*n*-octyl-*n*-propylammonium Aluminum Hydride

Hydride[a]	Solvent	Concn, M	% equatorial attack
$LiAlH_4$	Ether	0.1	68
$LiAlH_4$	Ether	0.5	55
$LiAlH_4$	THF	0.1	82
$LiAlH_4$	DME	0.1	78
$NaAlH_4$	THF	0.1	64
$NaAlH_4$	DME	0.1	63
$(n\text{-}C_8H_{17})_3(n\text{-}C_3H_7)\text{-}NAlH_4$	Benzene	0.1	47

[a] The ketone in the appropriate solvent was added to the hydride solution (H^-/ketone = 6). The reaction was quenched after 2 h at 0 °C.

equatorial attack. It is interesting that selectivity involving $NaAlH_4$ in THF and $LiAlH_4$ in diethyl ether is comparable. This result is consistent with the above interpretation since solvation of $NaAlH_4$ in THF is similar to that of $LiAlH_4$ in diethyl ether.[20]

Electronic Effects. Because the selectivity of $LiAl(OCH_3)_3H$ toward II showed no dependence on concentration, it was decided that electronic effects should be investigated. A series of para-substituted phenoxy derivatives of $LiAlH_4$ was examined with ketones I and III. When the substituents were *tert*-butyl, hydrogen, and chlorine, the results obtained with I and III showed no change in selectivity (Table VIII). Electronic effects, within a series of similar hydrides, seem to be of little importance. Surprisingly lithium triphenoxyaluminohydrides attack I and III more from the axial side than $LiAlH_4$, thus exhibiting a less apparent steric requirement. This is not inconsistent with the expected lower solvation and monomeric nature of $LiAl(OPh)_3H$ compound compared to $LiAlH_4$.

Solvation Effects. It has been shown[20] that in THF, $LiAlH_4$ is primarily a solvent separated ion pair at 0.1 M while it is predominantly a contact ion pair in diethyl ether at the same concentration. It was also shown[20] that four THF molecules will specifically solvate the lithium cation in diethyl ether solution. It was further suggested[20] that the difference in selectivity of $LiAlH_4$ in diethyl ether and THF may be attributed to the nature of the ion pair present in solution.

Table X. Reduction of 3,3,5-Trimethylcyclohexanone in Diethyl Ether by $LiAlH_4$ at Varying THF:$LiAlH_4$ Ratios

THF/$LiAlH_4$[a]	% THF	% equatorial attack
0	0	68
1	0.82	68
2	1.6	69
3	2.5	69
4	3.3	70
5	4.1	69
6	4.9	69
7	5.7	70
8	6.6	69
10	8.2	71
15	12	75
18	15	76
24	20	76
30	25	79
36	30	79
43	35	81
61	50	81
THF	100	82

[a] The ketone in diethyl ether solvent was added to the hydride in diethyl ether–THF mixed solvent (H^-/ketone = 6). The initial concentration of the ketone and hydride was 0.10 M. Temperature 0 °C. Reaction time was 2 h.

Table IX gives the results of reduction of III with $LiAlH_4$ and $NaAlH_4$ 0.1 M in diethyl ether, THF, and DME. In diethyl ether, $LiAlH_4$ gives 14% less equatorial attack than in THF. The observed 68% equatorial attack in diethyl ether does not agree well with the reported[19] value of 55%. However, reduction at 0.5 M does give 55% equatorial attack and hence the difference is due to a difference in concentration. Sodium aluminum hydride is insoluble in diethyl ether and gives only trace amounts of reaction. If solvation is important it was initially thought that $NaAlH_4$ in DME, a bidentate ligand, may differ from $NaAlH_4$ in THF as $LiAlH_4$ differs in THF from diethyl ether. However, $NaAlH_4$ in THF and DME gives similar results as does $LiAlH_4$ in the same two solvents. The indication is that THF and DME are similar toward $LiAlH_4$ and $NaAlH_4$ in terms of their solvating power and ability to form solvent separated ion pairs. Since $LiAlH_4$ in THF is more selective (82% equatorial attack) in its reaction with III than $NaAlH_4$ in THF (64% equatorial attack) or $LiAlH_4$ in ether (68% equatorial attack), it appears once again that solvent separated ion pairs provide for greater attack from the least hindered side of the molecule. Reduction of III by NR_4AlH_4 in benzene is the least selective solvent system (47% equatorial attack) in Table IX, and reduction of I by NR_4AlH_4 in benzene gives the same results (10% equatorial attack) as in THF. These results are consistent as well with the idea expressed above in that NR_4AlH_4 compounds would not be expected to be highly solvated in either benzene or THF and hence would not be very selective. The fact that reduction of I by NR_4AlH_4 was comparable in benzene to that in THF is further evidence that NR_4^+ is not solvated by THF and that solvation of cations such as Li^+ is very important in determining the selectivity of reduction.

Reduction of III by $LiAlH_4$ in the mixed solvent THF–diethyl ether was carried out at a ratio of THF to $LiAlH_4$ from 1 to 61. If the difference between $LiAlH_4$ in diethyl ether and THF is that one is a contact ion pair and the other is solvent separated, then the selectivity of $LiAlH_4$ should change noticeably at THF:$LiAlH_4$ = 4. We have shown by NMR that the first 4 mol of THF added to a diethyl ether solution of $LiAlH_4$ specifically solvate the lithium cation.[20] The selectivity does not change drastically at any THF:$LiAlH_4$ ratio (Table X).

Table XI. Reduction of 3,3,5-Trimethylcyclohexanone by $LiAlH_4$ in Diethyl Ether, Diethyl Ether–Benzene Mixtures, and THF at Varying Amine:$LiAlH_4$ Ratios

Solvent	Amine/$LiAlH_4$	Solubility of complex	% equatorial attack
Ether	0.5[b]	Sol	68
Ether	1.0[b]	Sol	69
Ether	2.0[b]	Insol	71
Ether	4.0[b]	Insol	72
Ether/benzene 93%	0.5[b]	Insol	64
Ether/benzene 85%	1.0[b]	Sol	68
Ether/benzene 94%	2.0[b]	Sol	70
Ether/benzene 94%	4.0[b]	Sol	71
THF	1.0[c]	Sol	74
THF	2.0[c]	Sol	74

[a] Ketone in diethyl ether added to $LiAlH_4$ in diethyl ether or ketone in benzene added to $LiAlH_4$ in mixed solvent (H^-/ketone = 6). The initial concentration of the ketone and hydride was 0.10 M. Temperature 0 °C. Reaction time was 2 h. [b] Amine is *N,N,N′,N′*-tetramethylethylenediamine. [c] Amine is *N,N,N′,N″,N‴,N‴*-hexamethyltriethylenetetraamine.

Table XII. Reduction of 3,3,5-trimethylcyclohexanone by $MAlH_4$ in Various Solvent Systems

Entry	$MAlH_4$	Solvent	% equatorial attack
1	NR_4AlH_4[b]	Benzene	47
2	NR_4AlH_4[b]	THF	55
3	$KAlH_4$	THF	60
4	$NaAlH_4$	THF	64
5	$NaAlH_4$	DME	63
6	$LiAlH_4$	Ether	68
7	$LiAlH_4$	THF	82
8	$LiAlH_4$	DME	78
9	$LiAlH_4$	Ether (+ TMED)	70
10	$LiAlH_4$	THF (+ amine)[a]	74
11	$NaAlH_4$	THF (+ crown ether)[c,e]	61
12	$NaAlH_4$	THF (+ crown ether)[d,e]	51
13	$KAlH_4$	THF (+ crown ether)[c,f]	50
14	$KAlH_4$	THF (+ crown ether)[d,f]	44

[a] *N,N,N′,N″,N‴,N‴*-Hexamethyltriethylenetetraamine. [b] Tri-*n*-octyl-*n*-propylammonium aluminum hydride. [c] Dicyclohexyl-18-crown-6. [d] Dibenzo-18-crown-6. [e] Crown ether: $NaAlH_4$ = 1.1 [f] Crown ether: $KAlH_4$ = 2.2.

Of course there should be a difference in the solvation of $LiAlH_4$·4THF in THF and $LiAlH_4$·4THF in ether. The fact that the selectivity increases gradually as the THF:$LiAlH_4$ ratio increases indicates that secondary solvation involving more than 4 mol of THF per mole of $LiAlH_4$ is involved in the reactive species and that the optimum degree of ion pair separation is brought about by more than 4 mol of THF per mole of $LiAlH_4$.

Similar experiments were carried out by adding tetramethylethylenediamine (TMED) to $LiAlH_4$ in diethyl ether and diethyl ether–benzene mixtures. Very little change in selectivity with TMED:$LiAlH_4$ ratio (Table XI) was observed. The reduction of III by $LiAlH_4$ in THF in the presence of *N,N,N′,N″,N‴,N‴*-hexamethyltriethylenetetraamine showed a decrease in selectivity from 82% equatorial attack in THF to 74%.

Table XII shows the results of reducing 3,3,5-trimethylcyclohexanone (III) with a variety of complex aluminum hydrides and solvent systems. Lithium aluminum hydride in THF is the most selective (82% equatorial attack). In cases where the cation is probably less solvated (entries 1–6) than $LiAlH_4$ in THF, the system is less selective. In cases where the cation is solvated by a single solvent molecule (crown ether), the system is also less selective. These results are consistent with the suggestion that complexation of the carbonyl oxygen by the cation takes place followed by transfer of the hydride to the carbonyl carbon. Removal of the cation from participation in the reaction pathway, either because of its inability to associate with the ketone or because it is complexed by another reagent, decreases the selectivity. Lithium aluminum hydride in THF represents the system involving the most ordering of *solvent and ketone* about the cation. This maximum in the amount of order in the system allows $LiAlH_4$ in THF to be the most selective.

Evaluation of Stereoselectivity of Other Hydrides. Data concerning the stereochemistry of reduction of a series of ketones with HBeCl and AlH_3 in diethyl ether and $LiAlH_4$, $LiAlD_4$, and $LiZnMe_2H$·AlH_3 in THF are tabulated in Table XIII. The reactions were run at 0 °C at a concentration of 0.10 M. The AlH_3 used in these studies is soluble in diethyl ether.[36] Results using AlH_3 in ether are similar to those observed for AlH_3 in THF. Although AlH_3 in diethyl ether gives almost twice the amount of equatorial attack on 4-*tert*-butylcyclohexanone as $LiAlH_4$ in THF, it is less selective toward camphor (V).

The new hydride $LiZnMe_2H$·AlH_3 gave more equatorial attack on I and III than did $LiAlH_4$. There is no methylation product according to gas chromatographic analysis.

Results using $LiAlH_4$ and $LiAlD_4$ are very similar. Therefore, there is no significant primary isotope effect influencing the stereoselectivity of $LiAlH_4$ reduction of ketones.

The new hydride HBeCl[37] is quite similar to $LiAlH_4$ in selectivity except for the reduction of 4-*tert*-butylcyclohexanone. It gives 46% equatorial attack which is comparable to $LiAl(OCH_3)_3H$ (44%). What causes HBeCl to have a larger steric requirement than $LiAlH_4$ is not readily apparent. The increased steric strain could be attributed to the fact that HBeCl is a dimer;[37] on the other hand, if this explanation is correct, HBeCl should be more selective than $LiAlH_4$ toward V, which it is not. More detailed mechanistic information is necessary to convincingly explain these results.

Orbital Symmetry Explanation of Stereochemical Results. Since the completion of the experimental work reported herein, Klein and others[13,38,39] have proposed a new theory of stereochemical control based on orbital symmetry arguments. Klein[12,39] has represented the orbital distortions involved in electrophilic attack and nucleophilic attack on cyclohexanone by A and B, respectively. A represents the interaction of the symmetrical β C–C σ^* orbital with the π orbital and B represents the interaction of the symmetrical β

A B

C–C σ orbital with the π^* orbital. Klein also has used the symmetrical σ–π interaction and the symmetrical σ^*–π^* interaction to demonstrate the distortion of the HOMO and LUMO of cyclohexanone. These interactions are represented in C and D. The carbonyl carbon atom's p orbital of the

C D

Table XIII. Reduction of Some Representative Ketones with Some Soluble Metal Hydrides

Ketone[a-c]	Hydride[c]	H^-/ketone	Solvent	% equatorial or exo attack
I	HBeCl	2	Ether	46
I	HBeCl	1	Ether	43
III	HBeCl	2	Ether	83
III	HBeCl	1	Ether	85
IV	HBeCl	2	Ether	92
V	HBeCl	2	Ether	14
I	$LiAlH_4$	6	THF	10
I	$LiAlD_4$	6	THF	9
III	$LiAlH_4$	6	THF	82
III	$LiAlD_4$	6	THF	85
IV	$LiAlH_4$	6	THF	93
IV	$LiAlD_4$	6	THF	92
V	$LiAlH_4$	6	THF	8
V	$LiAlD_4$	6	THF	8
I	AlH_3	4.5	Ether	19
I	AlH_3	1	Ether	18
III	AlH_3	4.5	Ether	77
III	AlH_3	1	Ether	66
IV	AlH_3	4.5	Ether	96
V	AlH_3	4.5	Ether	18
I	$LiZn(CH_3)_2H{\cdot}AlH_3$	6	THF	17
III	$LiZn(CH_3)_2H{\cdot}AlH_3$	6	THF	93

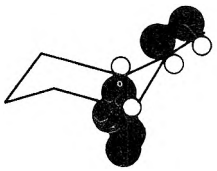
[a] Ketone in the appropriate solvent was added to the hydride. Temperature 0 °C. Reaction time was 2 h. [b] I = 4-*tert*-butylcyclohexanone, III = 3,3,5-trimethylcyclohexanone, IV = norcamphor, V = camphor. [c] All hydrides and ketones were initially 0.10 M.

HOMO is distorted to the equatorial side in A and C; therefore an electrophilic reagent is expected to attack the cyclohexanone from the electron-dense equatorial side. Similarly a nucleophile is more likely to attack the axial side because the carbonyl carbon atom's p orbital of the LUMO is distorted to that side as shown in B and D. Klein has pointed out that the axial β C–H bonds could in principle interact with the carbonyl carbon of cyclohexanone, but its effects would be expected to be opposite to the β C–C bonds because the two bond systems are antisymmetric about the C_6–C_1–C_2 plane and hyperconjugation of the π bond with the β C–C bonds is favored because they are more polarizable than the C–H bonds. However, Klein has further pointed out that involvement of the β C–C bonds and the axial β C–H bonds may be different in electrophilic and nucleophilic reactions.

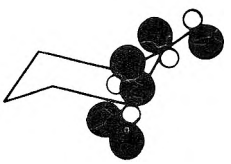
It seems to us that the LUMO arising from the β C–C σ^*–π^* interaction (D) is better represented by E, which would allow

E

more overlap between the σ^* and π^* orbitals. E does not predict axial attack by a nucleophile, which is what is usually observed for hydrides. F and G demonstrate the HOMO and



F

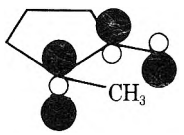


G

LUMO, respectively, for interaction of the π bond with the axial β C–H (σ–π and σ^*–π^* interactions). G, as does B, predicts axial attack by nucleophiles. However, it should be pointed out that F does not predict equatorial attack by a nucleophile.

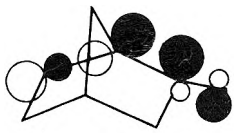
The reductions reported here were evaluated by considering several figures of orbital distortion (similar to B, D, E, and G) for each ketone. It was found that the reductions of the unhindered ketones reported here are consistently in agreement with the orbital distortion arising from axial (or pseudoaxial) β C–H σ^*–π^* interaction (similar to G). The only precedents for selecting one figure over another was their agreement or disagreement with observed results. Selecting figures on other bases, especially for the cyclohexanone ring system, is not straightforward and may be indeterminate.[13b]

H favors cis attack on VII (the methyl group is pseudo-



H

equatorial) as is observed for $LiAlH_4$. J favors exo attack on IV as is observed for all hydrides studied.



LUMO
J

Orbital distortion also allows an alternate explanation for the observed stereochemistry of II and VII with $Mg(AlH_4)_2$ and $ClMgAlH_4$.

Examination of conformations IIa and IIe suggest that IIa should be more able to stabilize an induced positive charge at the carbonyl carbon than IIe[39,40] because hyperconjugation should be greater for the more polarizable axial β C–C bond of IIa than the axial β C–H bond of IIe. Thus, this increased stabilization allows more of the reaction to proceed by IIa in the case of $Mg(AlH_4)_2$ and $ClMgAlH_4$ than $LiAlH_4$ (assuming that Mg^{2+} polarizes the carbonyl C–O bond more than Li^+). In the case of VII (Table IV) the difference in the stereochemical results with $Mg(AlH_4)_2$ and $ClMgAH_4$ as compared

to $LiAlH_4$ may be explained also by a change in conformation, i.e. reaction via the conformation of VII with the methyl group in a pseudoaxial position. The same two explanations applied to II for a change in conformation may be applied to VII. Additionally, an increase in the influence of orbital distortion for $Mg(AlH_4)_2$ and $ClMgAlH_4$ over $LiAlH_4$ (assuming that Mg^{2+} polarizes the carbonyl C–O bond more than Li^+) would be consistent with their greater amounts of axial attack on III and exo attack on V than $LiAlH_4$.

Conclusions

The most prominent theories of stereochemical control for reduction of ketones by metal hydrides are product development control, steric approach control, and torsional strain. The results reported in Table I show that $LiAlH_4$ gives more axial attack on 4-*tert*-butylcyclohexanone (I) and more equatorial attack on 3,3,5-trimethylcyclohexanone (III) than $NaAlH_4$. If these results are explained in terms of product development control and steric approach control, then $NaAlH_4$ in the case of I has an early transition state compared to $LiAlH_4$ whereas in the case of III a later transition state is involved. However, it seems reasonable that $NaAlH_4$ would have a transition state which is consistently earlier or later than that of $LiAlH_4$ with all ketones. If torsional strain and steric approach control are used to explain the above results, there is no necessity to invoke the concept of early and late transition states. For this reason and because of prior work of Eliel[10] and Klein,[11] product development control was not considered a viable concept in explaining the stereochemical results reported in this work.

The stereochemical evaluation of the $MAlH_4$ series as stereoselective reducing agents on selected model ketones show that results are dependent on the nature of M^+. This suggests that the reducing agent is the ion pair $M^+AlH_4^-$ and not just AlH_4^-. Comparison of $LiAlH_4$ to $LiBH_4$, showed $LiBH_4$ to be less selective toward III, IV, and V which may be explained on the basis that the BH_4^- ion is smaller than the AlH_4^- ion.

It was further demonstrated that the different conformations of a conformationally mobile ketone such as 2-methylcyclohexanone (II) are important in determining the stereochemical results of $MAlH_4$ reduction. Because the degree to which different conformations of II participate in the reduction of $MAlH_4$ as M^+ is varied from Li^+ to $ClMg^+$ to AlH_4Mg^+, it was suggested that the cation complexes the carbonyl oxygen, interacting with the C-2 methyl group, and effects a change in the conformation of the ketone during reduction.

The recently reported "compression effect" for controlling the stereochemistry of alkylation of cyclohexanones and cyclopentanones with excess $Al(CH_3)_3$ in benzene does not seem to be operative in the reduction of the ketones using complex metal hydrides.

Contrary to previous reports, the selectivity of $LiAl(OCH_3)_3H$ is independent of concentration. Therefore, its greater selectivity over $LiAl(OBu\text{-}t)_3H$ does not depend on its greater degree of association at higher concentrations compared to $Li(OBu\text{-}t)_3H$ which is monomeric at all concentrations. The only explanation for the greater degree of selectivity of $LiAl(OCH_3)_3H$ compared to $LiAl(OBu\text{-}t)_3H$ is that conductance measurement indicate that $LiAl(OCH_3)_3H$ is more highly solvated and several aspects of the present studies indicate that the more highly solvated hydrides are more selective in attack at the least hindered side of the ketone.

Solvation and concentration studies conducted by reduction of 3,3,5-trimethylcyclohexanone (III) with $LiAlH_4$ showed $LiAlH_4$ to be more selective at lower concentrations in THF, and more selective in THF than diethyl ether. The greater selectivity of $LiAlH_4$ in THF could not be attributed to any specific solvation (e.g., $LiAlH_4$·4THF), but rather to a more general solvation of the Li^+ cations in which selectivity was shown to be a formation of both primary and secondary solvation.

Certain stereochemical results were shown to be consistent with distortion of the π^* orbital due to interaction with $\beta\sigma^*$ (or σ) orbitals. The different possible orbital interactions must be studied in more detail in order to determine the most favorable interaction and to see if this interaction agrees with the observed stereochemistry of reduction. We have attempted to explain the stereochemical results reported herein with a consistent type of orbital interaction (σ^*–π^*); however, we realize that a specific type of orbital interaction may vary considerably from ketone to ketone and with the mechanism of reduction (or addition).

Experimental Section

Materials. Fisher reagent grade anhydrous diethyl ether was distilled under nitrogen from $LiAlH_4$ prior to use. Fisher reagent grade tetrahydrofuran (THF), benzene, and 1,2-dimethoxyethane (DME) were distilled under nitrogen from $NaAlH_4$ prior to use. Fisher reagent grade *N,N,N',N'*-tetramethylethylenediamine (TMED) was distilled from and stored over Linde 4A Molecular Sieve. A commerical sample (Ames Laboratory) of *N,N,N',N'',N''',N'''*-hexamethyltriethylenetetraamine was vacuum distilled (67–70 °C, 0.05 mm) from 4A molecular sieve and immediately used. Dibenzo-18-crown-6 and dicyclohexyl-18-crown-6 ethers were obtained from Drs. D. J. Cram and H. O. House, respectively, and were used without further purification. 2-Methylcyclohexanone (Eastman), norcamphor (Aldrich), camphor (Aldrich), 3,3,5-trimethylcyclohexanone (Chemical Samples), and 4-*tert*-butylcyclohexanone (Frinton) were purified by vacuum distillation or sublimation. 2-Methylcyclopentanone, 3-methylcyclopentanone, and *cis*-3,4-dimethylcyclopentanone (Chemical Samples) were used without further purification except for drying with activated Linde 4A Molecular Sieve. *cis*-2-Methyl-4-*tert*-butylcyclohexanone (98% pure by gas chromatographic analysis) was obtained by the method of Allinger.[41] Solutions of ketones were prepared by dissolving a known amount of ketone in a known volume of solvent using syringes and flasks fitted with a three-way stopcock and which had been flash flamed under nitrogen. Lithium aluminum hydride, $NaAlH_4$, $LiAlD_4$, and $LiBH_4$ were obtained from Alfa Inorganics. Solutions were prepared by distilling solvent onto the hydride and stirring the resulting slurry at least 24 h. The slurry was filtered in a drybox through a fritted glass funnel. The clear and colorless solutions of $LiAlH_4$, $LiAlD_4$, and $NaAlH_4$ were standardized by aluminum and gas evolution analysis. The $LiBH_4$, which also was clear and colorless, was standardized by lithium analysis.

Tri-*n*-octyl-*n*-propylammonium aluminum hydride (NR_4AlH_4) was prepared as reported previously.[18] A THF solution was standardized by aluminum analysis (Al:H ratio = 1.00:3.83). The solvent was removed from this solution under vacuum resulting in the isolation of a cream-colored solid. The solid was dissolved in benzene and the benzene removed under vacuum overnight followed by redissolution of the resulting powder in benzene to give a clear yellow solution (H:Al:Br = 3.77:1.00:0.001).

Magnesium aluminum hydride and $ClMgAlH_4$ were prepared by previously reported methods.[42] The $Mg(AlH_4)_2$ prepared was a white solid which exhibited a Mg:Al:H ratio of 0.92:2.00:7.76. A THF solution of $ClMgAlH_4$ exhibited a Cl:Mg:Al:H ratio of 0.97:0.97:1.00:3.92.

Activated magnesium hydride was prepared from NaH and activated $MgBr_2$ as previously described.[43] A measured volume of the MgH_2–NaBr slurry was removed with stirring and standarized by hydrogen analysis (gas evolution). The MgH_2 was not dried in order to avoid loss of activity.

Sodium aluminum hexahydride (Na_3AlH_6) was prepared as previously described[44] by allowing sodium, aluminum, and hydrogen to react at 2000 psi and 160 °C in toluene. Analysis of the resulting solid gave the ratio Na:Al:H = 3.0:1.1:6.2. X-ray powder diffraction analysis showed only lines reported for Na_3AlH_6.

The other hydrides used in this study, Li_2ZnH_4,[45] $LiZn(CH_3)_2H$·AlH_3,[46] $NaMgH_3$,[47] NR_4MgH_3[47] (NR_4 = tri-*n*-octyl-*n*-propylammonium ion), $KAlH_4$,[48] HBeCl,[37] and AlH_3,[36] were also obtained by previously reported methods.

Methanol and *tert*-butyl alcohol were distilled from magnesium and sodium, respectively. Phenol, 4-*tert*-butylphenol, and 4-chlorophenol were dried under vacuum at room temperature and stored over

activated 4A molecular sieve in THF. The trialkoxy and triaryloxy derivatives of $LiAlH_4$ were prepared by slowly adding 3 mol of the alcohol or phenol in THF to 1 mol of $LiAlH_4$ in THF. The lithium trimethoxyaluminohydride was prepared at 0 °C and used within 24 h. The analyses were as follows: lithium trimethoxyaluminohydride, Al:H = 1.00:0.99; lithium tri-*tert*-butoxyaluminohydride, Al:H = 1.00:1.00; lithium triphenoxyaluminohydride, Al:H = 1.00:0.98; lithium tri-4-chlorophenoxyaluminohydride, Al:H = 1.00:0.97; lithium tri-4-*tert*-butylphenoxyaluminohydride, Al:H = 1.00:0.97.

Magnesium analyses were carried out by EDTA titration of an aliquot of the hydrolyzed sample at pH 10 using Eriochrome Black T as an indicator (aluminum if present was masked with triethanolamine). Aluminum analyses were carried out by EDTA–zinc acetate back titration at pH 4 using dithizone as an indicator. Halide analyses were carried out by Volhard titration. Hydride analyses were carried out by measuring the volume of H_2 evolved by an aliquot of the sample on hydrolysis. Lithium and sodium analyses were carried out by flame photometry.

Reduction Procedures. A 50 ml Erlenmeyer flask with a magnetic stirring bar was flash flamed under nitrogen and then fitted with a rubber septum. The homogeneous reactions were run at two ratios, H^-/ketone = 6.0 and H^-/ketone = 1. For the excess hydride reactions 6.0 ml of 0.50 M hydride in THF was added to the flask. The flask was cooled to 0 °C and 4.0 ml of 0.50 M ketone in THF added. In the reactions with excess ketone, 2.0 ml of hydride solution was added to 8.0 ml of ketone at 0 °C. The reactions were quenched after about 2 h with distilled water or a saturated NH_4Cl solution. The internal standard was added and GLC analyses were carried out.

Samples of norcamphor and 3,3,5-trimethylcyclohexanone reacting with $LiBH_4$ were removed periodically and the absorbance of the n $\rightarrow \pi^*$ transition measured. The reactions were complete within 2 h. Reactions of camphor require a longer time before completion.

The heterogeneous reactions required adding the solid hydride to a tared flask in a drybox. With the weight of hydride known, the appropriate volumes of solvents and ketone solutions were added. The MgH_2 was not weighed but a measured volume of the slurry was added to the flask. The reactions were run with excess hydride and constant stirring.

The reactions of 3,3,5-trimethylcyclohexanone (III) with $LiAlH_4$ in diethyl ether and THF mixtures were run at 0 °C for 2 h. To a known amount of a standard solution of $LiAlH_4$ in diethyl ether was added diethyl ether and a THF–diethyl ether mixture so that the resulting solution was 0.10 M in $LiAlH_4$ and the ratio THF:Li was known. The THF:Li ratio varied from 1.0 to 61. To this solution was added the appropriate amount of III (0.10 M in diethyl ether) so that the ratio H^-/ketone = 6.0.

Reactions of III with $LiAlH_4$ in diethyl ether in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMED) were conducted similarly. Benzene was added to certain reactions to help increase the solubility of the complex when the complex was insoluble in diethyl ether. Reaction of III with $LiAlH_4$ in THF in the presence of *N,N,N',N'',N''',N'''*-hexamethyltriethylenetetraamine was also conducted similarly.

The reactions of III with $LiAlH_4$ in diethyl ether, and $NaAlH_4$ and $KAlH_4$ in THF, in the presence of crown ethers were conducted at 0 °C for 2 h. To a known weight of crown ethers was added solvent, then the hydride solution followed by ketone.

A 20-ft 5% Carbowax 20M on Chromosorb G or 15-ft 10% Carbowax 20M on Diatoport S column was used to separate the products of reaction of camphor (V) (150 °C), norcamphor (IV) (125 °C), 3,3,5-trimethylcyclohexanone (III) (125 °C), and 4-*tert*-butylcyclohexanone (I) (150 °C). Products from 2-methylcyclohexanone (II) and 2-methylcyclopentanone (VII) were separated on a 15-ft 5% diglycerol column at 75 °C.

Retention times varied slightly from column to column. For ketones I, II, III, IV, V, and VII the order of elution was always the same: the ketone first; the axial alcohol (I, II, III), exo alcohol (IV, V), and cis alcohol (II, VII) second; and equatorial alcohol (I, II, III), endo alcohol (IV, V), and trans alcohol (II, VII) last. The *cis*-2-methyl-4-*tert*-butylcyclohexanone and its alcohols were separated on a 10-ft 10% Carbowax 6M on Chromosorb G at 180 °C. The order of elution was ketone, axial alcohol, equatorial alcohol.

Relative retention times are given for each ketone, cis or exo alcohol, trans or endo alcohol, and standard, respectively as follows: I, 1.00, 1.11, 1.32, 0.65; II, 1.00, 2.25, 2.95, 1.28; III, 1.00, 1.69, 1.44, 3.06; IV, 1.00, 1.46, 1.56, 0.83; V, 1.00, 1.39, 1.53, 0.62; VI, 1.00, 1.74, 2.33, (−); and VII, 1.00, 2.33, 3.30, (−). The internal standard used to measure yields for ketones I, II, IV, and V was III. Ethyl benzoate was used as the internal standard for III. No internal standard was used with VI and VII. Ratio of alcohols were also determined by NMR for VI and VII (also VIII and IX). The weight percent recovery of product for NMR purposes was 80% or better.

The reactions of the cyclopentanones were carried out as described above. The reaction mixture was quenched and dried with $MgSO_4$. The clear portion of the mixture was removed and put in another flask. The $MgSO_4$ and hydrolysates were washed several times with diethyl ether. The washings were combined and added to the original solutions. The solvent was then removed under reduced pressure and 0.5–1.0 ml of Me_2SO-d_6 added. Me_4Si was the reference.

The ratio of 2-methylcyclopentanols, 3-methylcyclopentanols, and *cis*-3,4-dimethylcyclopentanols was measured by NMR in Me_2SO-d_6. The assignments for the hydroxyl protons have been described by Battioni.[33] The hydroxyl proton NMR signal locations are *cis*-2-methylcyclopentanol, δ 4.10; *trans*-2-methylcyclopentanol, 4.38; *cis*-3-methylcyclopentanol, 4.35; *trans*-3-methylcyclopentanol, 4.26; *cis,cis*-3,4-dimethylcyclopentanol, 4.37; and *trans,trans*-3,4-dimethylcyclopentanol, 4.23.

The ratio of alcohols from reduction of *cis*-2-methyl-4-*tert*-butylcyclohexanone with $Mg(AlH_4)_2$ was also measured by NMR. Results from NMR and GLC analyses were in complete agreement. The hydroxyl proton NMR signals are located at δ 4.32 and 4.00 for the equatorial and axial alcohols, respectively, in Me_2SO-d_6 with Me_4Si as the reference.

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Registry No.—I, 98-53-3; II, 583-60-8; III, 873-94-9; IV, 497-38-1; V, 76-22-2; VI, 3211-27-6; VII, 1120-72-5; VIII, 1757-42-2; IX, 19550-72-2; $LiAlH_4$, 16853-85-3; $NaAlH_4$, 13770-96-2; $Mg(AlH_4)_2$, 30472-12-9; $ClMgAlH_4$, 12522-22-4; MgH_2, 7693-27-8; $NaZnH_3$, 34397-46-1; Li_2ZnH_4, 38829-84-4; $NaMgH_3$, 59034-14-9; Na_3AlH_6, 17069-12-4; $LiAl(OBu\text{-}t)_3H$, 17476-04-9; $LiAl(OCH_3)_3H$, 12076-93-6; $Li(Cl\text{-}p\text{-}C_6H_4O)_3AlH$, 59034-15-0; $Li(PhO)_3AlH$, 59034-16-1; $Li(t\text{-}Bu\text{-}p\text{-}C_6H_4O)AlH$, 59034-17-2; $(n\text{-}C_8H_{17})_3(n\text{-}C_3H_7)NAlH_4$, 26026-60-8; $KAlH_4$, 16903-34-7; HBeCl, 42016-55-7; $LiAlD_4$, 14128-54-2; $LiZn(CH_3)_2H{\cdot}AlH_3$, 59092-43-2.

References and Notes

(1) For recent review see H. O. House, "Modern Synthetic Organic Reactions", W. A. Benjamin, New York, N.Y., 1972, p 45 ff.
(2) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1972, p 116 ff.
(3) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).
(4) M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199 (1968).
(5) M. Cherest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968).
(6) M. Cherest, H. Felkin, and C. Frajerman, *Tetrahedron Lett.*, 379 (1971).
(7) M. Cherest and H. Felkin, *Tetrahedron Lett.*, 383 (1971).
(8) J. Klein and D. Lichtenburg, *J. Org. Chem.*, **35**, 2654 (1970).
(9) J.-C. Richer, *J. Org. Chem.*, **30**, 324 (1965).
(10) J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, *Tetrahedron Lett.*, 6127 (1968).
(11) E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970).
(12) J. Klein, *Tetrahedron Lett.*, 4307 (1973).
(13) N. T. Anh, O. Eisenstein, J.-M. Lefour, and M.-E. Tran Huu Dau, *J. Am. Chem. Soc.*, **95**, 6146 (1973); C. Liotta, *Tetrahedron Lett.*, 519 (1975).
(14) H. C. Brown, E. J. Mead, and B. C. S. Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).
(15) H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **83**, 4372 (1961).
(16) A. E. Finholt, E. C. Jacobson, A. E. Ogard, and P. Thompson, *J. Am. Chem. Soc.*, **77**, 4163 (1955).
(17) O. Strouf, *Collect. Czech. Chem. Commun.*, **37**, 2693 (1972), and references cited therein.
(18) R. Ehrlich, A. R. Young II, and D. D. Perry, *Inorg. Chem.*, **4**, 758 (1965).
(19) H. Haubenstock and E. L. Eliel, *J. Am. Chem. Soc.*, **84**, 2363 (1962).
(20) E. C. Ashby, F. R. Dobbs, and H. P. Hopkins, Jr., *J. Am. Chem. Soc.*, **95**, 2823 (1973), and unpublished results.
(21) E. C. Ashby, J. P. Sevenair, and F. R. Dobbs, *J. Org. Chem.*, **36**, 197 (1971).
(22) G. Chauviere, Z. Welvart, D. Eugene, and J.-C. Richer, *Can. J. Chem.*, **47**, 3285 (1969).
(23) S. R. Landor and J. P. Regan, *J. Chem. Soc. C*, 1159 (1967).
(24) A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron*, **18**, 705 (1962).
(25) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, N.Y., 1972, p 113.
(26) E. C. Ashby, J. R. Boone, and J. P. Oliver, *J. Am. Chem. Soc.*, **95**, 5427 (1973).
(27) H. C. Brown and H. R. Deck, *J. Am. Chem. Soc.*, **87**, 5620 (1965).
(28) "CRC Handbook of Chemistry and Physics", 47th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1966, p F-124.
(29) D. M. S. Wheeler and J. W. Huffman, *Experientia*, **16**, 516 (1960).
(30) B. Rickborn and M. T. Wuesthoff, *J. Am. Chem. Soc.*, **92**, 6894 (1970).
(31) J. Laemmle, E. C. Ashby, and P. V. Roling, *J. Org. Chem.*, **38**, 2526 (1973).
(32) N. L. Allinger, M. T. Tribble, and M. A. Miller, *Tetrahedron*, **28**, 1173 (1972).
(33) J.-P. Battioni and W. Chodkiewiz, *Bull. Soc. Chim. Fr.*, 1824 (1971).
(34) D. C. Ayers and W. Sawdaye, *Chem. Commun.*, 527 (1966).

(35) H. C. Brown and Nung Min Yoon, *J. Am. Chem. Soc.*, **88**, 1464 (1966).
(36) E. C. Ashby, J. R. Sanders, P. Claudy, and R. Schwartz, *J. Am. Chem. Soc.*, **95**, 6485 (1973).
(37) E. C. Ashby, P. Claudy, and R. D. Schwartz, *Inorg. Chem.*, **13**, 192 (1974).
(38) J. Klein and H. Stollar, *Tetrahedron Lett.*, 2541 (1974).
(39) J. Klein, *Tetrahedron Lett.*, 3349 (1974).
(40) R. C. Bingham and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **93**, 3187 (1971).
(41) N. L. Allinger, H. M. Blatter, L. A. Freiberg, and F. M. Karkowski, *J. Am. Chem. Soc.*, **88**, 2999 (1966).
(42) E. C. Ashby, R. D. Schwartz, and B. D. James, *Inorg. Chem.*, **9**, 325 (1970).
(43) E. C. Ashby and R. D. Schwartz, *Inorg. Chem.*, **10**, 355 (1971).
(44) E. C. Ashby and B. D. James, *Inorg. Chem.*, **8**, 2468 (1969).
(45) E. C. Ashby and J. Watkins, *Inorg. Chem.*, **12**, 2493 (1973).
(46) E. C. Ashby and J. J. Watkins, *Inorg. Chem.*, submitted.
(47) E. C. Ashby and S. Srivastava, *Inorg. Chem.*, in press.
(48) E. C. Ashby, G. Brendel, and H. E. Redman, *Inorg. Chem.*, **2**, 499 (1963)

Stereochemical Control of Reductions. 5.[1] Effects of Electron Density and Solvent on Group Haptophilicity[2]

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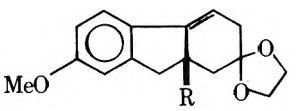
7-Methoxy-10a-hydroxymethyl-1,2,3,9,10,10a-hexahydrophenanthrene (**2**) was synthesized and the stereochemistry of its cis (**8**) and trans (**5**) reduction products established. The directive effect of the CH_2OH group was examined by heterogeneous catalytic hydrogenation of **2** over a Pd/C catalyst, leading to cis–trans mixtures whose proportion of **8** increased (6–61%) as the solvent dielectric constant was lowered (DMF, EtOH, THF, DME, diglyme, Bu_2O, dioxane, hexane). This is interpreted primarily in terms of competition between substrate CH_2OH and solvent for active catalyst sites. Use of a Pt/C catalyst gave a nearly identical solvent order, but with higher proportions of **8** throughout (9–80%). Compound **2** was converted to its Li, Na, and K alkoxides and these, when hydrogenated over Pd/C in diglyme, gave increasing proportions of **8** (60–69%) in the product mixture compared to the protonated group (23%). This is interpreted as reflecting increasing electron density available to bind oxygen to the catalyst surface during reduction. These principles may be useful in improving stereochemical control in catalytic hydrogenation.

Numerous reports[4] of heterogeneous catalytic hydrogenations deal with instances in which the presence of certain functional groups in the substrate molecule has led to product stereochemistry opposite that expected on the basis of steric hindrance.[4b] This evidently can arise from a propensity of the functional group, most frequently hydroxyl, to bind to the catalyst surface during reduction in such a way as to enforce addition of hydrogen from its own side of the molecule, an effect we have termed haptophilicity.[5]

Our previous work[5] on the directing effects of various substrate functional groups during hydrogenation led us to the general conclusion that a group's haptophilicity is probably directly related to, among other things, its ability to donate electrons toward the catalytic surface. This conclusion suggested to us several specific ways in which the haptophilicities of groups might be altered so as to affect predictably the stereochemistry of reductions. For example, conversion of an acidic group to its anion should increase its electron-donating ability and hence its haptophilicity (cf. **1**, R = COOH, COOLi, COONa).[5] Additionally, the effective haptophilicity of many R groups would probably be increased if competition from polar and especially hydroxylic solvents were eliminated, since OH has a high haptophilicity.



1

Synthesis and Stereochemistry of Materials. We wished to test these ideas experimentally; however, it was clear that for several R groups the system **1** would be insensitive to increases in haptophilicity, leading to higher percentages of cis product, simply because the percentage of cis product was already very high (e.g., R = CH_2OH → 95% cis).[5,6] For this reason we have turned our attention to the closely related system **2**, which was prepared by reduction of the known ester **3**.[7] Compound **2** not only was soluble in a variety of solvents of low polarity but, on catalytic hydrogenation under reaction conditions similar to those used with **1**, gave a product mixture rich in the trans isomer (94% trans, 6% cis), allowing us ample leeway in enhancing the haptophilicity of the CH_2OH group. This relatively high percentage of trans product obtained from **2** supports our previous speculation[5] that the ketal group in **1** may be haptophilically involved in the contrastingly high cis specificity (95%) observed in hydrogenation of **1**, R = CH_2OH.[5,6] Scheme I shows the sequences by which the

Scheme I

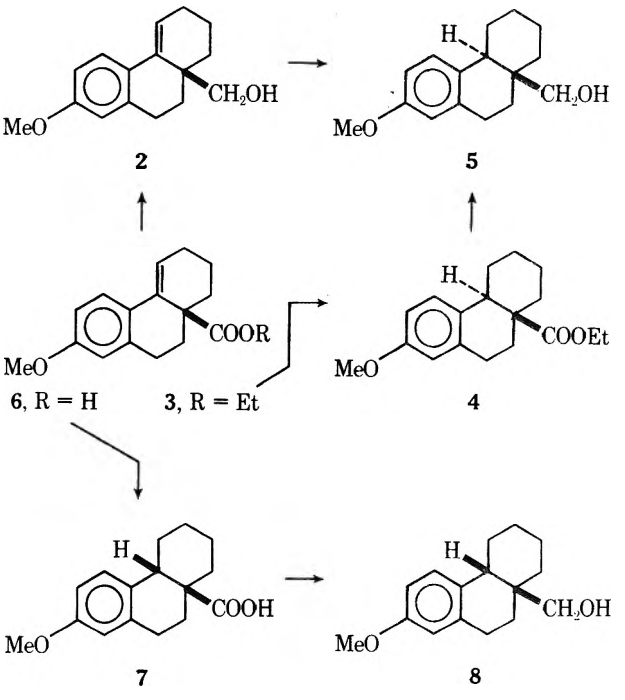


Table I. Products from Hydrogenation of 2 at 1 atm and 25 °C

Solvent	Dielectric constant[a]	Pd/C catalyst		Pt/C catalyst	
		% yield	Ratio of 8:5[b]	% yield	Ratio of 8:5[b]
Hexane	1.9	89	61:39	90	80.5:19.5
Dioxane	2.2	96	26:74	95	46.5:53.5
Bu_2O	3.1	94	26.5:73.5	90	50.5:49.5
Diglyme	7.2	81	18.5:81.5	98	43:57
DME	7.2	94	20:80	96	36:64
THF	7.6	93	18:82	90	30:70
EtOH	24.6	96	6:94		
DMF	36.7	99	6:94	90	9:91

[a] Values taken from ref 11. [b] Values considered accurate to ±2%, e.g., 61 ± 2:39 ± 2.

stereochemistries of the reduction products of 2 were established.

Our stereochemical assignments for 4 and 7, and hence for 5 and 8, are based as follows. The unsaturated ethyl ester 3 has a single infrared carbonyl absorption at 1720 cm^{-1}. Catalytic reduction with Pd/C yielded a major product whose ir spectrum has a carbonyl doublet (1735, 1720 cm^{-1}), indicating rotation which is more severely restricted than in 3. This is consistent only with trans stereochemistry in the reduction product, and conforms to the spectral patterns found for the corresponding compounds of series 1 (where the cis product lacks such a doublet).[6] This stereochemical result also fulfilled our expectations based on the established low haptophilicity of the ester function.[5,6]

Lithium–ammonia reduction of the unsaturated carboxylic acid 6 was expected to yield products representing protonation of an equilibrium mixture of the conformers of the benzylic anion reduction intermediate. The cis and trans forms of this should provide equally good ring overlap with the benzylic anion, so that conformational preferences should be controlled here by steric and electrostatic repulsions. While the latter are very difficult to assess, the cis juncture is known to be favored in decalin and octalin systems by introduction of angular substituents more bulky than H.[8] Hence, on the assumption that rates of protonation are comparable, this equilibrium mixture was expected to give largely or entirely cis product. This reduction yielded at least 80% of a single carboxylic acid, whose $LiAlH_4$ reduction product (8) was not identical with that from $LiAlH_4$ reduction of 4, but melted some 50° lower, consistent with the less planar and less rigid cis structure.

Solvent Effects on Haptophilicity. Little of the existing data[9,10] concerning solvent effects on hydrogenation stereochemistry is derived from compounds specifically chosen to elucidate mechanisms. Much of it was gleaned incidentally during synthetic studies and is far from exhaustive, and much, stemming from the period before VPC and NMR, suffers "from both inadequate product analysis and isomerization of initially formed products".[9] The best that can be safely summarized from the morass of available, often conflicting, data is that the interrelationship of the solvent's functional group, bulk, viscosity, dielectric constant, pH, etc., with catalyst, substrate, pressure, and temperature is so intricate that prediction of results is frequently hazardous even when only one variable is changed.

Against this background we wished to examine with compound 2 the proposition that substrate haptophilicity may be diminished by competition with the solvent. We envisioned this as a preempting of active sites on the catalyst surface by solvents containing polar functional groups, particularly ones of known high haptophilicity. However, such a process might operate by several mechanisms, not only making sites unavailable for haptophilic substrate interactions, but probably also increasing steric interactions by adding bulk at the catalyst surface near whatever sites are available. A similar result could also be produced by the fact that such solvents could solvate and thus mask the substrate haptophilic group, making it bulkier.

Although they do not allow us to distinguish among these mechanisms, our results, shown in Table I, are strikingly consistent with the basic idea of solvent competition and indicate that dielectric constants seem to provide a rough guide to this sort of solvent effect. It seems clear that some of the previously observed solvent effects on stereochemistry may have been of this origin, which we may call competitive solvent haptophilicity. It is not our intention to present here a complete or rigid solvent haptophilicity series, since so specific a ranking might well fail when other variables are changed. In fact, since 2 has been chosen specifically to illustrate haptophilic effects by eliminating complicating structural features, most other systems will probably present situations which are less clear-cut. Rather, we wish to suggest that, in the absence of perturbing factors, to the extent that haptophilic effects operate in a given system the extremes of stereospecificity are likely to be achieved with extremes of solvent dielectric constant.

It should be pointed out that the data for palladium and for platinum closely parallel each other, but with the platinum series giving consistently higher percentages of cis product. Although in general Pd catalysts seem to favor the thermodynamic product epimer more frequently than does Pt,[10] our results appear consistent with the general observation that Pt catalysts are the more sensitive to poisoning.[10a]

Haptophilic Enhancement by Anion Formation. We had already demonstrated in the case of 1 that increasing the electron density on a carboxyl group by anion formation leads to increased haptophilicity, which varies with the cation used.[5] We wished also to apply this idea to the hydromethyl group of 2. For these experiments it seemed clear that alcohols, for reasons of proton exchange, and hydrocarbons, because of substrate insolubility, would be inappropriate solvents. Diglyme was finally chosen because of its combination of low dielectric constant with ability to dissolve salts by cation solvation. It was found that at 25 °C and 1 atm conversions in the hydrogenation of salts of 2 with our Pd/C catalyst were essentially nil. This did not surprise us unduly, as we had already speculated upon the relationship between haptophilicity and catalyst poisoning,[5] and we found that by increasing the pressure to 3 atm the reductions could be carried to completion, although isolated yields were only in the 70–80% range (Table II). The small difference in cis–trans isomer ratio obtained for R = CH_2OH here and in Table I is the result of this change in hydrogen pressure.

The results in Table II coincide remarkably with those found for carboxylate in system 1: an increase in the amount of cis product on going from the protonated group to the alkali metal salts, and an increase in cis product as the size of the cation is increased. These results, together with the mild

Table II. Products from Hydrogenation of Salts of 2 with Pd/C Catalyst at 3 atm and 25 °C

Group	Solvent	% yield	Ratio of 8:5[a]
CH_2OH	Diglyme	95	23:77
CH_2OLi	Diglyme	71	60:40
CH_2OLi	Bu_2O	95	63:37
CH_2ONa	Diglyme	74	66.5:33.5
CH_2OK	Diglyme	81	69:31

[a] Values considered accurate to ±2%, e.g., 23 ± 2:77 ± 2.

catalyst-poisoning effect of the salts, speak eloquently for the idea that the adhesion of acidic functional groups to the catalyst surface can be enhanced by anion formation[12] and further controlled by choice of cation.

The two effects demonstrated here extend considerably our fundamental understanding of the concept and nature of haptophilicity and the practical usefulness of the ranking of group haptophilicities we previously presented.[5] Even for nonideal cases our results suggest a systematic basis for attempting to exploit more fully the steric and electronic features of a given system to achieve stereochemical control.

Experimental Section[13]

Catalytic Hydrogenation of 7-Methoxy-10a-carbethoxy-1,2,3,9,10,10a-hexahydrophenanthrene (3). A solution of 577 mg (2.02 mmol) of 3[7] in 30 ml of absolute EtOH was hydrogenated at 25 °C and 1 atm over 60 mg of 5% Pd/C catalyst. Concentration of the filtered reaction solution provided material recrystallized from pentane to give 351 mg (60.5%) of 4 as rhombic platelets: mp 41–42 °C; ir 1735, 1720 cm^{-1}; NMR δ 1.05 (3 H t, J = 7 Hz), 1.2–2.9 (13 H complex), 3.7 (3 H s), 3.95 (2 H q, J = 7 Hz), 6.35–6.7 (2 H complex), 7.1 (1 H d, J = 9 Hz); MS m/e 288 (33%, M^+), 215 (29%), 214 (100%), 171 (32%).

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.77; H, 8.39.

$LiAlH_4$ Reduction of 4. Compound 4 (234 mg, 0.81 mmol), when treated with 66 mg (1.65 mmol) of $LiAlH_4$ in Et_2O, gave incompletely reduced material after 1 h of reflux and was recovered and resubjected to $LiAlH_4$ (133 mg, 3.3 mmol) by refluxing in 50 ml of dry THF for 6 h under N_2. The mixture was worked up by titration with saturated aqueous Na_2SO_4, filtration, and concentration to give material melting at 110–116 °C. Two recrystallizations from pentane produced 46 mg (23%) of 5 as fine felted needles, mp 117–120.5 °C, identical with material produced by hydrogenation of 2. An analytical sample melted at 121–123 °C: ir ($CHCl_3$) 3620, 3460 cm^{-1}, no C=O absorption; uv 212, 224, 281, 289 nm; NMR δ 0.8–3.1 (14 H complex), 3.3 (1 H d, J = 11.5 Hz), 3.7 (1 H d, J = 11.5 Hz), 3.8 (3 H s), 6.55–6.8 (2 H m), 7.1 (1 H d, J = 9 Hz); MS m/e 246 (100%, M^+), 228 (51%), 215 (99%), 171 (68%), 147 (99%).

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.12; H, 8.91.

$LiAlH_4$ Reduction of 3. A slurry of 200 mg (5.0 mmol) of $LiAlH_4$ in 40 ml of dry Et_2O was stirred under N_2 during dropwise addition of 572 mg (2.0 mmol) of 3 in 10 ml of dry Et_2O. After addition the mixture was refluxed for 2 h, stirred overnight at 25 °C, and worked up by titration with saturated aqueous Na_2SO_4. The decantate was combined with the hexane washings of the precipitate and passed through a short Al_2O_3 column. Concentration gave a solid recrystallized from MeOH to provide 465 mg (95%) of 2 as fine felted needles: mp 116–116.5 °C; ir 3660 cm^{-1}, no carbonyl absorption; uv 218, 262.5, 297 nm; NMR δ ca. 1.4 (1 H s, disappears on shaking with D_2O), 1.1–3.0 (10 H complex), 3.55 (2 H s), 3.8 (3 H s), 6.2 (1 H t, J = 4 Hz), 6.6–6.9 (2 H complex), 7.45 (1 H d, J = 8 Hz); MS m/e 244 (62%, M^+), 226 (25%), 214 (43%), 213 (100%), 198 (38%).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.58; H, 8.35.

Catalytic Hydrogenation of 2. A preparative hydrogenation was carried out involving 490 mg (2.0 mmol) of **2**, 62.5 mg of 5% Pd/C catalyst, and 30 ml of absolute EtOH. After 45 min of stirring at 25 °C and 1 atm, uptake of H_2 had ceased and the usual filtration and concentration procedure yielded 478 mg (97%) of **5**, mp 115–118 °C. Recrystallization from Et_2O gave material melting at 121–123 °C, which was identical (ir, mixture melting point) with that obtained by $LiAlH_4$ reduction of **4**.

Saponification of 3. Compound 3 (858 mg, 3.0 mmol), when treated with 2.0 g of 85% KOH in 80 ml of EtOH–H_2O, gave primarily starting material after 24 h of reflux and was recovered and resubjected to 85% KOH (2.30 g, 35 mmol) by refluxing in 90 ml of methoxyethanol (bp 124 °C) for 24 h under N_2. Acidification with aqueous HCl, extraction with Et_2O, and concentration gave 751 mg (97%) of crude solid which was recrystallized from absolute EtOH to provide 569 mg (73.5%) of **6** as white needles: mp 174–176 °C dec; ir 3300–2100, 1690 cm^{-1}; uv 218, 262, 297 nm; NMR δ 0.8–2.95 (10 H complex), 3.75 (3 H s), 6.2 (1 H t, J = 5 Hz), 6.65 (2 H complex), 7.5 (1 H d, J = 9 Hz); MS m/e 258 absent, 214 (80%, $M^+ - CO_2$), 213 (100%), 212 (80%), 186 (55%), 171 (67%).

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.59; H, 7.16.

Li–NH_3 Reduction of 6. A solution of 100 mg (0.39 mmol) of **6** in 10 ml of dry 1:1 THF–Et_2O was added over 1 min to a stirred solution of 39 mg (5.6 mg-atoms) of Li in 16 ml of liquid NH_3. After 15–20 min the blue reaction mixture was quenched with solid NH_4Cl, and NH_3 was allowed to evaporate. Addition of aqueous HCl and extraction with Et_2O provided 100 mg (99%) of crude solid, which was sublimed at 160 °C (0.08 mm) and recrystallized from Et_2O–pentane to give 81 mg (80%) of **7** as flat matted crystals: mp 150–151 °C; ir 3600–2300, 1700 cm^{-1}; uv 212, 224, 282.5, 290 nm; NMR δ 1.0–3.35 (13 H complex), 3.75 (3 H s), 6.7 (2 H complex), 7.05 (1 H d, J = 8 Hz); MS m/e 260 (100%, M^+), 215 (72%), 214 (98%), 213 (74%), 186 (40%), 171 (65%).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.67; H, 7.83.

$LiAlH_4$ Reduction of 7. A slurry of 40 mg (1.0 mmol) of $LiAlH_4$ in 10 ml of dry Et_2O was stirred under N_2 during dropwise addition of 100 mg (0.385 mmol) of **7** in 15 ml of dry Et_2O. After addition the mixture was refluxed for 3 h, stirred overnight at 25 °C, and worked up by titration with saturated aqueous Na_2SO_4. The organic filtrate was concentrated to a viscous oil which was purified by chromatography on Al_2O_3 and distilled at 150 °C (1.0 mm) to give ca. 80 mg (85%) of solid. Repeated recrystallization from hexane yielded pure **8**: mp 71 °C; ir 3660, 3510 cm^{-1}, no carbonyl absorption; uv 211, 223, 281, 288.5 nm; NMR δ 1.0–3.0 (13 H complex), 3.3 (1 H d, J = 11 Hz), 3.45 (1 H d, J = 11 Hz), 3.8 (3 H s), 6.65 (2 H complex), 6.95 (1 H d/d, J = 2, 7 Hz); MS m/e 246 (100%, M^+), 228 (61%), 215 (51%), 171 (58%), 147 (51%).

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.92; H, 9.02.

Procedure for Hydrogenations. Table I. Hydrogenations were carried out with a low-pressure apparatus at 1 atm (76 ± 2 cm) and room temperature (25 ± 2 °C) using 5% Pd/C and 5% Pt/C catalysts supplied by Engelhard Industries, Newark, N.J. Diglyme, DME, THF, and Bu_2O (distilled from $LiAlH_4$) and benzene, hexane, and dioxane (distilled from Na) were stored over 4A molecular sieves. Toluene and DMF were distilled from CaH_2 and stored over molecular sieves or CaH_2. Absolute EtOH (Commercial Solvents Corp. Gold Shield) was used without further purification.

To a flask containing a Teflon-covered magnetic stirring bar and 3.4 mg of catalyst was added a solution of 24.4 mg (0.10 mmol) of 2 in 1.6 ml of solvent. The flask was then alternately evacuated and filled with H_2 several times to remove air. The final charge of H_2 was adjusted to 1 atm with a mercury leveling bulb and stirring was begun. When at least the theoretical quantity of H_2 had been absorbed and uptake had ceased (typically ca. 1 h, occasionally longer), the product was isolated by filtration (catalyst washed with additional solvent) and removal of all solvent under vacuum. The residue was sublimed at ca. 110 °C (ca. 0.05 mm) and the cold finger weighed immediately before and after removal of the sublimate.

Table II. Compound 2 (24.4 mg, 0.10 mmol) was dissolved in 1.0 ml of dry solvent and 1.0 equiv of base was introduced under N_2. The mixture was stirred for 5 min at 35 °C for formation of the Li salt (ethereal MeLi, diglyme), refluxed for 24 h to produce the Na salt (NaH, diglyme), and refluxed for 2–3 h in the case of the K salt (KH, THF). In each instance the mixture was evaporated to dryness under vacuum and the residue was weighed. Infrared analysis verified complete alkoxide formation by lack of OH absorption.

Salts were used immediately after isolation, employing the amounts of catalyst and solvent described above, but with a Parr apparatus at 25 °C and 3.0 atm for 3 h. Workup was by filtration, dilution with water, adjustment of pH to 3 with aqueous HCl, and extraction with Et_2O. After being dried and concentrated, the extract was sublimed and weighed as described above.

Analysis of Product Mixtures. The entire sublimate was washed from the cold finger with dry MeOH and this solution was used directly for VPC analysis. NMR did not provide adequate resolution

of the appropriate peaks at 60 MHz to be useful for mixture analysis. Typical VPC retention times for **2**, **8**, and **5**, respectively, were 6, 10, and 13 min with the Apiezon column at 270 °C and 6, 13, and 16 min for the SE-30 column at 235 °C. Traces were integrated by planimeter and calibrated with traces from prepared mixtures of 8 and **5**.

Control Hydrogenations. Except in one instance control hydrogenations to establish absence of equilibration were run on the trans product (**5**), since evidence suggests that it is the less stable epimer.[8] These reactions employed substrate, catalyst, and solvent (diglyme) in the ratio indicated above, with material recoveries of 98–100%, and in no instance gave detectable evidence for epimerization: **5**, Pd/C, 1 atm; **8**, Pd/C, 1 atm; **5**, Pt/C, 1 atm; **5**, Pd/C, 3 atm; Na salt of **5**, Pd/C, 3 atm. Isomerizations through catalyst-associated states (e.g., double-bond migration) were tested for and found absent or negligible in the closely related system **1**;[5] for this reason such processes are believed also to be unimportant in the reactions of **2**.

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Registry No.—**2**, 53547-99-2; **3**, 59434-75-2; **4**, 59434-76-3; **5**, 59434-77-4; **6**, 59434-78-5; **7**, 59434-79-6; **8**, 59434-80-9.

References and Notes

(1) Part 4: H. W. Thompson and E. McPherson, *J. Am. Chem. Soc.*, **96**, 6232 (1974).
(2) Taken in part from the Ph.D. Thesis of E. M., Rutgers University, 1975.
(3) Undergraduate Research Participant, spring 1968.
(4) (a) For references, see previous papers in this series and R. J. Sehgal, R. U. Koenigsberger, and T. J. Howard, *J. Org. Chem.*, **40**, 3073 (1975). (b) However, see S. Siegel and J. R. Cozort, *ibid.*, **40**, 3594 (1975).
(5) H. W. Thompson and R. E. Naipawer, *J. Am. Chem. Soc.*, **95**, 6379 (1973).
(6) H. W. Thompson, *J. Org. Chem.*, **36**, 2577 (1971).
(7) R. A. Barnes, H. P. Hirschler, and B. R. Bluestein, *J. Am. Chem. Soc.*, **74**, 32 (1952); see also S. J. Daum, P. E. Shaw, and R. L. Clarke, *J. Org. Chem.*, **32**, 1427 (1967), and P. N. Chakrabortty, R. Dasgupta, S. K. Dasgupta, S. R. Ghosh, and U. R. Ghatak, *Tetrahedron*, **28**, 4653 (1972).
(8) (a) F. Sondheimer and D. Rosenthal, *J. Am. Chem. Soc.*, **80**, 3995 (1958); R. J. Balf, B. Rao, and L. Weiler, *Can. J. Chem.*, **49**, 3135 (1971); (b) A. J. Birch, H. Smith, and R. E. Thornton, *J. Chem. Soc.*, 1339 (1957); W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Am. Chem. Soc.*, **89**, 1483 (1967); W. S. Johnson, *Acc. Chem. Res.*, **1**, 1 (1968); (c) H. W. Thompson, G. E. Linkowski, and J. M. Gottlieb, unpublished results.
(9) H. O. House, "Modern Synthetic Reactions", 2d ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 26–28.
(10) (a) R. L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, New York, N.Y., 1965, pp 34–49; (b) P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals", Academic Press, New York, N.Y., 1967, pp 104–107.
(11) J. A. Riddick and W. B. Bunger, "Technique of Organic Chemistry—Organic Solvents", Vol II, 3d ed, Wiley-Interscience, New York, N.Y., 1970; I. P. Gol'dshtein, E. N. Gur'yanova, N. M. Alpatova, and Yu. M. Kessler, *Elektrokhimiya*, **3**, 1011 (1967); *Chem. Abstr.*, **68**, 99624v (1968).
(12) Such an effect may be at least partly responsible for the increased β-hydrogenation reported when reduction of 4-cholesten-3β-ol is carried out using a base-treated catalyst: M. C. Dart and H. B. Henbest, *J. Chem. Soc.*, 3563 (1960).
(13) Melting points were determined with a Mel-Temp apparatus and are uncorrected, as are boiling points. Infrared spectra were taken using a Beckman IR-10 spectrometer and, unless otherwise specified, CCl_4 solutions. Ultraviolet spectra were taken with a Beckman DB-5 grating spectrometer, with 95% EtOH as the solvent. NMR spectra were taken on a Varian A-60 instrument, using CCl_4 or $CDCl_3$ solutions with Me_4Si and/or CH_2Cl_2 internal standards. Mass spectra were determined with an Atlas CH-5 magnetic sector instrument at 70 eV ionization potential. VPC analyses were carried out using 4 ft × 0.25 in. columns packed with 10% Apiezon L on 80–100 mesh firebrick (Hewlett-Packard 5750) and with SE-30 on 80–100 mesh firebrick (Varian Aerograph 1520). Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Steric Effects. 6. Hydrolysis of Amides and Related Compounds

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Data for eight sets of acidic and basic hydrolysis of amides, 18 sets of acidic and basic hydrolysis of *N*-acylimidazoles, and one set of acidic hydrolysis of hydroxamic acids were correlated with the modified Taft equation $\log k_X = \psi\upsilon_X + h$. Data for one set of basic hydrolysis of amides were correlated with the equation $\log k_X = \alpha\sigma_{IX} + \beta\sigma_{RX} + \psi\upsilon_X + h$. Best results were obtained upon the exclusion of the *tert*-butyl group from the correlations. The magnitude of the steric effect upon acid-catalyzed amide or *N*-acylimidazole hydrolysis is the same as the magnitude of the steric effect upon the base-catalyzed hydrolysis of amides or *N*-acylimidazoles. This is in contrast to the behavior of esters, for which a significant difference in the magnitude of the steric effect upon esterification of acid-catalyzed hydrolysis and upon base-catalyzed hydrolysis exists. The magnitude of the steric effect upon the acidic or basic hydrolysis of amides and related compounds is roughly comparable to the magnitude of the steric effect upon esterification, acidic or basic ester hydrolysis, and ester alcoholysis.

In previous papers of this series we have examined steric effects upon rates of esterification and acid-catalyzed hydrolysis of esters[1] and upon rates of base-catalyzed hydrolysis of esters.[2] It seemed of interest to extend these investigations to the question of steric effects upon the rates of hydrolysis of amides and related compounds. The objectives of this work are twofold: first, to determine whether the magnitude of the steric effect upon rates of acid-catalyzed hydrolysis of amides and related compounds is significantly different from the magnitude of the steric effect upon the rates of base-catalyzed hydrolysis; second, to compare the magnitude of the steric effect upon amide hydrolysis rates with the magnitude of the steric effect upon ester hydrolysis rates and upon esterification rates.

Twenty-seven sets of data taken from the literature for the rates of acid-catalyzed or base-catalyzed hydrolysis of amides, *N*-acylimidazoles, and hydroxamic acids were correlated with the modified Taft equation[1]

$$\log k_X = \psi\upsilon_X + h \tag{1}$$

by means of linear regression analysis. The data used in the correlations are set forth in Table I. The υ values required were generally taken from the first paper in this series;[1] some υ values are from our unpublished results. The results of the correlations are presented in Table II. The data for set 2 were correlated with the equation

$$\log k_X = \alpha\sigma_{IX} + \beta\sigma_{RX} + \psi\upsilon_X + h \tag{2}$$

as this set includes a number of nonalkyl substituents and involves base-catalyzed hydrolysis. Presumably the mechanism of amide hydrolysis is similar to that of ester hydrolysis. In that event, acid-catalyzed amide hydrolysis should be a

Table I. Data Used in Correlations

1. $10^4 k_2$, $XCONH_2 + H_3O^+$ in H_2O at 75.0 °C[a]
Me, 10.3; Et, 12.2; Pr, 6.89; Bu, 5.15; *i*-$PrCH_2$, 1.91; *t*-$BuCH_2$, 0.395; $ClCH_2$, 8.54; *i*-Pr, 6.64; *sec*-Bu, 2.08; *t*-Bu, 2.63
2. $10^4 k_2$, $XCONH_2 + OH^-$ in H_2O at 75.0 °C[a]
Me, 11.3; Et, 9.98; Pr, 4.32; Bu, 3.23; *i*-$PrCH_2$, 1.00; *t*-$BuCH_2$, 0.086; $ClCH_2$, 1430; *i*-Pr, 3.95; *sec*-Bu, 1.02; Cl_2CH, 18 400; *t*-Bu, 1.24; CCl_3, 135 000
3. $10^4 k_2$, $XCONH_2 + H_3O^+$ in H_2O at 65 °C[b]
Et, 5.64; Pr, 2.56; Bu, 2.70; *i*-Bu, 0.545; $ClCH_2$, 5.52; $BrCH_2$, 4.79; $MeOCH_2$, 3.79; Me, 4.30; *t*-Bu, 0.935
4. $10^4 k_2$, $XCONH_2 + H_3O^+$ in H_2O at 75 °C[b]
Et, 12.0; Pr, 5.99; Bu, 5.93; *i*-Bu, 1.29; $PhCH_2$, 5.19; c-$C_6H_{11}CH_2$, 1.24; $ClCH_2$, 12.1; *t*-$BuCH_2$, 0.193; $MeOCH_2$, 8.98; Me, 10.3; *i*-Pr, 6.06; Et_2CH, 0.176; *sec*-Bu, 1.51; c-C_6H_{11}, 3.96; c-C_5H_9, 9.04; *t*-Bu, 2.26
5. $10^4 k_2$, $XCONH_2 + H_3O^+$ in H_2O at 85 °C[b]
Et, 26.9; Pr, 13.0; *i*-Bu, 2.96; $PhCH_2$, 12.9; c-$C_6H_{11}CH_2$, 2.98; *t*-$BuCH_2$, 0.465; Me, 21.9; *i*-Pr, 13.7; Et_2CH, 0.477; *sec*-Bu, 3.86; c-C_6H_{11}, 8.90; c-C_5H_9, 11.5; *t*-Bu, 5.14
6. $10^4 k_2$, $XCONH_2 + H_3O^+$ in H_2O at 95 °C[b]
$PhCH_2$, 22.5; c-$C_6H_{11}CH_2$, 6.75; *t*-$BuCH_2$, 1.03; *i*-Pr, 29.6; Et_2CH, 1.04; *sec*-Bu, 8.50; *c*-C_6H_{11}, 20.5; c-C_5H_9, 29.6
7. $10^4 k_2$, $XCONH_2 + OH^-$ in H_2O at 75.0 °C[c]
Me, 13.6; Et, 13.1; Pr, 7.05; Bu, 5.52; *i*-Bu, 1.97; $PhCH_2$,[d] 17.7; c-$C_6H_{11}CH_2$, 1.77; c-C_6H_{11}, 4.24; c-C_5H_9, 7.80; *sec*-Bu, 1.65; *i*-Pr, 6.61; *t*-Bu, 2.57
8. $10^4 k_2$, $XCONH_2 + OH^-$ in H_2O at 85.0 °C[c]
Me, 24.6; Et, 25.5; Pr, 12.3; Bu, 10.4; *i*-Bu, 4.03; $PhCH_2$,[d] 29.4; c-$C_6H_{11}CH_2$, 3.94; c-C_6H_{11}, 6.22; *c*-C_5H_9, 13.6; *sec*-Bu, 3.38; *i*-Pr, 11.0; *t*-Bu, 5.08
9. $10^4 k_2$, $XCONH_2 + OH^-$ in H_2O at 95.0 °C[c]
Et, 44.0; Pr, 22.5; Bu, 18.9; *i*-Bu, 8.14; $PhCH_2$,[d] 47.3; c-$C_6H_{11}CH_2$, 6.80; c-C_6H_{11}, 12.2; c-C_5H_9, 27.3; *sec*-Bu, 5.79; *i*-Pr, 19.6; *t*-Bu, 10.3
10. *k*, *N*-acylimidazoles + H_2O in H_2O, μ = 1.0 M catalyzed by imidazole at 30 °C[e]
Me, 0.14; Et, 0.16; *i*-Pr, 0.26; *t*-Bu, 0.39; Pr, 0.12; *t*-$BuCH_2$, 0.023; Et_3C, 0.0002
11. *k*, *N*-acylimidazoles + H_2O in H_2O, μ = 1.0 M, catalyzed by imidazolinium ion at 30 °C[e]
Et, 0.034; *i*-Pr, 0.056; *t*-Bu, 0.11; Pr, 0.025; *t*-$BuCH_2$, 0.0045; Et_3C, 0.00007
12. *k*, *N*-acylimidazoles + H_3O^+ in 0.1 M aqueous HCl at 30 °C[f]
t-Bu, 31.6; *i*-Pr, 7.57; Et, 4.54; Pr, 2.74; *i*-Bu, 0.814; *t*-$BuCH_2$, 0.123; Et_3C, 0.0101; Me, 4.08
13. *k*, *N*-acylimidazoles + H_3O^+ in 1.20 M aqueous HCl at 30 °C[f]
t-Bu, 25.4; *i*-Pr, 5.77; Et, 3.11; Pr, 2.23; *t*-$BuCH_2$, 0.127; Et_3C, 0.00768
14. *k*, *N*-acylimidazoles + H_3O^+ in 2.38 M aqueous HCl at 30 °C[f]
t-Bu, 18.4; *i*-Pr, 4.28; Et, 2.53; Pr, 1.61; *i*-Bu, 0.496; *t*-$BuCH_2$, 0.129; Et_3C, 0.00663
15. *k*, *N*-acylimidazoles + H_3O^+ in 3.60 M aqueous HCl at 30 °C[f]
t-Bu, 12.4; *i*-Pr, 3.15; Et, 1.94; Pr, 1.24; *i*-Bu, 0.412; *t*-$BuCH_2$, 0.123; Et_3C, 0.00495
16. *k*, *N*-acylimidazoles + H_3O^+ in 4.77 M aqueous HCl at 30 °C[f]
t-Bu, 8.50; *i*-Pr, 2.28; Et, 1.36; Pr, 1.06; *i*-Bu, 0.362; *t*-$BuCH_2$, 0.125; Et_3C, 0.00282
17. *k*, *N*-acylimidazoles + H_3O^+ in 5.97 M aqueous HCl at 30 °C[f]
t-Bu, 5.86; *i*-Pr, 1.70; Et, 1.25; Pr, 0.884; *i*-Bu, 0.374; *t*-$BuCH_2$, 0.125; Et_3C, 0.00174
18. *k*, *N*-acylimidazoles + H_3O^+ in H_2O, 1.0 M in NaCl, 0.1 M in HCl at 30 °C[f]
t-Bu, 26.1; *i*-Pr, 5.47; Et, 3.08; Pr, 2.29; *t*-$BuCH_2$, 0.0843; Et_3C, 0.00960
19. *k*, *N*-acylimidazoles + H_3O^+ in H_2O, 2.0 M in NaCl, 0.1 M in HCl at 30 °C[f]
t-Bu, 15.9; *i*-Pr, 4.06; Et, 2.55; Pr, 1.43; *t*-$BuCH_2$, 0.0633; Et_3C, 0.00598
20. *k*, *N*-acylimidazoles + H_3O^+ in H_2O, 3.0 M in NaCl, 0.1 M in HCl at 30 °C[f]
t-Bu, 13.2; *i*-Pr, 2.76; Et, 1.49; Pr, 1.10; *t*-$BuCH_2$, 0.0406; Et_3C, 0.00446
21. *k*, *N*-acylimidazoles + H_3O^+ in H_2O, 4.0 M in NaCl, 0.1 M in HCl at 30 °C[f]
t-Bu, 9.42; *i*-Pr, 1.91; Et, 1.08; Pr, 0.700; *t*-$BuCH_2$, 0.0293; Et_3C, 0.00262
22. *k*, *N*-acylimidazoles + H_3O^+ in H_2O, 5.0 M in NaCl, 0.1 M in HCl at 30 °C[f]
t-Bu, 6.19; *i*-Pr, 1.18; Et, 0.683; Pr, 0.493; *t*-$BuCH_2$, 0.0200; Et_3C, 0.00208
23. *k*, *N*-acylimidazoles + H_3O^+ in 0.1 M aqueous HCl at 20.0–21.1 °C[g]
Me, 2.19; Et, 2.70; *i*-Pr, 4.71; *t*-Bu, 20.8; Pr, 1.57; *i*-Bu, 0.394; *t*-$BuCH_2$, 0.0627; Et_3C, 0.00535
24. *k*, *N*-acylimidazoles + H_3O^+ in 0.1 M aqueous HCl at 39.3–39.7 °C[g]
Me, 6.57; Et, 7.79; *i*-Pr, 12.0; Pr, 4.65; *i*-Bu, 1.42; *t*-$BuCH_2$, 0.197; Et_3C, 0.0211
25. *k*, *N*-acylimidazoles + H_3O^+ in 0.19 M HCl in 50% v/v dioxane–H_2O at 30 °C[g]
Et, 1.71; *i*-Pr, 3.02; *t*-Bu, 16.6; Pr, 1.07; *i*-Bu, 0.259; *t*-$BuCH_2$, 0.0470; Et_3C, 0.00415
26. *k*, *N*-acylimidazoles + H_3O^+ in 75% dioxane–H_2O, 0.19 M in HCl at 30 °C[g]
Et, 0.748; *i*-Pr, 1.27; *t*-Bu, 7.40; Pr, 0.454; *i*-Bu, 0.133; *t*-$BuCH_2$, 0.0255; Et_3C, 0.00291
27. *k*, *N*-acylimidazoles + OH^- in H_2O, μ = 1.0 M at 30 °C[e]
Me, 19 000; Et, 32 000; *i*-Pr, 50 000; *t*-Bu, 32 000; Pr, 28 000; *t*-$BuCH_2$, 13 000; Et_3C, 42
28. $10^5 k_2$, XCONHOH + H_3O^+, in H_2O, μ = 0.494 M, catalyzed by TsOH at 50.5 °C[h]
Me, 44.2; Et, 45.0; *i*-Pr, 15.7; *t*-Bu, 8.71; $PhCH_2$, 17.1

[a] A. Bruylants and F. Kezdy, *Rec. Chem. Prog.*, **21**, 213 (1960); P. D. Bolton, *Aust. J. Chem.*, **19**: 1013 (1966). [b] P. D. Bolton, *Aust. J. Chem.*, **22**, 527 (1969); **24**, 471 (1971). [c] P. D. Bolton and G. L. Jackson, *ibid.*, **24**, 969 (1971). [d] Excluded from correlation. [e] T. H. Fife, *J. Am. Chem. Soc.*, **87**, 4597 (1965). [f] J. A. Fee and T. H. Fife, *J. Phys. Chem.*, **70**, 3268 (1966). [g] J. A. Fee and T. H. Fife, *J. Org. Chem.*, **31**, 2343 (1966). [h] D. C. Berndt and J. K. Sharp, *ibid.*, **38**, 296 (1973).

function of steric effects only[1] and base-catalyzed hydrolysis should be a function of both electrical and steric effects. The other sets of base-catalyzed hydrolysis have not been correlated with eq 2, however, as only one nonalkyl substituent, the benzyl group, is available in these sets (sets 7, 8, 9). Correlation with these sets was therefore carried out with eq 1, excluding the value for the benzyl group, as we have previously shown that in the base-catalyzed hydrolysis of esters, data sets involving only alkyl groups show only steric effects upon hydrolysis rates.[2] The σ_I constants required for correlation with

Table II. Results of Correlations with Equation 1

Set	ψ	h	r^a	F^b	$s_{est}{}^c$	$s_\psi{}^c$	$s_h{}^c$	n^d
1	−1.44	1.81	0.920	43.85[e]	0.189	0.217[e]	0.192[e]	10
1A	−1.75	2.01	0.984	215.0[e]	0.0905	0.119[e]	0.0991[e]	9
3	−1.34	1.41	0.873	22.48[f]	0.186	0.282[g]	0.214[e]	9
3A	−2.26	1.99	0.955	62.21[e]	0.107	0.287[e]	0.194[e]	8
4	−1.87	2.11	0.942	109.3[e]	0.204	0.179[e]	0.162[e]	16
4A	−2.07	2.24	0.980	323.3[e]	0.123	0.115[e]	0.101[e]	15
5	−1.74	2.34	0.933	73.64[e]	0.214	0.203[e]	0.194[e]	13
5A	−1.93	2.46	0.979	233.3[e]	0.126	0.126[e]	0.118[e]	12
6A	−1.99	2.88	0.973	108.1[e]	0.151	0.191[e]	0.196[e]	8
7	−1.35	1.77	0.887	33.21[e]	0.163	0.235[e]	0.198[e]	11
7A	−1.87	2.14	0.974	145.9[e]	0.0824	0.155[e]	0.123[e]	10
8	−1.28	1.98	0.894	35.82[e]	0.148	0.213[e]	0.180[e]	11
8A	−1.78	2.34	0.988	336.9[e]	0.0516	0.0969[e]	0.0769[e]	10
9	−1.15	2.14	0.834	18.31[f]	0.167	0.270[g]	0.235[e]	10
9A	−1.79	2.61	0.976	139.7[e]	0.0695	0.151[e]	0.124[e]	9
10	−1.50	0.336	0.875	16.36[g]	0.603	0.372[g]	0.458[n]	7
10A	−1.59	0.239	0.976	78.75[e]	0.289	0.179[e]	0.221[n]	6
11	−1.50	−0.223	0.866	11.97[j]	0.655	0.434[j]	0.570[o]	6
11A	−1.55	0.394	0.983	86.12[f]	0.251	0.167[g]	0.221[m]	5
12	−1.40	1.62	0.773	8.891[i]	0.764	0.471[j]	0.566[j]	8
12A	−1.53	1.52	0.964	66.46[e]	0.303	0.188[e]	0.225[g]	7
13	−1.49	1.73	0.786	6.475[k]	0.884	0.586[k]	0.770[k]	6
13A	−1.56	1.50	0.971	50.12[g]	0.331	0.220[g]	0.292[h]	5
14	−1.42	1.48	0.777	7.601[j]	0.783	0.516[j]	0.656[k]	7
14A	−1.50	1.32	0.973	72.30[f]	0.268	0.177[g]	0.226[g]	6
15	−1.42	1.38	0.791	8.365[j]	0.747	0.492[j]	0.625[k]	7
15A	−1.50	1.22	0.979	90.07[e]	0.240	0.158[e]	0.202[g]	6
16	−1.48	1.33	0.813	9.349[j]	0.721	0.475[j]	0.604[k]	7
16A	−1.56	1.18	0.984	124.1[e]	0.212	0.140[e]	0.179[g]	6
17	−1.56	1.33	0.840	11.98[i]	0.684	0.450[h]	0.573[k]	7
17A	−1.63	1.19	0.989	171.9[e]	0.189	0.125[e]	0.159[g]	6
18	−1.45	1.67	0.767	5.711[k]	0.916	0.607[k]	0.797[m]	6
18A	−1.52	1.43	0.958	33.21[i]	0.396	0.263[h]	0.349[j]	5
19	−1.49	1.55	0.785	6.440[k]	0.886	0.587[k]	0.771[m]	6
19A	−1.55	1.33	0.961	36.67[g]	0.386	0.257[g]	0.341[j]	5
20	−1.46	1.37	0.767	5.667[k]	0.927	0.614[k]	0.806[m]	6
20A	−1.53	1.13	0.957	32.80[i]	0.402	0.267[h]	0.354[j]	5
21	−1.50	1.24	0.770	5.830[k]	0.935	0.619[k]	0.813[n]	6
21A	−1.56	0.997	0.962	37.10[g]	0.387	0.257[g]	0.341[k]	5
22	−1.45	1.01	0.764	5.599[k]	0.923	0.612[k]	0.803[n]	6
22A	−1.51	0.775	0.961	36.18[g]	0.379	0.252[g]	0.334[m]	5
23	−1.42	1.39	0.761	8.231[j]	0.804	0.495[j]	0.596[k]	8
23A	−1.56	1.29	0.959	56.59[e]	0.333	0.207[e]	0.248[g]	7
24A	−1.48	1.70	0.961	59.84[e]	0.309	0.192[e]	0.230[e]	7
25	−1.45	1.31	0.744	6.207[k]	0.885	0.583[k]	0.741[m]	7
25A	−1.54	1.13	0.957	44.00[f]	0.352	0.233[g]	0.297[h]	6
26	−1.33	0.868	0.727	5.597[k]	0.855	0.563[k]	0.716[n]	7
26A	−1.42	0.692	0.955	41.42[f]	0.334	0.221[g]	0.282[k]	6
27	−1.45	5.57	0.890	19.00[g]	0.538	0.332[g]	0.408[e]	7
27A	−1.50	5.51	0.937	28.59[g]	0.452	0.281[g]	0.345[e]	6
28	−0.970	2.07	0.902	13.13[j]	0.154	0.268[j]	0.214[g]	5
28A	−2.16	2.80	0.975	38.77[i]	0.0682	0.347[j]	0.223[g]	4

[a] Correlation coefficient. [b] F test for significance of correlations. Superscripts indicate confidence levels (CL). [c] Standard errors of the estimate, ψ, and h. Superscripts indicate confidence levels of the Student's t test. [d] Number of points in the set. [e] 99.9% CL (confidence level). [f] 99.5% CL. [g] 99.0% CL. [h] 98.0% CL. [i] 97.5% CL. [j] 95.0% CL. [k] 90.0% CL. [l] 90.0% CL. [m] 80.0% CL. [n] 50.0% CL. [o] 20.0% CL. [p] <20.0% CL.

eq 2 are taken from our compilation[3] with the exception of the value for $CHCl_2$ (0.30)[4] and the value for CCl_3 (0.38) which we have calculated from the value for CH_2CCl_3. Values of σ_R used were generally obtained from the equation

$$\sigma_R = \sigma_p - \sigma_I \quad (3)$$

using σ_p values reported by McDaniel and Brown.[5] Values of σ_R for the $CHCl_2$ (0.03) and CCl_3 (0.05) groups were obtained from $\sigma_R{}^\circ$ values reported by Sheppard[4] using $\sigma_R{}^\circ = 0.67\sigma_R$.

Results

Results of the correlations with eq 1 are given in Table II. Results of the correlations with eq 2 are reported in Table III. In all sets containing the t-Bu group, correlation is improved by excluding the value for this substituent. Such sets in Tables II and III are designated by the letter A. Sets involving acid-catalyzed hydrolysis of amides (sets 1, 3–6) gave excellent correlations both with and without the exclusion of the t-Bu group (as determined by the confidence level of the F test). Better results were obtained for the correlations excluding the t-Bu group.

With respect to base-catalyzed amide hydrolysis, set 2 was correlated with eq 2, with excellent results, set 2A giving best results. Sets 7, 8, and 9 were correlated with eq 1; excellent results were obtained, although better results were shown by

Table III. Results of Correlations with Equation 2

Set	α	β	ψ	h	R^a	F^b	$r_{12}{}^c$	$r_{13}{}^c$
2	8.94	8.64	−1.50	2.95	0.978	57.60[f]	0.961[f]	0.267[g]
2A	10.9	5.69	−2.09	3.05	0.988	99.29[f]	0.959[f]	0.389[g]

Set	$r_{23}{}^c$	$s_{est}{}^d$	$s_\alpha{}^d$	$s_\beta{}^d$	$s_\psi{}^d$	$s_h{}^d$	n^e
2	0.132[g]	0.465	3.87[h]	8.96[i]	0.537[h]	0.783[j]	12
2A	0.246[g]	0.351	3.02[j]	6.85[i]	0.461[j]	0.592[j]	11

[a] Multiple correlation coefficient. [b] F test for significance of correlation. Superscript indicates confidence level. [c] Partial correlation coefficients of σ_I on σ_R, σ_I on v, σ_R on v. Superscripts indicate confidence levels. [d] Standard errors of the estimate, α, β, ψ, and h. Superscripts indicate confidence levels of Student's t tests. [e] Number of points in the set. [f] 99.9% CL. [g] <90.0% CL. [h] 95.0% CL. [i] 50.0% CL. [j] 99.0% CL.

Table IV. Test of Taft Assumption

Acid set	$-\psi_{acid}$	$s_{\psi\ acid}$	n	Base set	$-\psi_{base}$	$s_{\psi\ base}$	n	$\Delta\psi$	t_{acid}	t_{base}
1A	1.75	0.119	9	2A	2.09	0.461	11	0.34	2.857[a]	0.738[b]
4A	2.07	0.115	15	7A	1.87	0.155	10	0.20	11.739[c]	1.290[b]
5A	1.93	0.126	12	8A	1.78	0.0969	10	0.15	1.90[b]	1.548[c]
6A	1.99	0.191	9	9A	1.79	0.151	9	0.20	1.047[b]	1.325[b]
12A	1.53	0.188	7	27A	1.50	0.281	6	0.03	0.160[d]	0.107[d]
11A	1.55	0.167	5	10A	1.59	0.179	6	0.04	0.240[d]	0.223[d]

[a] 95.0% CL. [b] 50% CL. [c] 80.0% CL. [d] 20.0% CL.

the A sets. Fifteen sets of acid-catalyzed N-acylimidazole hydrolysis rate constants were correlated with eq 1. Of 14 sets including the t-Bu group, two gave good, four gave fair, and eight gave poor results. Of 15 sets excluding the t-Bu group, nine gave excellent, four gave very good, and two gave good results. For imidazole-catalyzed hydrolysis of N-acylimidazoles (set 10) correlation with eq 1 gave very good results including and excellent results excluding the t-Bu group. For imidazolium-catalyzed hydrolysis of N-acylimidazoles (set 11) correlation with eq 1 gave fair results including and excellent results excluding the t-Bu group. In the case of the base-catalyzed hydrolysis of N-acylimidazoles (set 27) very good results were obtained with or without the t-Bu group, although the results without t-Bu are somewhat better. For the acid hydrolysis of hydroxamic acids (set 28) fair results including and good results excluding the t-Bu group were obtained.

Discussion

We have previously shown[2] that the Taft hypothesis that the magnitude of the steric effect upon rates of esterification or acid-catalyzed ester hydrolysis is the same as the magnitude of the steric effect upon base-catalyzed ester hydrolysis is incorrect. Thus, there is a significant difference between the magnitudes of these steric effects in ester hydrolysis. The question then arises, is there also a significant difference between the magnitudes of the steric effects on the acid-catalyzed and the base-catalyzed hydrolysis of amides and related compounds. As all of the available data have been determined in water, comparison is straightforward. In Table IV, the ψ values for acidic and basic hydrolysis of amides under comparable reaction conditions, and of N-acylimidazoles are presented. Also compared are ψ values of imidazole (base) catalyzed hydrolysis and the imidazolium (acid) catalyzed hydrolysis of N-acylimidazoles. Values of the Student's t test for the difference between ψ_{acid} and ψ_{base} have been calculated. t_{acid} values and t_{base} values were determined from the standard error of ψ_{acid} and ψ_{base}, respectively. The results of the comparisons show clearly that there is no significant difference between the magnitudes of the steric effect on acid-catalyzed and base-catalyzed hydrolysis of amides and related compounds. It must be pointed out, however, that while the Taft hypothesis has been shown to be valid for amide hydrolysis this is only true in the case of water. Unfortunately data are not available to test the hypothesis in other solvent systems. The solvent systems upon which the Taft separation of polar and steric effects rests are generally water–ethanol and water–acetone mixtures.

We now turn our attention to a comparison of steric effects upon rates of hydrolysis and related reactions of esters with steric effects upon rates of hydrolysis of amides and related compounds. (For values of ψ see paragraph at end of paper regarding supplementary material.)

The magnitude of ψ for the acidic hydrolysis of amides and related compounds is seen from Table IV to be comparable to the magnitude of ψ for esterification and the acidic hydrolysis of esters. Acidic alcoholysis of acyl-2-naphthoates gives somewhat higher ψ values. The magnitude of ψ for the basic hydrolysis of amides and N-acylimidazoles is somewhat less than that of ψ for most of the basic ester hydrolyses. It seems reasonable to conclude that steric effects upon the acidic or basic hydrolysis of amides and related compounds are roughly comparable in magnitude to steric effects upon esterification, acidic and basic hydrolysis, and ester alcoholysis.

We have noted above that the t-Bu group deviates significantly in all of the 26 sets in which it occurs. Two distinct types of behavior can be discerned. In all of the amide hydrolysis sets which contain the methyl, ethyl, isopropyl, and *tert*-butyl groups, and in the hydroxamic acid hydrolysis as well, the methyl, ethyl, and isopropyl group rate constants are greater than the *tert*-butyl group rate constant. In the case of the N-acylimidazoles the rate constants lie in the sequence t-Bu > i-Pr > Et in most of the sets studied. Obviously, then, the t-Bu group in the case of amide hydrolysis is behaving differently than in the case of N-acylamidazole hydrolysis. Bolton and Jackson[7,8] have reported in the case of both acidic and basic hydrolysis that best correlation with E_S values using

the Taft–Pavelich equation

$$\log k = \rho^*\sigma^* + \delta_{Es} + \log k_0 \quad (4)$$

gives best results with separate lines for amides bearing groups with one or two α hydrogen atoms. It might be argued then that groups with no α hydrogens should lie on still another correlation line. It must be noted, however, that these authors find best results on correlation with the equation

$$\log k = \rho^*\sigma^* + \delta_{Es}{}^c + h(n-3) + \log k_0 \quad (5)$$

and that while substituents with both one and two α hydrogens give an excellent fit to this equation, the t-Bu group deviates significantly. Bolton and Jackson have ascribed the effect of the t-Bu group to hyperconjugation. This is based on an analysis involving the $(n-3)$ term in eq 5, which is considered to represent hyperconjugation by Hancock et al.[9] In our opinion this term represents an additional steric parameter, a point we shall take up in a future paper in this series.

It should be pointed out that our results for acid- and base-catalyzed ester hydrolysis,[1,2] our unpublished results for the reactions of aldehydes, acyl chlorides, and thioesters with hydroxide ion, water, and alcohols, and for the reaction of esters with ammonia show that the point for the t-Bu group lies on the correlation line. This leads us to the conclusion that the t-Bu group generally behaves normally in nucleophilic additions to the carbonyl group. Amide hydrolyses represent *an exception to this generalization.*

Supplementary Material Available. A table of ψ values for various reactions (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) M. Charton, *J. Am. Chem. Soc.*, **97**, 1552 (1975).
(2) M. Charton, *J. Am. Chem. Soc.*, **97**, 3691 (1975).
(3) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964).
(4) W. A. Sheppard, *Tetrahedron*, **27**, 945 (1971).
(5) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).
(6) R. W. Taft in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, p 565.
(7) P. D. Bolton and G. L. Jackson, *Aust. J. Chem.*, **24**, 471 (1971).
(8) P. D. Bolton and G. L. Jackson, *Aust. J. Chem.*, **24**, 969 (1971).
(9) C. K. Hancock, E. A. Meyers, and B. J. Yager, *J. Am. Chem. Soc.*, **83**, 4211 (1961).

Sodium–Ethylenediamine Reductive Dimerization of Naphthalene to 5,6,7,12,13,14-Hexahydro-5,13:6,12-dimethanodibenzo[*a,f*]cyclodecene

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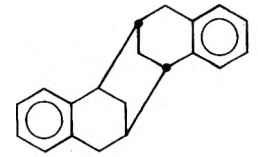
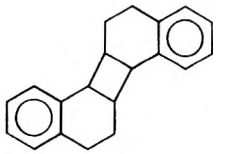
Crystallographic studies of the $C_{20}H_{20}$ reduced dimer, mp 179–180 °C, obtained from treatment of naphthalene with sodium and ethylenediamine showed the hydrocarbon to be the title compound. This analysis allowed ^1H NMR absorption assignments. Other properties of 1 and its oxidation products are reported.

The reaction of naphthalene or the dihydronaphthalenes with sodium and ethylenediamine[1a,b] affords a $C_{20}H_{20}$ reduced dimer, mp 179–180 °C, now shown by x-ray crystallographic analysis to have structure **1** rather than **2**[1a,b] earlier proposed.



1



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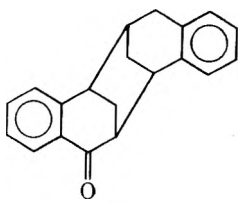

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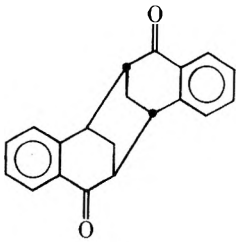


4

Dimer **1** is also formed by reaction of dihydronaphthalene with potassium *tert*-butoxide and dimethyl sulfoxide (Me_2SO).[2a] Wideman reported isolation of a crystalline 1,2-bisdialin, mp 179–180 °C, using the preceding reagents.[2b]

The crystal structure of the dibromo derivative of Heller's dimer, a nitrogen analogue of the title compound, has been determined[3a] and hydroxy ketone derivatives of the title compound have also been prepared.[3b] Otherwise structure **1** appears to be new.

We also report additional properties of **1** and its oxidation to the mono- and diketone, **3** and **4**.

Results and Discussion

Figure 1 shows a stereoview[4a,b] of the dimer which consists of five six-membered carbon rings having a crystallographic center of symmetry.

Other data derived from the crystallographic study are summarized in Figures 2 and 3. Figure 2 shows the skeletal numbering[5] and carbon–carbon bond lengths[6] of **1**. The bond angles as well as the torsion angles for the three unique ring systems of **1** are given in Figure 3. These torsional angles may be compared with those calculated for six-membered cycloalkanes.[7] Experimentally determined torsion angles for the cyclohexene ring agree best with torsion angles for the C_s barrier conformation calculated by Hendrickson.[7] Planarity of the benzene ring is indicated by torsion angles of approximately 0°. The bond angle formed by C(13)–C(14)–C(14a) shows a large distortion from the normal bond angle of 109.5° for a tetrahedral carbon atom. No other significant deviations from the expected bond distances and angles are observed.

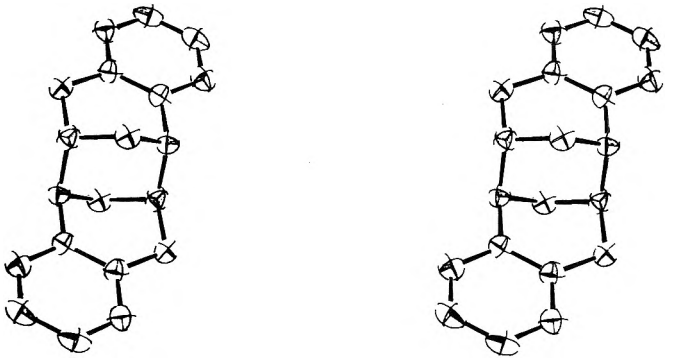


Figure 1. Stereoview of the carbon rings of 1.

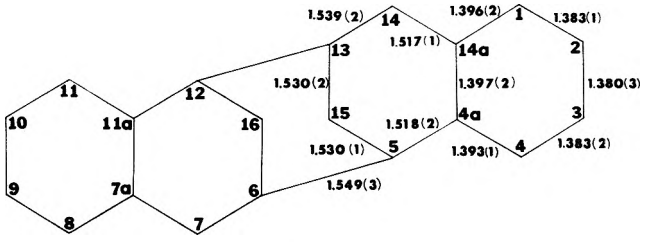


Figure 2. Carbon–carbon bond lengths and skeletal numbering for 1.

C–H bond distances range from 0.99(2) to 1.01(2) Å with an average value of 1.00(2) Å.

Our earlier assignment of structure 2 was based on the following evidence: (1) a strong ir band at 755 cm^{-1} suggesting four adjacent aromatic protons;[8a] (2) mass spectrum (70 eV) *m/e* (rel intensity) M^+ 260 (41), hemicleavage to *m/e* 130 (40), and 129 (100);[1b,8b,8c] (3) the presence of aromatic, benzylic, and aliphatic protons in the NMR spectrum in the ratio 8:6:6;[1b,8b] (4) GC retention time similar to other $C_{20}H_{20}$ dimers;[2a,8a,b] and (5) no obvious reaction on treatment with ozone or dilute bromine in carbon tetrachloride.[8a] More recently we have carried out pyrolysis studies of 1 which gave good yields of naphthalene, tetralin, and 1-methylindan in the ratio of 5.5:4.7:1.[8a] Attempts to dehydrogenate the hydrocarbon with Pd/C in refluxing 1-methylnaphthalene (bp 250 °C) or neat at 200 °C as well as 300 °C yielded unchanged 1. Oxidation of the hydrocarbon 1 with CrO_3 in acetic acid furnished a monoketone, 3, mp 178–179.5 °C, and a diketone, 4, mp 290–292 °C.[8a] The formation of only one monoketone and one diketone along with the high melting points and the poor solubility of 1 and the diketone were strong arguments for symmetry in the parent hydrocarbon 1 and the diketone 4. Comparison of the ir and Raman spectra[8a,d] of the diketone 4 showed no correspondence of the major absorption bands. This suggested a symmetrical molecule lacking a dipole moment consistent with cis-anti-cis stereochemistry for the cyclobutane ring junction of 2. These observations agree, of course, with structure 1 as well.

Unfortunately, the diketone 4 is very insoluble and consequently of limited utility in NMR studies. Subsequently, we have applied base-catalyzed deuterium exchange to 4 and have attempted the preparation of its enol acetate and its benzylidene derivative. The diketone was unaffected by these procedures.

The foregoing evidence is most consistent with 5,6,7,12,13,14-hexahydro-5,13:6,12-dimethanodibenzo[*a,f*]-cyclodecene-7,12-dione[5] as the structure of the diketone 4. The presence of the methano bridges in 4 explain its inertness to deuterium exchange and its failure to yield an enol acetate or benzylidene derivative.

We have also shown that the dimerization of dihydronaphthalene or the cyclization of 5 can proceed to 1 under

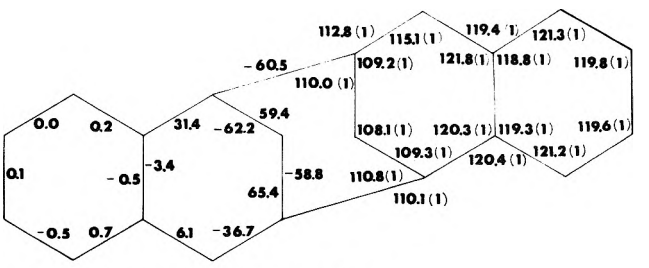
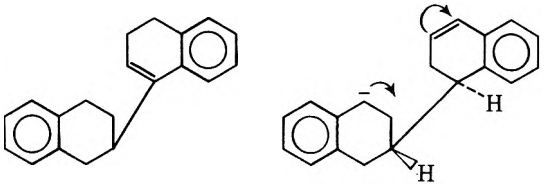


Figure 3. Bond and torsion angles for 1.

nonreducing conditions.[2a,8a,b] For this reason, we favor anionic routes over a radical dimerization process.

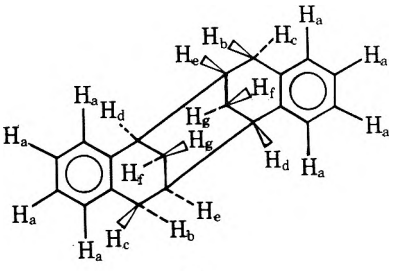
Structure 6 seems a likely intermediate to hydrocarbon 1



5 6

through the nucleophilic cyclization shown. A Dreiding model of 6 (anion assumed to be tetrahedral) shows that the conjugated double bond may be situated directly under the benzylic methylene group bearing the negative charge. This requires that 6 must have trans protons in order to cyclize to 1.

The rigorous crystallographic proof of structure for 1 allows conclusive assignment of peak absorption of its 100-MHz ^1H NMR spectrum. The rigidity of 1 provides a magnetically nonequivalent environment for geminal protons at C-7 and C-14 as well as C-15 and C-16 as shown for structure 7. Also, the centrosymmetry of 7 requires that each of these protons



7

has an equivalent proton at the corresponding reflection position.[6] These are labeled accordingly.

The nonequivalent geminal protons couple to give $J_{H_bH_c}$ = 18 Hz and $J_{H_fH_g}$ = 13 Hz which is readily shown by irradiating the doublet corresponding to H_f or H_g and noting coalescence. The same is true for the signals of H_b and H_c with one further complication: H_b is represented by a doublet of doublets and coalesces to a doublet ($J_{H_bH_e}$ = 6 Hz) on irradiation of H_c. The absence of a measurable coupling constant between the vicinal protons H_c and H_e ($J_{H_cH_e}$ = 0 Hz) while noting one for H_b and H_e can be rationalized by calculating the dihedral angles between H_b and H_e (θ_1 = 36°) and H_c and H_e (θ_2 = 82°) and comparing the observed coupling constants to those predicted by the Karplus equation.[9] The dihedral angles were calculated from final coordinates (Tables I, II, and III) and the calculated coupling constants of $J_{H_bH_e}$ = 5.30 Hz and $J_{H_cH_e}$ = −0.11 Hz show good agreement with the observed values.

The choice of the remaining doublet ($J_{H_dH_e}$ = 1.5 Hz) for the signal of H_d is supported by coalescence to a singlet upon irradiation of the H_e multiplet. This is further supported by the presence of the same doublet (slightly shifted) in the

Table I. Positional Coordinates of All Carbon Atoms [a]

	$x \times 10^4$	$y \times 10^4$	$z \times 10^4$
C(6)	6918 (2)	811 (2)	4952 (2)
C(7)	6702 (2)	−621 (2)	2834 (2)
C(7a)	4416 (2)	−1697 (2)	1231 (2)
C(8)	4067 (2)	−3153 (2)	−687 (2)
C(9)	2009 (2)	−4140 (2)	−2204 (2)
C(10)	256 (2)	−3698 (2)	−1824 (2)
C(11)	575 (2)	−2267 (2)	72 (2)
C(11a)	2639 (2)	−1257 (2)	1614 (2)
C(12)	2959 (2)	251 (2)	3711 (2)
C(16)	5015 (2)	1839 (2)	4698 (2)

[a] The atomic scattering factors for carbon were taken from "International Tables for X-Ray Crystallography", Vol. III, Kynoch Press, Birmingham, England, 1962, p 202. [b] The x, y, and z terms are expressed in fractions of the cell edges a, b, and c. Standard deviations for the last digit are in parentheses.

spectrum of the diketone 4 where H_d represents the only benzylic protons.

It is fortunate that H_b and H_c can be differentiated through their observed coupling constants with H_e. Such is not the case with H_f and H_g. Both parts of the doublets for H_f and H_g resemble broad unresolved triplets (5–8 Hz wide at peak half-height). Their shapes change to that of unresolved doublets on irradiation of H_e or H_d. It was noted that both H_e and H_d nearly halve the angle between H_f and H_g (all angles calculated to be 54–65°). The equal bond angles would explain why the splitting patterns of H_f and H_g are very similar and the magnitude of the bond angles could explain why the coupling constants may be small enough (calculated to be from 1.2 to 2.7 Hz) to be effectively hidden in the broad signals previously noted.

Experimental Section

Preparation of 5,6,7,12,13,14-Hexahydro-5,13:6,12-dimethanodibenzo[a,f]cyclodecene (1). The hydrocarbon dimer 1 was prepared by stirring 12.8 g of naphthalene, 10 g of sodium spheres, and 230 ml of anhydrous ethylenediamine at 50 °C for 2 h in a previously described stir-shredding device.[10] The reaction mixture was kept under a blanket of nitrogen. The product mixture was allowed to cool and was then cautiously poured onto crushed ice (1–2 kg). Aqueous HCl (2200 ml of 10%) was added and the resulting mixture was extracted with 2 × 500 ml of ether. The extract was washed with 50 ml of 10% HCl, then with water and finally dried ($MgSO_4$). Concentration and Kugelrohr distillation at 160–170 °C (0.1 mm) gave 4.2 g of a dimer fraction.

The above fraction was recrystallized from toluene to give 0.5 g of colorless 1: mp 179–180 °C; ir (KBr) prominent bands at 755, 741, and 712 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 260 (41), 131 (38), 130 (40), 129 (100), 128 (63), and 115 (21); ^1H NMR ($CDCl_3$) δ 7.25–6.97 (m, 8, ArH), 3.27 (d of d, $J_{H_bH_e}$ = 6 and $J_{H_bH_c}$ = 18 Hz, 2, $ArCH_2$), 2.87 (d, $J_{H_bH_c}$ = 18 Hz, 2, $ArCH_2$), 2.85 (d, $J_{H_dH_e}$ = 1.5 Hz, 2, ArCH), 2.21–1.94 (m, 2, $ArCH_2CH$), 1.78 (d, $J_{H_fH_g}$ = 13 Hz, 2, $ArCHCH_2$), and 1.34 (d, $J_{H_fH_g}$ = 13 Hz, 2, $ArCHCH_2$); uv max (95% ethanol) 260 nm (log ϵ 2.97), 266 (3.16), and 273 (3.20).

Anal. Calcd for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 92.25; H, 7.85.

Crystal Preparation and Measurement of Crystals. Crystals of 1, as clear needles suitable for data collection, were grown from a benzene–ethanol solution. Preliminary investigation of the data crystal on a Nonius CAD-4 automatic diffractometer indicated a triclinic space group. Least-squares cell dimensions were obtained from the averages of the $+2\theta$ and -2θ values of 20 pairs of reflections measured at ambient temperature (27 °C) using Cu $K\alpha_1$ radiation (λ = 1.5405 Å).

The 1162 intensity data, comprising all unique reflections with $2\theta \leq 130°$, were measured using Ni-filtered Cu $K\bar{\alpha}$ radiation (λ = 1.5418 Å) on a Nonius CAD-4 automatic diffractometer. The data were collected using θ–2θ scan technique in which the scan width was calculated as 1.0 + 0.1 tan θ. The maximum scan time was 50 s with ⅔ of the time spent while scanning the peak and ⅙ on each the left and right background. A total of 122 reflections were considered indistinguishable from background, having a net count less than $1.4(T)^{1/2}$ (T = total count). These reflections were assigned intensities equal to $1.0\sqrt{T}$.

Crystallographic Structure Determination and Refinement. The overall temperature factor and scale were determined.[11] The normalized structure factors E were calculated, and a statistical test of their distribution strongly indicated a center of symmetry. The space group was thus determined to be $P\bar{1}$.

The structure was solved by direct methods using the program MULTAN.[12] The phases for 151 normalized structure factors greater than 1.5 were used in generating an E map. The E map calculated from one of several phase sets revealed the position of all ten carbon atoms contained in the asymmetric unit. The initial structure factor calculation gave an R [$= \Sigma||kF_o| - |F_c||/\Sigma|kF_o|$] of 0.40. After three cycles of least-squares refinement, all carbon atoms were given anisotropic temperature factors. Two subsequent cycles of refinement resulted in an R which converged at 0.12. Positions of the ten hydrogen atoms in the asymmetric unit were calculated on the basis of geometric considerations and compared with peaks appearing in the calculated difference Fourier. All ten hydrogens were thus located and included in the refinement with isotropic temperature factors. The refinement was terminated when all shifts were less than ½ of the corresponding standard deviation. A final difference Fourier map was calculated in which all electron densities were between −0.15 and 0.15 e $Å^{-3}$.

All least-squares refinements were carried out by the block-diagonal least-squares program of Ahmed.[13] The unweighted R based on the final parameters (Tables I, II, and II) was 0.044 for all data.[14] Each amplitude was assigned a weight based on a previously described[15] experimental weighting scheme. The quantity minimized in the refinement was $\Sigma w_F(|KF_o| - |F_c|)^2$. The average value of $W_F\Delta F^2$ did not show significant variation with either $|F_o|$ or $\sin^2\theta/\lambda$ in the structure factor analysis, validating the weighting scheme which was used.

The crystallographic data follow: $C_{20}H_{20}$; mol wt 260.18; space group $P\bar{1}$; a = 6.9214 ∓ 0.0004 Å; b = 7.5066 ∓ 0.0008 Å; c = 7.9842 ∓ 0.0005 Å; V = 340.74 Å; Z = 1; F (000) = 140; α = 113.712° ∓ 0.006°; β = 113.142° ∓ 0.005°; γ = 91.523° ∓ 0.006°; D_c = 1.268 g/cm;[3] and D_m = 1.263 g/cm^3 (measured by flotation in CCl_4/C_7H_{16} mixture).

Preparation of 5,6,7,12,13,14-Hexahydro-5,13:6,12-dimethanodibenzo[a,f]cyclodecene-7,14-dione (4). A sample (2 g, 0.008 mol) of 1 and 27.5 ml (30.3 g of solution, 0.03 mol) of a 10% aqueous chromium trioxide acetic acid solution[16] were stirred in glacial acetic acid (1 l.) for 10 days. The solution was poured into water whereupon a white solid separated. This was filtered out and recrystallized from toluene to give 1.5 g of colorless crystals, mp 288–291 °C. Concentration of the mother liquor gave an additional 0.3 g of crystals, mp 283–288 °C. The total yield was 81%.

Recrystallization of the first crop of crystals from toluene–2-propanol (1:1) gave 1.2 g of colorless 4: mp 290–292 °C; ^1H NMR ($CDCl_3$) δ 8.11 (d, J = 7 Hz, 2, peri ArH), 7.68–7.22 (m, 6, ArH), 3.35 (broad s, 2, ArCH), 2.71 (broad s, 2, ArCOCH), and 2.26–1.76 (m, 4, $ArCHCH_2$); ir (KBr) prominent absorptions 1716, 1296, and 763 cm^{-1}; uv max (95% ethanol) 207 nm (log ϵ 4.70), 249 (4.48), and 295 (3.51); mass spectrum (70 eV) m/e (rel intensity) 288 (M^+, 71), 144 (100), 143 (43), 117 (1), 116 (1), and 115 (4).

Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.46; H, 5.61.

Preparation of 5,6,7,12,13,14-Hexahydro-5,13:6,12-dimethanodibenzo[a,f]cyclodecen-7-one (3). Hydrocarbon 1 (504 mg, 0.002 mol) and 0.28 g (0.003 mol) of a 10% aqueous chromium trioxide–acetic acid solution[16] were stirred in glacial acetic acid (450 ml) for 9 h. The solution was poured into water (1.2 l.) and extracted with chloroform (450 ml). Gas chromatography of the concentrated extract showed a mixture of 1:3:4 (5.7:8.6:1.0).[17a] The components were separated by toluene elution through neutral alumina. Recrystallization from ether of combined fractions containing 3 gave 143 mg (0.0005 mol, 27%) of colorless needles: mp 176–178 °C (further recrystallization from ether improved the mp to 178–179.5 °C); NMR ($CDCl_3$) δ 8.09 (d, J = 7 Hz, 1, peri ArH), 7.62–6.96 (m, 7, ArH), 3.31 (d of d, J = 7 and 18 Hz, 1, ArCH), 3.14 (d, J = 4 Hz, 1, ArCH), 3.06 (d, J = 4 Hz, 1, ArCH), 2.91 (d, J = 18 Hz, 1, ArCH), 2.61 (broad s, 1, ArCOCH), 2.30–2.04 (m, 1, $ArCH_2CH$), 1.96–1.63 (m, 3, $ArCHCH_2$), and 1.44 (d, J = 13 Hz, 1, $ArCHCH_2$); ir (KBr) 1670 (conjugated C=O) and 750 cm^{-1} (4 contiguous aromatic protons); uv max (95% ethanol) 253 nm (log ϵ 4.11), 274 (shoulder, 3.57), and 294 (broad, 3.29); mass spectrum (70 eV) m/e (rel intensity) M^+, 274 (32), 146 (90), 131 (21), 129 (100), 128 (25), and 115 (21).

Anal. Calcd for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 87.45; H, 6.58.

Attempted Catalytic Dehydrogenation of 1. A mixture of 1 (0.4 g), mp 177–179 °C, and 10% Pd/C (40 mg) was heated at 200–210 °C in a fused salt bath for 2 h. The reaction mixture was cooled, boiled with toluene (100 ml), and filtered to remove catalyst. The filtrate was rotary evaporated and pumped to dryness to give recovered **1**, mp 174–177 °C. The same sample was heated with new catalyst (40 mg) at 300 °C for 2 h and treated in the same manner to give 0.4 g of **1**, mp 169–175 °C, and mixed with starting material, mp 174–178 °C. GLC studies showed a single major peak with a trace of trailing impurity. Individual and mixed injections of starting material and sample showed identical retention times.[17b] A second sample of 1 (401 mg), catalyst (40 mg), and 1-methylnaphthalene (40 ml) were refluxed briskly for 2 h. The warm reaction mixture was filtered and washed with 90 ml of hot toluene. This solution was rotary evaporated and Kugelrohr distilled to remove toluene and 1-methylnaphthalene. The resulting tan solid was recrystallized from isohexane. The first crop yielded 345 mg, mp 177–179 °C (mixed with starting material, mp 176–179 °C); the second crop gave 28 mg, mp 175–177 °C, with a total return of 373 mg (93%) of recovered starting material. GLC studies of this sample showed results similar to those described above.

Acknowledgments. We thank the American Petroleum Institute for support during the early part of this work. We also thank the Continental Oil Co. for some current support, and the University of Oklahoma for providing computer time. We are grateful to Dr. P. W. Flanagan for his contribution in the early work.

Registry No.—**1**, 59434-72-9; **3**, 59434-73-0; **4**, 59434-74-1; naphthalene, 91-20-3; sodium, 7440-23-5; ethylenediamine, 107-15-3.

Supplementary Material Available. A listing of temperature factor parameters (Table II) and positional coordinates of hydrogen atoms (Table III) (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) L. E. Harris, D. V. Hertzler, O. C. Dermer, and E. J. Eisenbraun, *J. Org. Chem.*, **37**, 3039 (1972); (b) E. J. Eisenbraun, R. C. Bansal, D. V. Hertzler, W. P. Duncan, P. W. K. Flanagan, and M. C. Hamming, *ibid.*, **35**, 1265 (1970).
(2) (a) L. E. Harris, Ph.D. Thesis, Oklahoma State University, Stillwater, Okla., 1971; (b) L. G. Wideman, *J. Org. Chem.*, **35**, 1698 (1970).
(3) (a) I. W. Elliott and J. Bordner, *Tetrahedron Lett.*, **47**, 4481 (1971); (b) H. J. Teuber and G. Steinmetz, *Chem. Ber.*, **98**, 666 (1965).
(4) (a) To effectively utilize this stereoview, the reader should place the page on a table at normal reading distance, gaze past the structures, and rotate the page as needed until the figures merge. Alternatively, a stereoviewer can be used. (b) C. K. Johnson, ORTEP Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(5) We thank Drs. K. Loening and O. C. Dermer for advice on nomenclature.
(6) The centrosymmetry of **1** removes the need for labeling more than half the structures of Figures 2 and 3.
(7) J. B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 4537 (1961).
(8) (a) Unpublished data this laboratory; (b) D. V. Hertzler, Ph.D. Thesis, Oklahoma State University, Stillwater, Okla., 1969; (c) We thank Messrs. M. C. Hamming and G. W. Keen, Research and Development Department, Continental Oil Co., Ponca City, Okla., for this determination; (d) We thank Dr. J. P. Devlin of this Department for assistance and advice in obtaining and interpreting the Raman and infrared spectra.
(9) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(10) L. E. Harris, E. J. Eisenbraun, P. W. Flanagan, M. C. Hamming, and G. W. Keen, *J. Org. Chem.*, **37**, 336 (1972).
(11) A. J. C. Wilson, *Nature (London)*, **150**, 151 (1942).
(12) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(13) F. R. Ahmed, SFLS program, NCR-10 National Research Council, Ottawa, Canada, 1966.
(14) See paragraph at end of paper regarding supplementary material. The structure factor table may be obtained directly from Dr. Dick van der Helm, Department of Chemistry, University of Oklahoma, Norman, Okla. 73069.
(15) D. van der Helm, S. E. Ealick, and J. E. Burks, *Acta Crystallogr., Sect. B*, **31**, 1013 (1975).
(16) J. W. Burnham, W. P. Duncan, E. J. Eisenbraun, G. W. Keen, and M. C. Hamming, *J. Org. Chem.*, **39**, 1416 (1974).
(17) (a) The GLC studies were done on a Hewlett-Packard 5750 instrument with dual flame ionization detectors using a 8 ft × 0.25 in. copper column packed with 5% UC W-98 coated on 80–100 mesh AW DMCS-treated Chromosorb G operating at 270 °C. (b) Same conditions as ref 17a at 260 °C.

Approach to the Conformational Analysis of Mannich Bases

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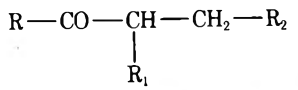
Conformational analysis of some Mannich bases and of the corresponding ammonium salts by NMR and CD indicates that in the solvents studied the hydrochlorides display a predominant conformation in which the two polar groups are gauche. In the case of the free bases, however, there is greater conformational freedom, the main factor in the equilibrium distribution of the conformers being the bulk of the substituents.

In a previous report on the stereochemistry of some α,β-disubstituted β-amino ketones[1] we observed that in solution the main factor in the distribution of the conformers at equilibrium is the bulk of the substituents, electrostatic interactions between the polar groups present in the molecule being of smaller importance. These last interactions are, on the other hand, very important in the case of the ammonium salts of the considered compounds, as other authors have demonstrated for analogous products of pharmacological and biological significance.[2]

Although there is abundant literature on the conformation of trisubstituted ethanes in solution (usually ethanes with halogens or alkyl groups),[3] no studies have been done on β-amino ketones with substituents in α or β position with respect to the carbonyl group. Continuing the studies on the reactivity and stereochemistry of Mannich bases, which are being carried out in our laboratories, in the present paper we report some aspects of NMR conformational analysis of 1-methyl- (Ia), 1-phenyl- (IIa), and 1-isopropyl-2-dimethylaminopropiophenone (IIIa) and their ammonium salts and of the NMR and CD studies of 3-methyl- (IVa) and 3-phenyl-4-dimethylaminobutan-2-one (Va), 3-phenyl- (VIa) and 3-methyl-4-piperidinobutan-2-one (VIIa), and of their hydrochlorides.

While derivatives I–III (R = C_6H_5) give easily analyzable NMR spectra, they do not allow a reliable CD conformational study owing to the presence of the conjugate aryl ketone chromophore, which makes problematic the use of the "octant rule".[4]



Ia, R = C_6H_5; R_1 = CH_3; R_2 = $N(CH_3)_2$

Ib, R = C_6H_5; R_1 = CH_3; R_2 = $\overset{+}{N}H(CH_3)_2$

IIa, R = C_6H_5; R_1 = C_6H_5; R_2 = $N(CH_3)_2$

IIb, R = C_6H_5; R_1 = C_6H_5; R_2 = $\overset{+}{N}H(CH_3)_2$

IIIa, R = C_6H_5; R_1 = $CH(CH_3)_2$; R_2 = $N(CH_3)_2$

IIIb, R = C_6H_5; R_1 = $CH(CH_3)_2$; R_2 = $\overset{+}{N}H(CH_3)_2$

IVa, R = CH_3; R_1 = CH_3; R_2 = $N(CH_3)_2$

IVb, R = CH_3; R_1 = CH_3; R_2 = $\overset{+}{N}H(CH_3)_2$

Va, R = CH_3; R_1 = C_6H_5; R_2 = $N(CH_3)_2$

Vb, R = CH_3; R_1 = C_6H_5; R_2 = $\overset{+}{N}H(CH_3)_2$

VIa, R = CH_3; R_1 = C_6H_5; R_2 = 

VIb, R = CH_3; R_1 = C_6H_5; R_2 = 

VIIa, R = CH_3; R_1 = CH_3; R_2 = 

VIIb, R = CH_3; R_1 = CH_3; R_2 = 

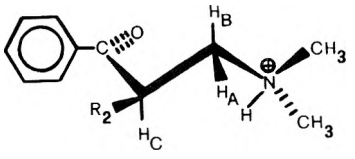
On the other hand, the NMR spectra of derivatives IV–VII are not all analyzable, while their CD spectra afford information on the conformational distribution.

Results and Discussion

NMR Studies. Examination of the NMR parameters of the ammonium salts Ib, IIb, and IIIb in a weakly polar solvent ($CDCl_3$) (see Table I) shows that the methylene protons are coupled both to the methine at C-1 and to the ammonium proton, and that this latter coupling has a different value for each of the two geminal nonequivalent protons. This shows that, at the temperature at which the spectra were recorded, the ammonium proton remains bound to the nitrogen long enough for the coupling to be observable.

A Karplus relationship between the coupling constants and the dihedral angle of CH–N^+H protons in several ammonium ions of cyclic compounds is implied in recent studies.[5,6]

On this basis, examination of the $J_{A,C}$, $J_{B,C}$, $J_{+NH,A}$, and $J_{+NH,B}$ for Ib, IIb, and IIIb leads us to assign to the system under examination, in the weakly polar solvent $CDCl_3$, a predominance of the arrangement with intramolecular interaction as shown below.



This scheme entails high values for $J_{B,C}$ and $J_{+NH,B}$ and low for $J_{A,C}$ and $J_{+NH,A}$ since the H_B, H_C, and $^+$NH protons will be approximately anti and H_A approximately gauche.

The suggested conformation also assumes an almost gauche disposition of the phenyl group and the substituent R_1, which will cause variations of J_{vic} when the bulk of R_1 changes, as found experimentally (see Table I).

Support for the idea of the suggested conformation in $CDCl_3$ is afforded by other experimental data, such as the analogous behavior of the α,β-disubstituted β-amino ketones described previously,[1] the results of the CD studies (vide infra), and the variations in the spectra of the quaternary ammonium salts in TFA (variations in all J values, marked shielding of the methine proton, and slight deshielding in the case of the two methylene protons).

In TFA, a highly polar solvent, intramolecular interactions[7] become less probable; it seems logical to assume that in this solvent the ammonium salts of I and II[8] adopt preferential conformations which are sterically favored, as is shown for example by the inversion of the relative values of $J_{+NH,A}$ and $J_{+NH,B}$ in TFA with respect to chloroform, and by the fact that in IIb the phenyl at C-1 gives a multiplet in $CDCl_3$ and approximately a singlet in TFA. Moreover, it is observed that the ammonium methyls of Ib, IIb, and IIIb and those of the isopropyl group in IIIb resonate as doublets at very different fields.

Although the nonequivalence is intrinsic for the presence of an asymmetric carbon, in the protonated compounds the relevant differences in the chemical shift of the methyls and the variations of this parameter with the solvent ($CDCl_3$ or TFA) may be interpreted on the basis of preferential steric dispositions involving different anisotropic contribution of the C_6H_5CO group.[7,9] Moreover, while the J of the H_C proton with the isopropyl methine has, in the free base IIIa, an averaged value (about 6.4 Hz), in the case of the hydrochloride IIIb in $CDCl_3$, its value is 3.45 Hz, thus confirming a different preferred conformation of the isopropyl group.

Chart I

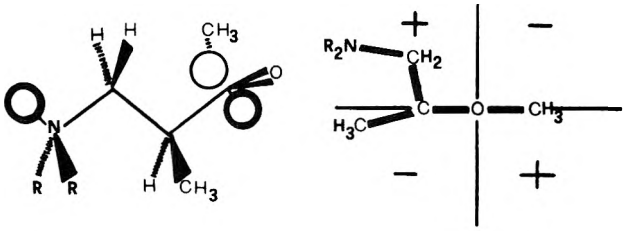
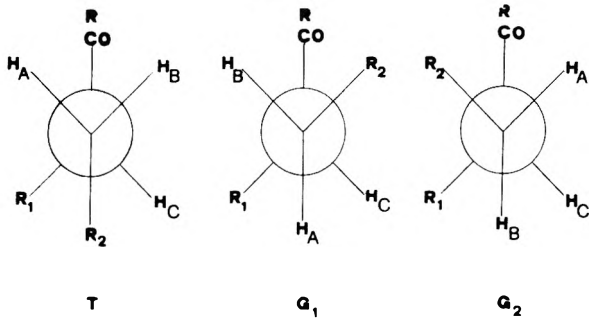


Chart II

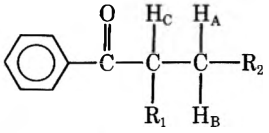


T G_1 G_2

Examination of the Newman projections along the C_1–C_2 bond of the proposed model indicates that the gauche G_1 form is predominant in $CDCl_3$, since the trans conformer T does not allow any interaction between the two polar groups, and the contribution of the gauche G_2 conformer at the equilibrium must be considered low for the steric hindrance arising from the presence of two gauche interactions.

The high experimental values of $J_{B,C}$ (which increase with the increasing bulk of R_1) and the low values of $J_{A,C}$ are in agreement with the foregoing hypothesis, and show that H_A must be gauche and H_B trans with respect to H_C in the preferred conformer G_1. The high value of $J_{B,C}$ further confirms the small weight of G_2 at the equilibrium. In the spectra of the Mannich bases I and II in TFA, the high polarity of the solvent tends to diminish the magnitude of intramolecular interactions and facilitates rotations around the bonds, as reported before; on the other hand, the G_1 rotamer remains preferred since a gauche relationship between the protons H_A and H_C (low values of $J_{A,C}$) and trans between H_B and H_C (high $J_{B,C}$) is again observed.

Table I.[a] NMR Parameters (δ) of Compounds Ia,b,c, IIa,b,c, and IIIa,b



Compd	R_1	R_2	Solvent	ν_A	ν_B	ν_C	ν_{R_1}	ν_{R_2}	$J_{A,B}$	$J_{A,C}$	$J_{B,C}$	$J^+_{NH,A}$	$J^+_{NH,B}$	J_{+NH,CH_3}	J_{R_1C}
			CS_2	2.23	2.61	3.54	1.11	2.15	−12.29	6.66	7.06				6.80
Ia	CH_3	$N(CH_3)_2$	Ac	2.29	2.69	3.81	1.14	2.17	−12.28	6.70	6.98				6.80
			Me_2SO	2.25	2.63	3.82	1.16	2.14	−12.08	6.73	7.27				6.90
			$CDCl_3$[b]	3.26	3.86	4.44	1.33	2.74; 2.95	−13.00	3.90	7.90	3.48	7.55	4.95	7.20
Ib	CH_3	$\overset{+}{N}H(CH_3)_2$	TFA	3.41	3.88	4.25	1.48	3.08; 3.21	−13.44	4.02	10.61	8.55	3.69	5.25	7.00
			CS_2	2.22	2.69	*c*	1.09	2.14	−12.20						
Ic	CH_3	$N(CH_3)_2$	Ac	2.27	2.61	*c*	1.09	2.17	−12.40						
			Me_2SO	2.24	2.67	*c*	1.09	2.14	−11.90						
			CS_2	2.44	3.22	4.64	*d*	2.16	−12.41	4.91	8.99				
IIa	C_6H_5	$N(CH_3)_2$	Ac	2.52	3.31	5.07	*d*	2.21	−12.42	5.11	9.01				
			Me_2SO	2.50	3.23	5.12	*d*	2.19	−12.05	5.41	9.12				
			$CDCl_3$[e]	3.36	4.13	5.91	*d*	2.73; 2.74	−12.91	3.81	7.87	3.87	6.44	5.10	
IIb	C_6H_5	$\overset{+}{N}H(CH_3)_2$	TFA	3.66	4.05	5.32	*f*	3.15; 3.18	−13.36	5.44	9.42	6.91	4.40	5.25	
			CS_2	2.45	3.23	*c*	*d*	2.17	−12.50						
IIc	C_6H_5	$N(CH_3)_2$	Ac	2.51	3.31	*c*	*d*	2.21	−12.30						
			Me_2SO	2.48	3.20	*c*	*d*	2.18	−12.00						
			CS_2	2.31	2.78	3.36	1.81 (CH); 0.90, 0.89 (2 CH_3)	2.09	−11.98	3.94	9.76				6.46
IIIa[g]	$CH(CH_3)_2$	$N(CH_3)_2$	Ac	2.38	2.86	3.64	1.86 (CH); 0.94, 0.92 (2 CH_3)	2.12	−12.01	3.84	10.10				6.40
			Me_2SO	2.31	2.81	3.65	1.89 (CH); 0.90, 0.87 (2 CH_3)	2.08	−11.92	3.72	10.25				6.45
			$CDCl_3$[h]	3.29	3.87	4.39	2.17 (CH); 0.80, 1.16 (2 CH_3)	2.58; 2.94	−12.78	0.86	9.31	2.10	7.50	5.10	3.45
IIIb[g]	$CH(CH_3)_2$	$\overset{+}{N}H(CH_3)_2$	TFA	*i*	*i*	*i*	*i* ; 0.91, 1.20 (2 CH_3)	3.04; 3.19	*i*	*i*	*i*	*i*	*i*	5.20	*i*

[a] The chemical shifts are in parts per million (δ) from Me_4Si as internal standard; the J are in hertz. The C_6H_5CO protons resonate as multiplets in the range δ 7.0–7.7 (3 H) and 7.7–8.4 (2 H). [b] ν_{N^+H} = 12.10. [c] H_C = D. [d] The aromatic protons of R_1 are multiplets superimposed on those of the C_6H_5CO fragment. [e] ν_{N^+H} = 12.85. [f] C_6H_5 resonates as singlet (δ 7.84). [g] J_{H,CH_3} of isopropyl fragment = 6.6/6.9 Hz. [h] ν_{N^+H} = 12.35. [i] The calculation of III in CF_3COOH at 60 MHz is not possible owing to the overlap of signals.

Table II.[a] NMR Parameters of Compounds IVa, Va,b, and VIa CH_3—CO—C(H_C)—C(H_A)—R_2 (R_1, H_B)

Compd	R_1	R_2	Solvent	ν_A	ν_B	ν_C	ν_{CH_3}	ν_{R_1}	ν_{R_2}	J_{AB}	J_{AC}	J_{BC}
			CS_2	2.07	2.44	2.65	2.01	0.96[b]	2.13	−12.00	6.13	8.89
IVa	CH_3	$N(CH_3)_2$	Ac	2.11	2.51	2.71	2.06	0.99[b]	2.14	−12.21	6.21	8.92
			Me_2SO	2.08	2.47	2.59	2.08	0.95[b]	2.11	−12.07	6.28	8.82
			CS_2	2.34	3.16	3.91	1.97	7.25[c]	2.16	−12.34	5.53	9.42
Va	C_6H_5	$N(CH_3)_2$	Ac	2.43	3.11	4.06	2.07	7.31[c]	2.19	−12.41	5.78	9.38
			Me_2SO	2.43	3.04	4.06	2.07	7.33[c]	2.16	−12.26	6.18	8.88
Vb	C_6H_5	$\overset{+}{N}H(CH_3)_2$	$CDCl_3$	3.22	4.03	4.79	2.18	7.41[c]	2.76; 2.88[d]	−13.24	4.64	7.54
VIa	C_6H_5		CS_2	2.35	3.05	3.80	1.98	7.38[c]	1.3–1.7; 2.2–2.6[e]	−12.74	5.04	9.50

[a] The chemical shifts are in parts per million (δ) from Me_4Si as internal standard; the J are in hertz. [b] $J_{H_CR_1}$ = 6.70/6.76 Hz. [c] C_6H_5 resonates as singlet. [d] ν_{+NH} = 12.15; $J_{+NH,A}$ = 4.99; $J_{+NH,B}$ = 4.05; J_{+NH,CH_3} = 5.00. [e] Intervals of multiplets of piperidine methylenes.

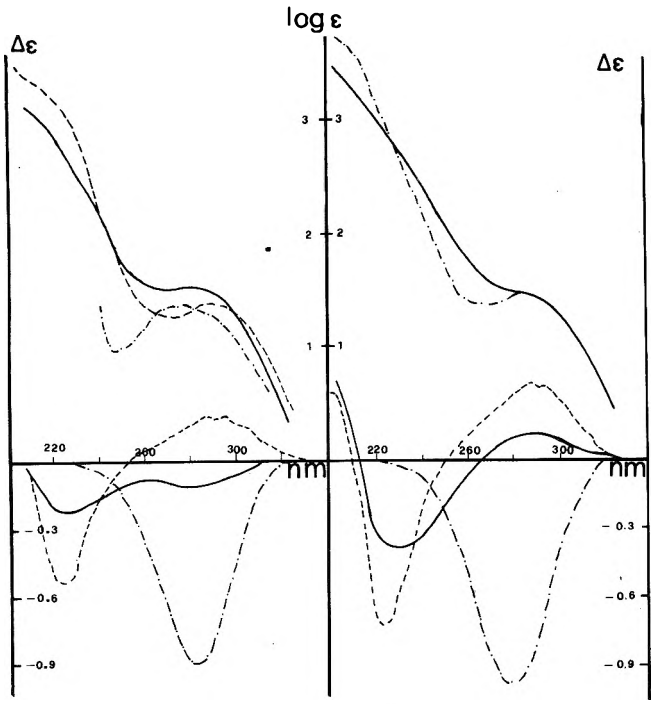


Figure 1. The absorption and circular dichroism of (−)-(*S*)-VIIa (right) and of (−)-(*S*)-IVa (left). Solvents: EtOH (—), EtOH–HCl (- - - -), cyclohexane (- - -).

Therefore, in the case of the ammonium salts of the Mannich bases I, II, and III, attraction between the two polar groups present in the molecule is very important in the distribution of the conformers at equilibrium. Examination of the NMR parameters of the free bases Ia, IIa, and IIIa (see Table I) shows a high field shift of the order of 1 ppm for protons H_A, H_B, and H_C with respect to the corresponding protons of the ammonium salts in $CDCl_3$.[10] This effect is attributable to the absence of the positive charge on the nitrogen, and to probable variations in magnetic anisotropy resulting from different orientations of the C_6H_5CO fragment. In addition, in the three compounds, the methyls of the dimethylamino group resonate as singlets and the diastereotopic methyls of the isopropyl group in IIIa show a very slight differences (<2 Hz) of chemical shift, also in different solvents; this indicates a greater conformational freedom of the free bases as compared with the corresponding ammonium salts.

Assignment of the protons H_A and H_B in the spectra of free bases may reasonably be effected by comparison with the parameters observed in the ammonium salts. The values of the chemical shifts and coupling constants obtained from the iterative analysis of the ABC pattern of the ethane residue emphasize the importance of the steric bulk of R_1 in the conformational equilibrium of these compounds. Thus, in Ia (R_1 = CH_3) the averaged $J_{A,C}$ and $J_{B,C}$ indicate almost equal participation of the trans and gauche conformers at the equilibrium, while for IIa and IIIa [R_1 = C_6H_5 and R_1 = $CH(CH_3)_2$, respectively] the order of magnitude of the two J_{vic} is in accordance with the presence of a preferential rotamer in which one coupling constant is trans and the other gauche.

On this basis, the preferential conformer (see Chart II) will be G_1. This agrees with the experimental finding that, when the order of substituents of the ethane residue remains unchanged, an increase in the bulk of R_1 [R_1 = CH_3 → C_6H_5 → $CH(CH_3)_2$] is accompanied by an increase in $J_{B,C}$, while $J_{A,C}$ decreases, and the conformer with smaller steric hindrance becomes preferential, i.e., that in which R_1 is gauche with respect to the two methylene protons (G_1). An approximate calculation of the relative weight of the conformers at the equilibrium can be derived from the J_{vic} values ($J_{A,C}$ and $J_{B,C}$).[11] If the values used by Bailey[11] for the amphetamines (J_{trans} = 12; J_{gauche} = 2 Hz) are taken as standard values, it is found that in the three solvents used the relative weights of the conformers at equilibrium are T:G_1:G_2 = 45:50:5 for Ia, 30:70:0 for IIa, and 20:80:0 for IIIa. The fact that in these three solvents having different dielectric constants there is no appreciable variation in the conformer distribution indicates that in these compounds, contrary to the findings of other authors for different series of compounds,[12] the influence of intramolecular interaction (for example N → CO) is small compared with the influence of steric factors. The percentage of conformer G_1 increases with the steric bulk of R_1, while the weight of conformer T is reduced, the presence of conformer G_2 being negligible in all cases.

In the case of Mannich bases having R = CH_3 and of their ammonium salts (see Table II, compounds IVa, Va and Vb, VIa), the 60-MHz NMR spectra are difficult to analyze on account of the strong overlap of the signals. This makes it difficult to extend the NMR conformational analysis to these derivatives.

Only for derivative V it was possible to obtain the spectral parameters of both the free base and its hydrochloride. The data obtained show that the situation is not very different from that of derivatives having R = C_6H_5. In this case, however, the coupling constants of H_A and H_B with the ammonium proton are nearly the same. For the free bases IVa and Va, the value of J_{vic} of the ethane residue indicates that also in this case, when the steric hindrance of R_1 increases, there is a smaller conformational freedom and an increase of the G_1 conformer's population.

The spectral parameters of the free base VIa are analogous to those of Va and show that here the variation of the alkylamino group has a small effect.

CD Studies. The CD and UV spectra of the bases IVa and VIIa having *S* absolute configuration[13] are shown in Figure 1. In cyclohexane the CD of both IVa and VIIa show two bands of opposite sign at ca. 290 and 225 nm. While the first band corresponds to an isotropic absorption maximum and is assignable to the carbonyl n → π* transition, the second band does not have a corresponding absorption maximum. The CD spectrum of IVa in methanol undergoes a drastic modification with sign inversion of the low-energy band and intensity decrease of the high-energy one. The CD spectrum of VIIa, in passing from cyclohexane to methanol, shows only an intensity decrease of both bands.

Protonation of the nitrogen causes in the CD spectra of both IV and VII a sign inversion with respect to cyclohexane, an intensity increase, and disappearing of the 225-nm band. Hudec[14] has carried out detailed research on amino ketones having a fixed stereochemistry. In particular he found that, when the nitrogen lone pair is trans periplanar to the Cα–Cβ bond, when N is on the β carbon, a new band is observed at ca. 220–240 nm, having opposite CD sign to that of the n → π* transition. There is in this case a "planar zig-zag" of bonds, connecting the oxo group and the heteroatom.[15] The nitrogen atom exerts in this case an "octantlike" effect. By adding acids the high-energy band disappears. The CD spectra of derivatives IVa and VIIa (with the exception of that of IVa in methanol, for the moment) show that a situation of the type described above is present in our case.

Of the possible conformations depicted only the trans one (T) allows a connection between the nitrogen lone pair and the p orbital (depicted as circles in Chart I) of the oxo group, through a planar "zig-zag" pattern of bonds. This stereochemically restricted condition implies also a well-defined rotation around the C–C=O bond as schematized in Chart

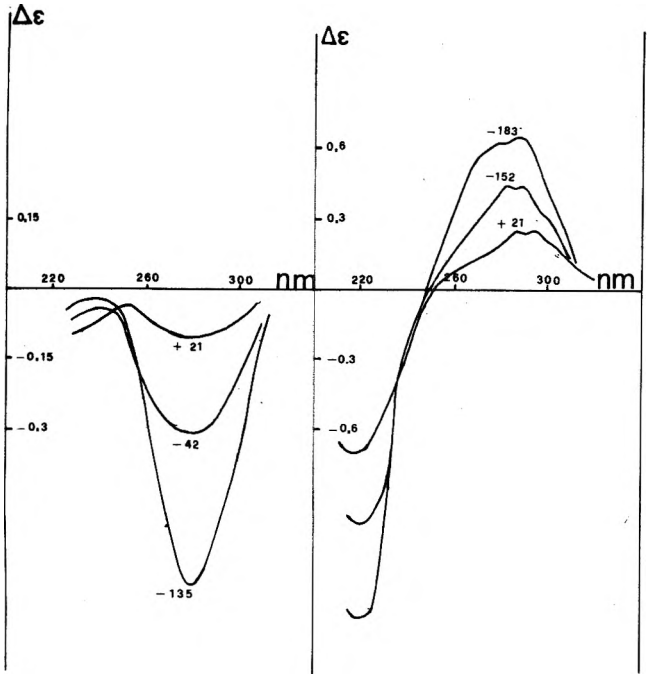


Figure 2. Low-temperature circular dichroism of (−)-(*S*)-IVa, solvent methanol–glycerol, 9:1 (v:v) (left), and methylcyclohexane–isopentane, 1:3 (v:v) (right).

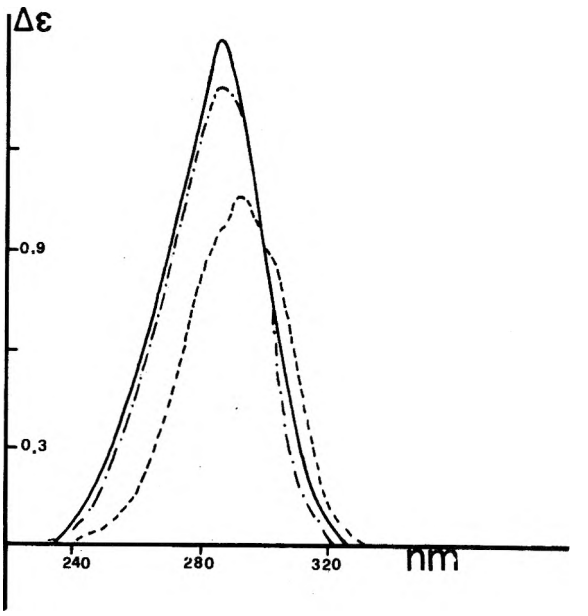


Figure 3. Circular dichroism of (+)-Va in cyclohexane (- - -) and methanol–HCl (—); circular dichroism of (+)-Vb in chloroform.

I (there are two possible rotamers having the desired "zig-zag" relation; however, the one having the methyl group pointing upwards is sterically hindered).

On the other hand, following the "octant rule"[4] this conformation should give (Chart I) for the isomer *S* a positive Cotton effect for the n → π* carbonyl transition in agreement with what is experimentally found.

The CD spectrum of derivative IVa in methanol causes some doubts, as one observes a sign inversion for the n → π* transition while the 225-nm band is still present and has the same sign of the n → π*. Low-temperature CD spectra of IVa in methylcyclohexane–isopentane and methanol–glycerol mixtures (Figure 2) contribute to clarify the case. In the hydrocarbon solvent the intensity of both bands increases with the decreasing of the temperature, showing that the most populated conformation (trans) is responsible for the observed spectrum; this is not the case for methanol–glycerol (Figure 2) where the intensity of the 280-nm n → π* transition increases, and that of the 225 nm, typical of the "zig-zag" trans conformation, decreases and practically disappears at −140 °C. This band is therefore caused by a conformer which is different from that responsible for the 280-nm band. This conformer (trans), although it gives rise to strong signals in the 220-nm region, must have higher energy, and its population is strongly reduced at low temperature. The solvent effect on derivative IVa can be understood as a passage from a predominant trans conformation in cyclohexane to a predominant "gauche" in methanol, the latter being probably stabilized by specific interactions with the solvent.

In derivative VII the presence of the bulky piperidine group destabilizes the gauche conformation and a change in CD is not observed (although the rotamers' ratio must be varied). The spectra of the base hydrochlorides have signs opposite to those of the free bases in cyclohexane, and a higher intensity. In agreement with what was previously found for aryl keto bases this seems to indicate gauche conformation, stabilized through polar interactions. Unfortunately, the use of the octant rule in this case is uncertain as "front octants" are involved. The CD spectra of derivatives V are shown in Figure 3. The CD spectrum of Va in cyclohexane has the same sign of that of Vb in methanol and chloroform. This fact indicates that in this case the gauche G_1 conformation is the most populated in all the conditions studied, in good agreement with what was found by the NMR analysis.

In conclusion, from the data reported above, one can say that in the free bases (R = alkyl or aryl) there is a great conformational freedom, and, depending on the substituents present, one passes from a dominant trans to a dominant gauche conformation. The base hydrochlorides, on the contrary, seem to exist predominantly in gauche conformations, the amount of this conformation being influenced by the polarity of the solvent.

Experimental Section

NMR spectra were run in the internal lock mode on a JEOL C 60-HL spectrometer (probe temperature 32 °C). The solutions were about 10–15% w/v. The chemical shift are in parts per million (δ) from Me_4Si as internal standard (±0.01) and the coupling constants in hertz (±0.05). The calculation of the ABC, $ABCX_3$, or ABCD patterns was carried out with iterative program LAOCN3°;[16] the root mean square error was in all cases less than 0.045. CD spectra were recorded using a Jouan II dichrograph; uv spectra, using an Unicam SP 700 spectrophotometer.

1-R_1-2-Dimethylaminopropiophenones and Hydrochlorides (Ia–IIIa, Ib–IIIb), 4-R_2-3-R_1-Butan-2-ones and Hydrochlorides (IVa–VIIa, IVb–VIIb). Ia,[17] IIa,[18] IIIa,[19] IVa,[20] Va and VIa,[21] VIIa,[22] and their hydrochlorides were prepared and purified as described in the literature.

1-R_1-1-Deuterio-2-dimethylaminopropiophenones (Ic and IIc). A complete H/D exchange in the α position to the carbonyl group occurs when a 0.5 M solution of Ia or IIa in D_2O/dioxane (1/1 v/v) was left to stand at room temperature for 48 h; after evaporation under vacuum of dioxane the deuterated compounds Ic and IIc were extracted with $(C_2H_5)_2O$ and purified by crystallization of their hydrochlorides. No H/D exchange was detected in the case of IIIa, even in more drastic conditions.

Resolution of (±)-3-Phenyl-4-dimethylaminobutan-2-one (Va). A solution of 15 g of (±)-Va in 20 ml of dry Me_2CO was added to a solution of 29.5 g of (−)-dibenzoyltartaric acid in 30 ml of dry Me_2CO. The precipitated salt was crystallized from absolute EtOH, mp 150–151 °C. The free base had $[\alpha]^{20}D$ +155° (c 1.1, MeOH).

Resolution of (±)-3-Methyl-4-dimethylaminobutan-2-one (IVa).[11] Working as described above a diastereoisomeric salt was obtained, which was crystallized from absolute EtOH and showed mp 135–136 °C. The free base had $[\alpha]^{20}D$ −26° (c 4, MeOH/HCl 10:1).

Resolution of (±)-3-Methyl-4-piperidinobutan-2-one (VIIa). Working as described above a diastereoisomeric salt was obtained;

after crystallization from dry Me_2CO it showed mp 138–139 °C. The free base had $[\alpha]^{20}D$ −28° (c 3, MeOH/HCl 10:1).

Acknowledgments. We thank C. N. R. (Rome) for financial support.

Registry No.—Ia, 91-03-2; Ib, 5400-92-0; Ic, 59434-10-5; IIa, 22563-99-1; IIb, 25287-79-0; IIc, 59434-11-6; IIIa, 2891-50-1; IIIb, 59434-12-7; (±)-IVa, 59461-64-2; (−)-IVa, 24190-15-6; (−)-IVa (−)-dibenzoyl tartrate, 24190-14-5; (±)-Va, 59434-13-8; (+)-Va, 59434-14-9; (+)-Va (−)-dibenzoyl tartrate, 59434-15-0; (+)-Vb, 59434-16-1; VIa, 27702-56-3; (−)-VIIa, 59434-17-2; (±)-VIIa, 59461-65-3; (−)-VIIa (−)-dibenzoyl tartrate, 59434-18-3; (−)-dibenzoyltartaric acid, 2743-38-6.

References and Notes

(1) R. Andrisano, A. S. Angeloni, and G. Scapini, *Gazz. Chim. Ital.*, **105**, 737 (1975).
(2) Y. Terui, M. Ueyama, S. Satoh, and K. Tori, *Tetrahedron*, **30**, 1465 (1974); A. F. Casy, M. M. A. Hassan, and E. C. Wu, *J. Pharm. Sci.*, **60**, 67 (1971); J. G. Henkel, K. H. Bell, and P. S. Portoghese, *J. Med. Chem.*, **17**, 124 (1974), and references cited therein.
(3) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2d ed, Pergamon Press, Oxford, 1969, p 280.
(4) W. Moffit, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4031 (1961).
(5) H. Booth and J. H. Little, *J. Chem. Soc., Perkin Trans. 2*, 1846 (1972).
(6) B. Bianchin and J. J. Delpuech, *Tetrahedron*, **30**, 2859 (1974).
(7) J. C. N. Ma and E. W. Warnhoff, *Can. J. Chem.*, **43**, 1849 (1965).
(8) The ABCD pattern of the spectrum of III in TFA at 60 MHz cannot be calculated, owing to superimposition of the signals, which are also partly obscured by ammonium methyls.
(9) G. M. Whitesides, D. Holtz, and J. D. Roberts, *J. Am. Chem. Soc.*, **86**, 2628 (1964).
(10) In order to facilitate the assignment of signals, the deuterated derivatives of Ia and IIa (i.e., Ic, IIc) were also examined; H_C/D exchange was not possible for IIIa. The spectral parameters for Ic and IIc are given in Table I.
(11) K. Bailey, A. W. By, K. C. Graham, and D. Verner, *Can. J. Chem.*, **49**, 3143 (1971).
(12) K. Bailey, *J. Pharm. Sci.*, **60**, 1232 (1971).
(13) L. Angiolini, P. Costa Bizzarri, and M. Tramontini, *Tetrahedron*, **25**, 4211 (1969).
(14) J. Hudec, *Chem. Commun.*, 829 (1970).
(15) D. N. Kirk and W. Klyne, *J. Chem. Soc., Perkin Trans. 1*, 1076 (1974).
(16) S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3863 (1964).
(17) A. W. Ruddy and J. S. Buckley, *J. Am. Chem. Soc.*, **72**, 718 (1950).
(18) H. O. House, D. J. Reif, and R. L. Wasson, *J. Am. Chem. Soc.*, **79**, 2490 (1957).
(19) J. Rouzand, G. Canqual, and L. Giarl, *Bull. Soc. Chim. Fr.*, 2030 (1965).
(20) H. J. Hegemeyer, *J. Am. Chem. Soc.*, **71**, 1119 (1949).
(21) W. Wilson and Z. Y. Kyi, *J. Chem. Soc.*, 1321 (1952).
(22) C. Mannich and W. Hof, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, 265, 589 (1927).

Carbonyl–Alkyne Exchange of 2*H*-Pyrans. A New Aryl Annelation Method

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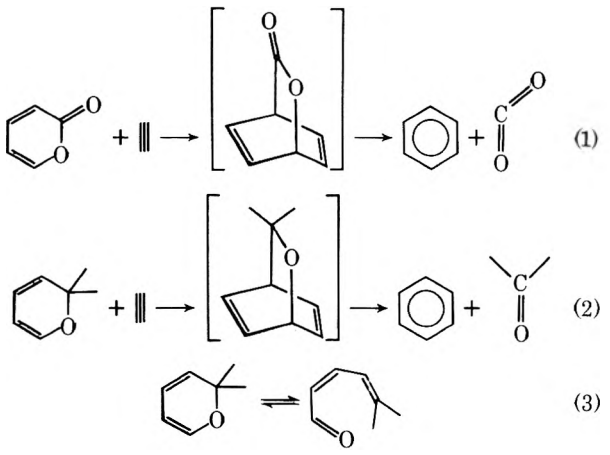
A synthesis of aryl derivatives is described which involves cycloelimination of ketones or aldehydes from the adducts obtained by cycloaddition of 2*H*-pyrans with acetylenic dienophiles. This carbonyl–alkyne exchange process is highly regiospecific. Even a 2*H*-pyran which constitutes only 20% of an equilibrium mixture with the corresponding dienone valence tautomer is shown to give good yields of the corresponding aryl derivatives upon reaction with methyl propiolate or dimethyl acetylenedicarboxylate.

Derivatives of α-pyrone react with alkynes to yield aryl derivatives and carbon dioxide (eq 1).[1] The intermediate Diels–Alder cycloadducts are generally unstable under the conditions of their formation. The analogous reaction of 2*H*-pyrans with alkynes to yield aryl derivatives and aldehydes or ketones (eq 2) has not been reported. One potential



(1)

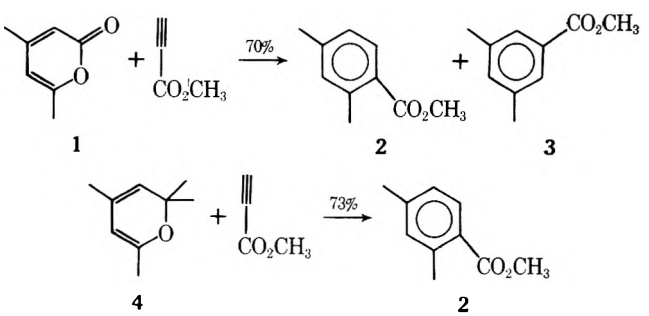
(2)

(3)

complication for such a carbonyl–alkyne exchange reaction is the fact that 2*H*-pyrans are in dynamic equilibrium with acyclic dienones (eq 3)[2] which might yield alternative products by Diels–Alder reactions. However, since 2*H*-pyrans are readily available by a variety of different synthetic routes,[3–16] it seemed worthwhile to examine the feasibility of carbonyl–alkyne exchange reactions with 2*H*-pyrans. We now report the first examples of the synthesis of aryl derivatives by the reaction of 2*H*-pyrans with acetylenic dienophiles.

Results and Discussion

In order to compare the carbonyl–alkyne exchange of α-pyrones and 2*H*-pyrans we examined the reactions of methyl propiolate with 4,6-dimethyl-α-pyrone (1) and with 2,2,4,6-tetramethyl-2*H*-pyran (4). Both reactions give good yields of



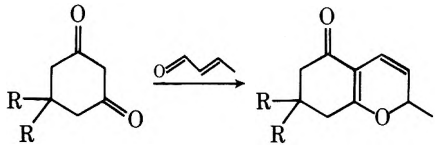
1 2 3

4 2

aryl derivatives. The α-pyrone (1) gives both methyl 2,4-dimethylbenzoate (2) and methyl 3,5-dimethyl benzoate (3) in a 4:1 ratio, respectively. The 2*H*-pyran (4) gives only 2. The carbonyl group in 1 is expected to direct[17] the initial Diels–Alder addition to favor product 3, while the ring oxygen and methyl groups in 1 direct the addition to favor product 2. For 4 the exclusive formation of 2, therefore, might be ascribed to the absence of the carbonyl group in the 2 position. However,

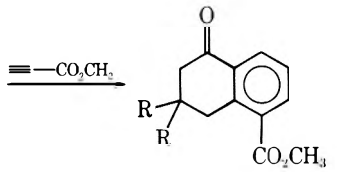
the regioselective reaction of **4** may also be due, at least in part, to steric hindrance by the substituents in the 2 position. Whatever the reason, all carbonyl–alkyne exchange reactions of 2*H*-pyrans examined are highly regiospecific.

β-Dicarbonyl compounds react with α,β-unsaturated aldehydes giving good to excellent yields of 2*H*-pyrans in a single step.[15,16] This synthesis in conjunction with the carbonyl–alkyne exchange reaction constitutes an effective new aryl annelation method. For example, 1,3-cyclohexanedione (**5a**) and its 5,5-dimethyl derivative (**5b**) give **6a** and **6b**, respectively, by reaction with crotonaldehyde.[16] These pyrans react regiospecifically with methyl propiolate to give methyl 5-oxo-5,6,7,8-tetrahydro-1-naphthoate (**7a**) and the 7,7-



5a, R = H
b, R = CH_3

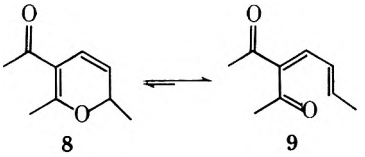
6a, R = H
b, R = CH_3



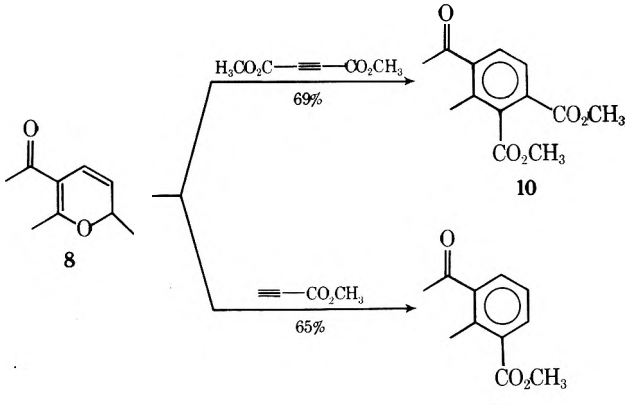
7a, R = H
b, R = CH_3

dimethyl derivative (**7b**), respectively. The assignment of the 1 position instead of the 2 position for the carbomethoxy substituent rests on an analysis of the ^1H NMR spectra of **7a** and **7b**. All of the aryl proton resonances in the NMR spectra of these compounds exhibit large (8 Hz) vicinal coupling. The ^1H NMR absorption due to the proton in the 1 position of the alternative 2-naphthoates would be a singlet or would exhibit only small long-range coupling.

Though the 2*H*-pyran **8** constitutes only 20% of an equilibrium mixture[16] with the dienone **9**, carbonyl–alkyne exchange reactions proceed normally to give good yields of aryl derivatives. Thus, the equilibrium mixture of **8** and **9** gives **10** by reaction with dimethyl acetylenedicarboxylate and gives **11** by regiospecific reaction with methyl propiolate. Whether the regiospecificity of the reactions of **4**, **5a**, **5b**, and **8** with



8 **9**

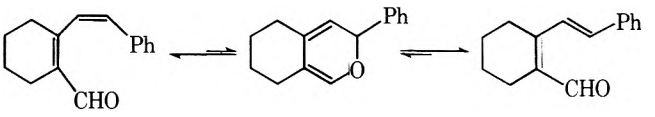


10

11

methyl propiolate is due to the electronic effect of the pyran oxygen or the steric effect of the substituents in the 2 position, it is noteworthy that both of these groups are not retained in the aryl products of these reactions. That is, the functionality which directs the initial alkyne cycloaddition is lost in the subsequent carbonyl cycloelimination.

Not all 2*H*-pyrans are present in the equilibrium mixture with dienones in sufficient concentrations to undergo carbonyl–alkyne exchange. Thus, the 2*H*-pyran **12** is not detectable in the ^1H NMR spectrum of the dienal **13c**.[18] When **13c** was heated with methyl propiolate under the usual conditions, no trace of carbonyl–alkyne exchange was detected. However, **13c** isomerized to **13t** presumably via the 2*H*-pyran **12**.[18]



13c **12** **13t**

Conclusions

The reaction of alkynes with 2*H*-pyrans is useful for the synthesis of certain aryl derivatives. The reaction is regiospecific with methyl propiolate. The ester group in the aryl product is exclusively ortho to the carbon derived from the 6 position of the pyran precursor. The functionality which directs the initial cycloaddition, the pyran oxygen or the substituents in the 2 position, is lost in the subsequent cycloelimination. In conjunction with a one-step conversion of 1,3-dicarbonyl compounds into 2*H*-pyrans, the carbonyl–alkyne exchange reaction constitutes an effective new aryl annelation method.

Experimental Section

General. Reported procedures were utilized for the preparation of 4,6-dimethyl-α-pyrone (**1**),[19] 2,2,4,6-tetramethyl-2*H*-pyran (**4**),[7] 2-methyl-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran (**6a**),[16] 5-oxo-5,6,7,8-tetrahydro-2,7,7-trimethyl-2*H*-1-benzopyran (**6b**),[16] 5-acetyl-2,6-dimethyl-2*H*-pyran (**8**),[16] and *cis*-2-(2-phenylvinyl)cyclohex-1-enecarboxaldehyde (**13c**).[18] NMR spectra were obtained on a Varian A-60A instrument. Preparative and analytical gas–liquid phase chromatography was performed with a Varian Aerograph 202B instrument. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz.

Carbonyl–Alkyne Exchange of 4,6-Dimethyl-α-pyrone (1) with Methyl Propiolate. A mixture of pyrone **1** (2.5 g, 20 mmol) and methyl propiolate (10 g, 0.12 mol) was boiled under reflux under nitrogen for 160 h. Fractional distillation with a short-path distilling head (Kontes) gave an isomeric mixture of methyl dimethylbenzoates, bp 100–112 °C (8 mm) (70%). The mixture was shown to consist of methyl 2,4-dimethylbenzoate (**2**, 78%) and methyl 3,5-dimethylbenzoate (**3**, 22%) by gas–liquid phase chromatography (GLC) on a 10 ft × 0.25 in. column packed with 5% Bentone 34 and 5% diisodecyl phthalate on 60/80 Chromosorb W at 120 °C. Relative retention times were **2**, 1.0; **3**, 1.2. Pure samples of the isomeric products were obtained by preparative GLC and identified by NMR spectral comparison with authentic samples.

Carbonyl–Alkyne Exchange of 2,2,4,6-Tetramethyl-2*H*-pyran (4) with Methyl Propiolate. A mixture of pyran **4** (2.5 g, 18 mmol) and methyl propiolate (2.1 g, 25 mmol) was boiled under reflux under nitrogen for 100 h. Fractional distillation with a short-path distilling head gave methyl 2,4-dimethylbenzoate, bp 106–109 °C (10 mm) (73%).

Methyl 5-Oxo-5,6,7,8-tetrahydro-1-naphthoate (7a). A mixture of the pyran **6a**[16] (3.2 g, 19 mmol) and methyl propiolate (10 g, 0.12 mol) was boiled under reflux under nitrogen for 60 h. Excess methyl propiolate was recovered by distillation and the residual oil was distilled under reduced pressure through a short-path distillation head to give **7a** which crystallized in the receiver, bp 125–128 °C (0.1 mm) (70%). Recrystallization from cold methanol gave white crystals: mp 53–55 °C; NMR (CCl_4) δ 2.15 (2 H, m, J = 6 Hz, C7), 2.60 (2 H, t, $J_{7,8}$ = 6 Hz, C8), 3.28 (2 H, t, $J_{5,6}$ = 6 Hz, C6), 3.87 (3 H, s, CO_2CH_3), 7.28 (1 H, apparent t, $J_{2,3} = J_{3,4}$ = 8 Hz, C3), 7.95 (1 H, dd, J = 8, $J_{2,4}$ = 1.5 Hz), 8.15 (1 H, dd, J = 8, $J_{2,4}$ = 1.5 Hz).

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.40; H, 5.45.

Methyl 7,7-Dimethyl-5-oxo-5,6,7,8-tetrahydro-1-naphthoate (7b). A mixture of the pyran **6b**[16] (4.3 g) and methyl propiolate (10 g) was treated as above for **7a**. The ester **7b** was obtained: bp 118–121 °C (0.05 mm) (60%); NMR ($CDCl_3$) δ 1.08 (6 H, s, C7 methyls), 2.53 (2 H, s, C8), 3.22 (2 H, s, C6), 3.92 (3 H, s, CO_2CH_3), 7.36 (1 H, apparent t, $J_{2,3} = J_{3,4} = 8$ Hz, C3), 8.09 (1 H, dd, $J = 8$, $J_{2,4} = 1.5$ Hz), 8.16 (1 H, dd, $J = 8$, $J_{2,4} = 1.5$ Hz).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.23; H, 7.05.

Dimethyl 4-Acetyl-3-methylphthalate (10). An equilibrium mixture of the pyran 8 and the dienedione **9**[16] (0.91 g, 6 mmol) and dimethyl acetylenedicarboxylate (0.84 g, 6 mmol) was combined and heated under a reflux condenser under nitrogen at 110 °C for 10 h. The crude product was dissolved in CCl_4 (3 ml). The solution deposited white crystals at 0 °C which were collected by filtration at 0 °C with pressure: mp 75–76 °C (69%); NMR ($CDCl_3$) δ 2.39 (3 H, s), 2.56 (3 H, s), 3.90 (3 H, s, CO_2CH_3), 3.95 (3 H, s, CO_2CH_3), 7.57 (1 H, d, $J_{5,6}$ = 8.5 Hz), 7.91 (1 H, d, $J_{5,6}$ = 8.5 Hz); (CCl_4) δ 2.30 (3 H, s,), 2.50 (3 H, s), 3.86 (6 H, s, CO_2CH_3), 7.55 (1 H, d, $J_{5,6}$ = 8 Hz), 7.77 (1 H, d, $J_{5,6}$ = 8 Hz).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.20; H, 5.63.

Methyl 3-Acetyl-2-methylbenzoate (11). An equilibrium mixture of the pyran 8 and the dienedione **9**[16] (2.7 g, 18 mmol) and methyl propiolate (10 g) were treated as above for **7a**. The ester **11** was obtained: bp 117–119 °C (0.1 mm) (65%); NMR ($CDCl_3$) δ 2.54 (3 H, s, CH_3), 2.58 (3 H, s, CH_3), 3.90 (3 H, s, CO_2CH_3), 7.0–8.0 (3 H, multiplets, C4,5,6).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.31; H, 6.27.

Isomerization of 13c in the Presence of Methyl Propiolate. A mixture of the dienal **13c**[18] (0.38 g, 1.8 mmol) and methyl propiolate (1 g, 12 mmol) was boiled under reflux under nitrogen for 60 h. Excess methyl propiolate was distilled into a cold trap (−78 °C) under reduced pressure (0.1 mm). The NMR spectrum of the residual oil (CCl_4) was identical with that reported[18] for the trans isomer(**13t**).

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Registry No.—**1**, 675-09-2; **4**, 5526-16-9; **6a**, 58133-98-5; **6b**, 58134-01-3; **7a**, 59599-49-4; **7b**, 59599-50-7; **8**, 58134-11-5; **9**, 17448-92-9; **10**, 59599-51-8; **11**, 59599-52-9; **13c**, 21451-41-2; methyl propiolate, 922-67-8; dimethyl acetylenedicarboxylate, 762-42-5.

References and Notes

(1) K. Alder and H. F. Rickert, *Ber.*, **70**, 1357 (1935); N. P. Shusherina, R. Ya. Levina, and V. M. Shotakovskii, *Zh. Obshch. Khim.*, **29**, 3237 (1954); E. Wenkert, D. B. R. Johnston, and K. G. Dave, *J. Org. Chem.*, **29**, 2534 (1964); A. B. Evnin and D. Seyferth, *J. Am. Chem. Soc.*, **89**, 952 (1967); D. Seyferth, D. R. Blank, and A. B. Evnin, *J. Am. Chem. Soc.*, **89**, 4793 (1967); G. Markl and R. Fuchs, *Tetrahedron Lett.*, 4691 (1972).
(2) T. A. Gosink, *J. Org. Chem.*, **39**, 1942 (1974); E. N. Marvell, G. Caple, T. A. Gosink, and G. Zimmer, *J. Am. Chem. Soc.*, **88**, 619 (1966); E. N. Marvell, T. Chadwick, G. Caple, T. Gosink, and G. Zimmer, *J. Org. Chem.*, **37**, 2922 (1972); A. F. Kluge and C. P. Lillya, *ibid.*, **36**, 1977, 1989 (1971); G. Maier and M. Wiessler, *Tetrahedron Lett.*, 4987 (1969); A. Duperrier and J. Dreux, *ibid.*, 3127 (1970).
(3) G. Büchi and N. C. Yang, *J. Am. Chem. Soc.*, **79**, 2318 (1957).
(4) W. Surbev, V. Theus, L. Colombi, and H. Schinz, *Helv. Chim. Acta*, **39**, 1299 (1956).
(5) R. Gompper and O. Christmann, *Chem. Ber.*, **94**, 1784 (1961).
(6) A. Hinnen and J. Dreux, *Bull. Soc. Chim. Fr.*, 1492 (1964).
(7) P. Rouillier, D. Gagnaire, and J. Dreux, *Bull. Soc. Chim. Fr.*, 689 (1966).
(8) J. Royer and J. Dreux, *Tetrahedron Lett.*, 5589 (1968).
(9) J-P. Montillier and J. Dreux, *Bull. Soc. Chim. Fr.*, 3638 (1969).
(10) P. Schiess and H. L. Chia, *Helv. Chim. Acta*, **53**, 485 (1970).
(11) J. W. Huffman and T. M. Hsu, *Tetrahedron Lett.*, 141 (1972).
(12) G. Fodor and C-P. Hsiung, *Justus Liebigs Ann. Chem.*, 1742 (1974).
(13) M. Trolliet, R. Longeray, and J. Dreux, *Tetrahedron*, **30**, 163 (1974).
(14) K. Jankowski and R. Luce, *Tetrahedron Lett.*, 2069 (1974).
(15) Zh. A. Krasnaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2178 (1970).
(16) Ae. de Groot and B. J. M. Jansen, *Tetrahedron Lett.*, 3407 (1975).
(17) For a discussion with leading references see W. Carruthers, "Some Modern Methods of Organic Synthesis", Cambridge University Press, New York, N.Y., 1971, p 156 ff.
(18) P. Schiess and C. Sutter, *Helv. Chim. Acta*, **53**, 1713 (1970).
(19) N. R. Smith and R. H. Wiley, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 337.

Electron Spin Resonance Studies of Structure and Conformation in Anion Radicals Formed during the Autoxidation of Hydroxylated Coumarins

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Coumarins containing hydroxyl groups in the aromatic ring are autoxidized in alkaline solution with the formation of semiquinone radicals, which have been studied by means of ESR spectroscopy. The hyperfine splitting data are consistent with some of these radicals possessing a closed pyrone ring, and others being cinnamic acid semiquinones formed as a result of pyrone ring opening. The cinnamic acid semiquinones are apparently observed in the trans configuration, and the effect of the side chain on the aromatic ring splittings is similar to those of alkyl and aryl groups. A qualitative model, considering delocalization of spin density from the aromatic nucleus into the side chain by both π overlap and hyperconjugation, is successful in relating conformational changes resulting from substitution, and the resultant extranuclear hyperfine splittings.

The coumarins form a group of natural products of considerable importance, being widely distributed throughout the plant kingdom.[1] Much of the interest in the chemistry of this group has arisen from their physiological activity, which manifests itself particularly in the hydroxylated derivatives.

One of the most valuable methods of structure determination for coumarins[1] is furnished by the alkaline degradation reaction, which invariably involves opening of the pyrone ring. In the course of our work on oxidation processes of some groups of natural products, we have studied the autoxidation, in alkaline solution, of coumarins containing hydroxyl groups in the aromatic ring. Under our conditions oxidation accompanies the alkaline degradation, and the intermediate semiquinone anion radicals involved in the combined process are conveniently studied by ESR spectroscopy.[2] We report here the useful relationships between the structures of the initial coumarins and the information gained from an ESR study of the radicals formed during these autoxidation reactions.

Experimental Section

Materials. Caffeic acid (3,4-dihydroxycinnamic acid), chlorogenic acid [3-(3,4-dihydroxycinnamoyl)quinic acid], 7-hydroxycoumarin, 7-hydroxy-4-methylcoumarin, esculetin (6,7-dihydroxycoumarin),

4-methylesculetin, and 4-methyldaphnetin (7,8-dihydroxy-4-methylcoumarin) were purchased from Ralph N. Emanuel Ltd., Wembley, England.

6-Hydroxycoumarin-3-carboxylic acid was prepared from 2,5-dihydroxybenzaldehyde and malonic ester by means of the Knoevenagel reaction.[3] Decarboxylation of this compound yielded 6-hydroxycoumarin.

6-Hydroxy-3-methylcoumarin and 7-hydroxy-3-methylcoumarin were prepared by means of the Perkin reaction, condensing the appropriate dihydroxybenzaldehyde with a mixture of propionic anhydride and sodium propionate.[4] 6-Hydroxy-3-phenylcoumarin was prepared in a similar manner employing acetic anhydride and sodium phenylacetate.[5]

6-Hydroxy-4-methylcoumarin and 6-hydroxy-3,4-dimethylcoumarin were synthesized by means of the Kostanecki–Robinson reaction, condensing 2,5-dihydroxyacetophenone with acetic anhydride–sodium acetate and propionic anhydride–sodium propionate, respectively.[6]

6-Hydroxy-4-phenylcoumarin was prepared in a similar manner from 2,5-dihydroxybenzophenone. The latter was prepared from hydroquinone dimethyl ether according to the method of Bogert and Howells,[7] but with some modification during the last stage of the synthesis. The demethylation of 2-hydroxy-5-methoxybenzophenone, carried out strictly according to the procedure of these workers, proved unsuccessful. However, the demethylation process could be carried out by the following method.

The monomethyl ether (10 g) was refluxed for 3 h with 50 ml of hydriodic acid (sp gr 1.70) and 20 ml of acetic anhydride, the mixture poured into cold water, and the yellow product crystallized from benzene (yield 81%, mp 124–125°C).

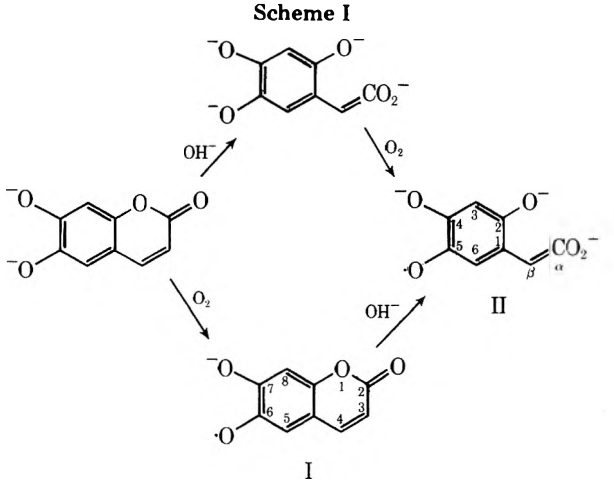
Autoxidations and ESR Spectra. Autoxidation of the coumarins was carried out by addition of sodium hydroxide solution to a solution of the coumarin (0.02 M in 50% aqueous ethanol), and shaking the mixture in air. This was then transferred to an aqueous cell in the cavity of a Varian E-3 instrument and the spectrum recorded. In general the observation of secondary radicals was favored by high pH and longer exposure to the air.

The 7-hydroxycoumarins were autoxidized under the same conditions, but with the additional presence of 0.5 M hydrogen peroxide.

Results and Discussion

Structure and Formation of Anion Radicals. Coumarins containing two ortho hydroxyl groups in the aromatic ring appear to behave like substituted catechols,[8] and are autoxidized in mildly alkaline solution to give well-resolved ESR spectra corresponding to the *o*-semiquinone anions. Esculetin, for example, in dilute alkaline solution, gives rise initially to an ESR spectrum ascribed to radical I (Scheme I and Figure

Scheme I



1). This spectrum, however, slowly decays and is replaced by that due to radical II, formed by opening of the pyrone ring under the alkaline conditions employed. This latter spectrum is observed immediately if strong alkali (5% NaOH) is employed in the autoxidation mixture. An identical spectrum with that of radical II is observed on autoxidation of caffeic acid (3,4-dihydroxycinnamic acid) under the same strongly

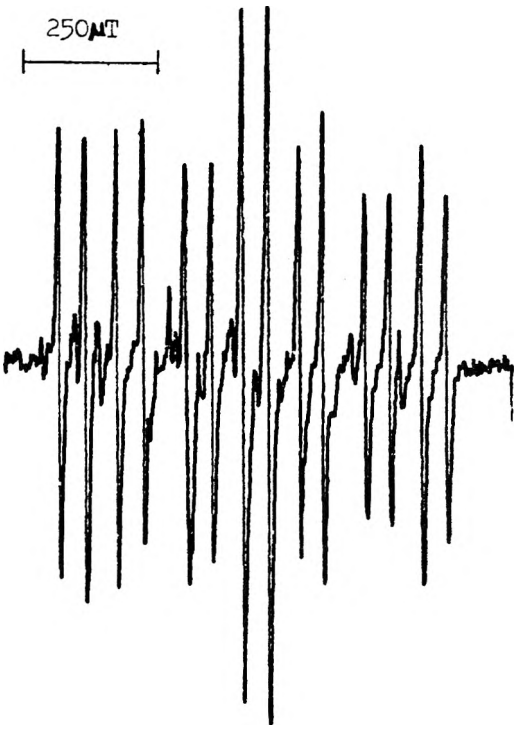
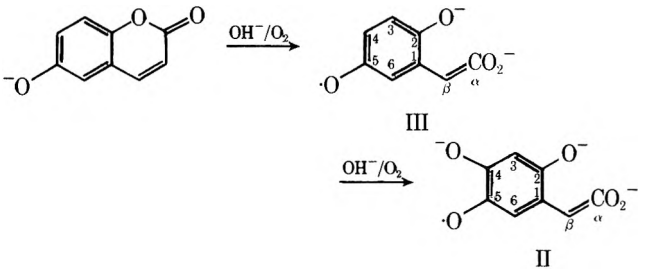


Figure 1. ESR spectrum of the primary radical (I) from esculetin (6,7-dihydroxycoumarin).

alkaline conditions, a secondary radical of the type observed by Stone and Waters[8] in their study of substituted catechol semiquinones. A primary oxidation product of caffeic acid can be observed on autoxidation in mildly alkaline solution (see Table I).

In the case of 6-hydroxycoumarins, semiquinone radical formation occurs only as a result of pyrone ring opening (Scheme II), giving spectra with hyperfine splittings highly

Scheme II



characteristic of para semiquinones (see Table I).[9] On more prolonged autoxidation in strongly alkaline solution, hydroxylation leads to the observation of secondary species,[9] the semiquinones of trihydroxycinnamic acids, and identical with the species formed by ring opening of the esculetins.

The 7-hydroxycoumarins form resorcinol derivatives in alkaline media,[1b] leading to no stable radical anions. However, in the presence of hydrogen peroxide, hydroxylation of the resorcinol can occur,[10] to again give the trihydroxycinnamic acid semiquinones (Scheme III). The latter are thus definitely

Scheme III

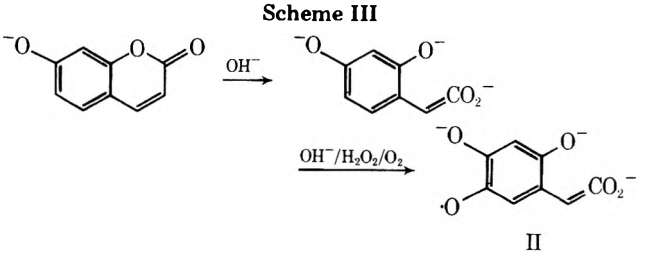


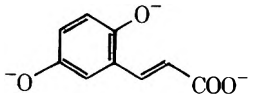
Table I. Radicals Observed during the Autoxidation of Hydroxycoumarins, with Their Hyperfine Splitting Constants

Registry no.	Radical anion	Hyperfine splittings, μT^a					
		Pyrone ring		Aromatic ring			
		a_3	a_4	a_5	a_6	a_7	a_8
305-01-1	6,7-Di-OH-coumarin	338	106	234			47
529-84-0	6,7-Di-OH-4-Me-coumarin	278	58 (Me)	220			45
2107-77-9	7,8-Di-OH-4-Me-coumarin	152	33 (Me)	308	51		
		Side chain		Aromatic ring			
		a_α	a_β	a_2	a_3	a_4	a_5	a_6
636-01-1	2,5-Di-OH-cinnamic acid	85	170		240	213		213
59433-76-0	α-Me-2,5-di-OH-cinnamic acid	100 (Me)	153		236	230		180
57707-19-4	β-Me-2,5-di-OH-cinnamic acid	14	0 (Me)		254	222		184
59433-77-1	α-Ph-2,5-di-OH-cinnamic acid	70 (Ph)[b]	136		250	214		191
59433-78-2	β-Ph-2,5-di-OH-cinnamic acid	9	0 (Ph)		258	216		204
56437-15-1	2,4,5-Tri-OH-cinnamic acid	175	283		44			132
59433-79-3	α-Me-2,4,5-tri-OH-cinnamic acid	259 (Me)	320		47			69
59433-80-6	β-Me-2,4,5-tri-OH-cinnamic acid	24	0 (Me)		47			96
59433-81-7	α,β-DiMe-2,4,5-tri-OH-cinnamic acid	58 (Me)	0 (Me)		50			96
59433-82-8	α-Ph-2,4,5-tri-OH-cinnamic acid	177 (Ph)[b]	294		44			95
59433-83-9	β-Ph-2,4,5-tri-OH-cinnamic acid	19	0 (Ph)		45			113
59433-84-0	α-CO_2H-2,4,5-tri-OH-cinnamic acid		250		40			125
59433-85-1	α-CO_2H-2,3,5-tri-OH-cinnamic acid		67			67		501
59433-86-2	α,β-Di-Me-2,3,5-tri-OH-cinnamic acid	10 (Me)	0 (Me)			62		422
57707-18-3	β-Me-2,3,4-tri-OH-cinnamic acid	6	0 (Me)				83	540
331-39-5	3,4-Di-OH-cinnamic acid	130	236	23			119	282
59434-09-2	3,4-Di-OH-cinnamoylquinic acid	120	240	63			120	260

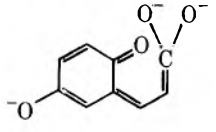
[a] Numbering systems for radicals as given in the text. [b] Total splitting from phenyl group.

characterized by their formation from a variety of different starting materials.

In view of obtaining identical ESR spectra from autoxidation of the *trans*-cinnamic acid derivative, caffeic acid, and from ring opening of coumarins, it appears that the radicals we observe in both cases have adopted the more stable trans configuration with respect to the side chain double bond. In fact, there is good evidence for suggesting that during the oxidative degradation of coumarins, semiquinones with the cis configuration are either not formed at all to any appreciable extent, or are not sufficiently long lived for observation. For example, while the trans forms of *o*-hydroxycinnamic acid anions appear to contain a truly aromatic ring (IV), the corresponding cis forms are best represented by *o*-quinonoid structures such as V.[1b]



IV

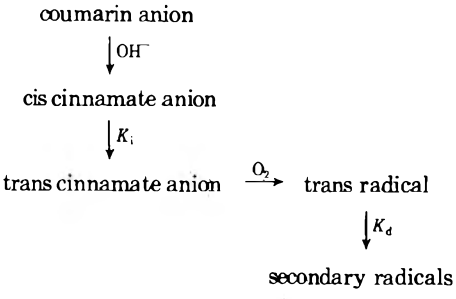


V

In this case, while the trans forms are readily autoxidized in the ring to give long-lived semiquinone radical anions, the cis forms are expected to be more resistant to the oxidation process, which may not occur to any appreciable extent under such relatively mild oxidizing conditions. A number of such cases of resistance to autoxidation have been found where the aromaticity of the quinol anion is disturbed by substituents.[11] In any event, the shorter lifetimes of radical anions from cis forms such as V, if produced at all, would probably preclude their observation in the presence of more stable semiquinones.

In support of these ideas is the difficulty we have experienced in obtaining spectra of primary radicals (Scheme II) from 6-hydroxycoumarins containing substituents in the 3 position, where cis to trans isomerizations are known to be relatively slow under our conditions.[1b] No sign of primary radicals was observed in two of these cases, from the 3-carboxyl and 3,4-dimethyl derivatives. If our premise that we observe only trans forms is correct, then the chances of observing the primary species will decrease with the decreasing rate of cis to trans isomerization of the anion precursor. When

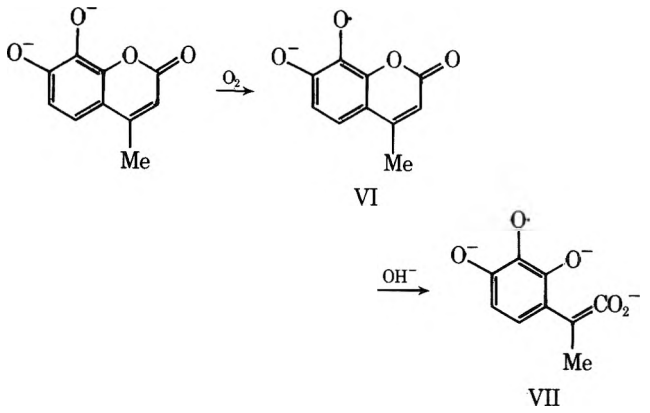
Scheme IV



the isomerization rate is very slow relative to the rate at which primary radicals are destroyed, by further oxidation to secondary species via the quinone[9] (i.e., $k_i \ll k_d$), then the concentration of primary radicals may be sufficiently low to preclude observation. In such cases only secondary species will be observed, as we have found for the 3-carboxyl and 3,4-dimethyl derivatives. These observations could not be readily explained if we made the assumption that the radicals we observe during coumarin autoxidation were of the cis form.

In addition to not observing primary radicals from the 3-carboxyl- and 3,4-dimethyl-6-hydroxycoumarins, these are the only cases where a mixture of isomeric secondary species is obtained. These isomeric mixtures are a feature of the ESR spectra observed during autoxidation of alkyl-[9] and phenylquinols,[12] but the factors influencing the relative concentrations of each isomeric radical are not fully understood.

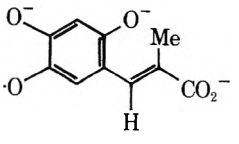
The autoxidation of 4-methyldaphnetin (7,8-dihydroxy-4-methylcoumarin) is readily understood in terms of formation of the primary catechol semiquinone (VI), and secondary formation of the ring-opened radical (VII), with hyperfine splittings highly characteristic of a pyrogallol semiquinone.[8]



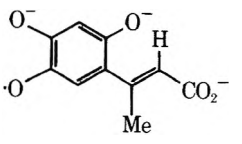
Hyperfine Splittings and Conformation. Little difficulty is encountered in identifying the radical intermediates from their ESR spectra and from a knowledge of the initial coumarin. The semiquinone ring splittings are unambiguously determined in the spectra of radicals containing a fully methylated extranuclear fragment (see Table I), and are found to be close to the corresponding splittings in unsubstituted semiquinones.[9] This relatively small effect of the side chain in the cinnamic acid semiquinones is comparable to that of a phenyl[12] or alkyl[9,13] group, as might be expected since the same types of mild interaction with the semiquinone nucleus will be involved. The aromatic ring proton splittings are also rather insensitive to the nature of substitution in the side chain (α or β substitution of protons by Me or Ph, see Table I), being chiefly dictated by the particular hydroxylation pattern of the ring.

For the semiquinones with an intact coumarin ring, the effect of the –OCO– grouping appears to be small with respect to the aromatic ring splittings. These radicals are all ortho semiquinones, the hyperfine splittings of which are in general fairly insensitive toward substitution in the nucleus.[8,14] As a result of these small substituent effects in both the open and closed ring radicals, the aromatic proton splittings are readily identified with particular hydroxylation patterns for the aromatic ring (see Table I). This information, together with the observed conditions of radical generation, could be of some value in the analysis of coumarins with indefinite structures.

The spin density distribution in the remaining extranuclear fragment of each radical is, on the other hand, highly dependent on whether or not the pyrone ring is open, and on any substitution of the proton at C_β or C_4 (see Table I). The effect of such substitution at C_β by a methyl group, for example, is very striking indeed, compared to the relatively small effect of a methyl group at the α position. This is illustrated in Figure 2, which shows the ESR spectra of the isomeric secondary radicals VIIIa and VIIIb. With β-methyl substitution (VIIIb),



VIIIa



VIIIb

spin density is effectively cut off from the side chain protons, suggesting that conformational changes with respect to the bond joining this fragment and the aromatic ring are responsible for the widely different spectra.

To examine the situation more closely, we can make use of a relatively simple qualitative model, to reflect the effects of such conformational changes on the delocalization of spin density from the semiquinone nucleus into the remaining fragment. Turning our attention first to the cinnamic acid semiquinones, since the side chain has little influence on spin

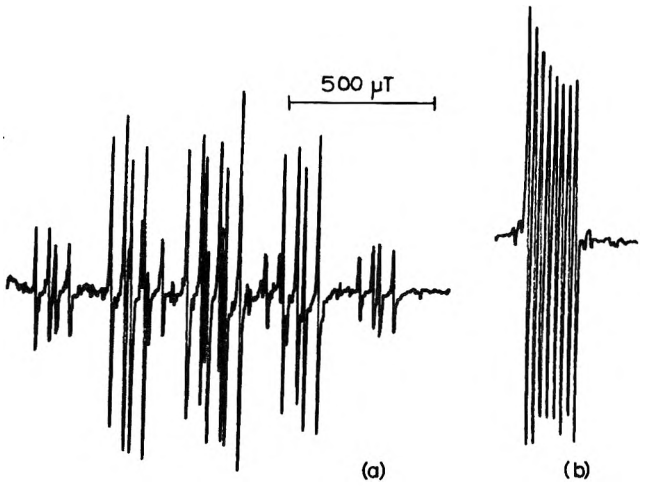


Figure 2. ESR spectra of the isomeric secondary radicals VIIIa and VIIIb from (a) 6-hydroxy-3-methylcoumarin and (b) 6-hydroxy-4-methylcoumarin.

densities in the aromatic ring, it may be treated, to a good approximation, simply as a substituent drawing spin density from the $p\pi$ orbital of the aromatic ring carbon to which it is attached. In this respect, the model is no different from that used to examine hyperconjugation in alkyl semiquinones,[15] or π–σ delocalization in aryl semiquinones.[16] In support of such a model is the observation that for a series of cinnamic acid semiquinones containing the same side chain but different aromatic ring hydroxylation patterns, the splittings from α and β protons are roughly proportional to the expected spin densities at the aromatic ring carbon, i.e., those found for corresponding ring positions in unsubstituted semiquinones.[9] Similar relationships have been found for alkyl[9] and aryl[16] splittings in a series of differently hydroxylated semiquinone anions.

For closed ring radicals, the model remains the same, since the –OCO– grouping should form an effective barrier to any spin transfer from its neighboring aromatic ring carbon. The problem is thus reduced to that of an "allylic fragment", made up of the nuclear ring carbon atom C_r, and the extranuclear carbons, C_α and C_β (Figure 3a). The extranuclear hyperfine splittings then arise by delocalization of spin density from the $p\pi$ orbital of C_r, and we can envisage two extreme mechanisms by which this delocalization can occur.

The mechanism of $p\pi$–$p\pi$ overlap (Figure 3b) will clearly lead to effective delocalization for a planar allylic system, but the resultant spin densities at C_α and C_β follow a $\cos^2\theta$ relation as the system leaves planarity (where θ is the dihedral angle between $p\pi$ orbitals on C_r and C_β). Near-planar allyl radicals[17] reflect the $p\pi$–$p\pi$ overlap mechanism, in agreement with MO theory, which predicts high positive spin density at C_α and a small negative value at C_β. Protons and alkyl groups at C_α and C_β, in this case, show splittings characteristic of π radicals (e.g., $a^H \sim a^{Me}$).[17]

The second mechanism is that of hyperconjugation or π–σ delocalization, whereby spin is transmitted by overlap of the $p\pi$ orbital of C_r with σ orbitals of the carbon framework.[16,18,19] The effectiveness of this spin transfer mechanism varies with $\sin^2\theta$, being most important in a perpendicular allylic system. The ESR spectrum of a near-perpendicular allyl radical has recently been observed,[20] confirming the view that hyperconjugation in these systems is very important for spin transfer to an atom directly bonded to C_β (Figure 3c), but falls off rapidly with distance from the radical center (C_r). With regard to the radicals under discussion in this paper, we can expect a strong hyperconjugative interaction, leading to positive spin density on a vinylic β proton, as the dihedral

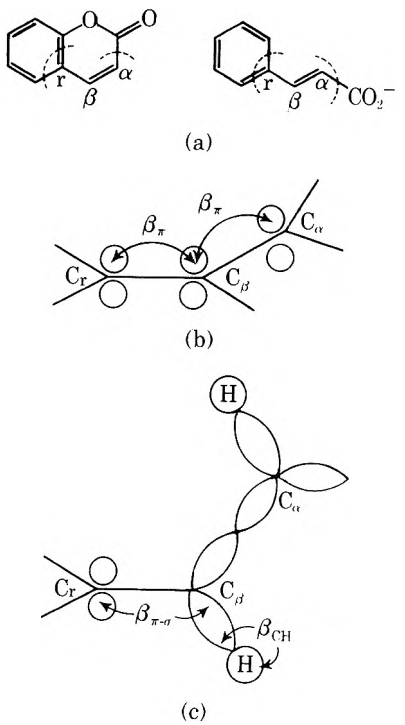


Figure 3. Mechanism of spin delocalization: (a) "allylic fragment" for closed ring and side chain; (b) π–π delocalization ($\theta = 0°$); (c) σ orbitals of allylic fragment at $\theta = 90°$ showing effective π–σ overlap for a vinylic β proton.

angle approaches 90°, but much less significant interactions involving methyl and α protons.

In the model just described, we have rather artificially separated the total spin delocalization into that arising by two extremes of mechanism. However, the model is rather useful for gaining a qualitative picture of the dependence of extranuclear hyperfine splittings on the dihedral angle (i.e., conformational changes at the C_r-C_β bond).

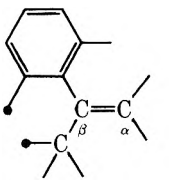
For any extranuclear hyperfine splitting, we can write

$$a^H = a^H_{\pi-\pi} + a^H_{\pi-\sigma} = a^H_{\pi-\pi(0°)} \cos^2\theta + a^H_{\pi-\sigma(90°)} \sin^2\theta$$

With this relationship in mind, it is instructive to examine certain trends in these hyperfine splittings with ring opening, and with substitution in the side chain or pyrone ring. For example, an examination of the extranuclear proton splittings in the closed ring radicals from 6,7-dihydroxycoumarins shows that the effect of introducing a 4-methyl group (β position) on the value of a^H_3 is small, and that $a^H_3(\alpha) > a^H_4(\beta)$. Clearly, in this case, the pyrone ring is held in a near-planar conformation wtth effective π–π delocalization, leading to large α splittings. However, when the constraints on planarity are removed by ring opening, we find $a^H_\beta > a^H_\alpha$, and the effect of a β-methyl group now is to reduce splittings drastically. We would expect some increase in the value of the dihedral angle θ on ring opening, and the observed splitting trends are consistent with a decrease in π–π overlap and an increase in the hyperconjugative interaction involving the β proton. The effect of a β-methyl group, as might be expected on steric grounds, is to further increase θ to a value approaching 90°.

The lack of splitting from the β-methyl protons is probably a fortuitous cancelling of small contributions from π–π spin (−Ve) and π–σ spin (+Ve), indicating that despite a favorable conformation for the latter mechanism, the separation of methyl protons from the radical center renders the contribution small compared to that for a vinylic β proton. Comparison of splittings from α protons and α-methyl protons, on the other hand, shows that they have comparable values in otherwise equivalent radicals. This is indicative of their major contribution coming from the π–π delocalization mechanism.

The presence of a methyl, phenyl, or carboxyl group at C_α has apparently little effect on the dihedral angle θ, suggesting that the only steric interactions responsible for the observed conformational effects are between the aromatic ring and the other group on C_β. The magnitude of the steric interactions



involved with the introduction of a β-methyl or β-phenyl group need not necessarily be very large to bring about a significant change in θ. A loss of stabilization by π–π delocalization of spin with increasing dihedral angle is expected to be somewhat compensated for by the increased hyperconjugation. The C_r–C_β bond will, of course, be subject to torsional vibrations, particularly in the open ring radicals, the average value of $\cos^2\theta$ determining the hyperfine splittings.

In conclusion, it may be stated that the ESR investigation of semiquinone intermediates formed during the alkaline autoxidation of hydroxylated coumarins can lead to structural, conformational, and mechanistic information. The cinnamic acid and coumarin semiquinones provide a particularly lucid example of how ESR hyperfine splitting data can be related, by simple qualitative theory, to conformational changes affecting the delocalization of spin.

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References and Notes

(1) (a) F. M. Dean, "Naturally Occurring Oxygen Ring Compounds", Butterworths, London, 1963; (b) S. Wawzonek in "Heterocyclic Compounds", Vol. 2, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1951, Chapter 6.
(2) P. Ashworth, *Tetrahedron Lett.*, 1435 (1975).
(3) F. Cramer and H. Windel, *Chem. Ber.*, **89**, 354 (1956).
(4) E. Cingolani, A. Schiavello, and C. Sebastiani, *Gazz. Chim. Ital.*, **83**, 647 (1953).
(5) N. R. Krishnaswamy, T. R. Seshadri, and B. R. Sharma, *Indian J. Chem.*, **4**, 120 (1966).
(6) R. D. Desai and C. K. Mavani, *Proc. Indian Acad. Sci., Sect. A*, **25**, 353 (1947).
(7) M. T. Bogert and H. P. Howells, *J. Am. Chem. Soc.*, **52**, 837 (1930).
(8) T. J. Stone and W. A. Waters, *J. Chem. Soc.*, 1488 (1965).
(9) P. Ashworth and W. T. Dixon, *J. Chem. Soc., Perkin Trans. 2*, 1130 (1972).
(10) P. Ashworth and W. T. Dixon, *J. Chem. Soc., Perkin Trans. 2*, 739 (1974).
(11) P. Ashworth, unpublished work.
(12) P. Ashworth and W. T. Dixon, *J. Chem. Soc., Perkin Trans. 2*, 2264 (1972).
(13) P. Ashworth, *Mol. Phys.*, **30**, 313 (1975).
(14) M. Brustolon, L. Pasimeni, and C. Corvaja, *J. Chem. Soc., Faraday Trans. 2*, 403 (1973).
(15) C. Trapp, C. A. Tyson, and G. Giacometti, *J. Am. Chem. Soc.*, **90**, 1394 (1968).
(16) P. Ashworth and W. T. Dixon, *J. Chem. Soc., Perkin Trans. 2*, 1533 (1973).
(17) J. K. Kochi and P. J. Krusic, *J. Am. Chem. Soc.*, **90**, 7157 (1968).
(18) J. A. Pople and D. L. Beveridge, *J. Chem. Phys.*, **49**, 4725 (1968).
(19) W. J. Van den Hoek, B. A. C. Rousseeuw, J. Smidt, W. G. B. Huysmans, and W. J. Mijs, *Chem. Phys. Lett.*, **13**, 429 (1972).
(20) H. Regenstein and A. Berndt, *Angew. Chem., Int. Ed. Engl.*, **13**, 144 (1974).

Notes

Stereochemical Control in the Acylation of 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose. A Route to 1-*O*-Acyl-α- and -β-D-glucopyranoses

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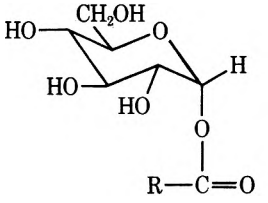
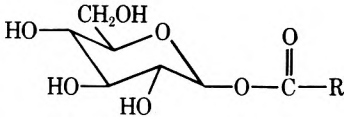
A recent report[2] has implicated several D-glucosyl fatty acid esters as active plant growth regulating compounds. Although the stereochemistry of these natural products was not rigorously established, they were tentatively assigned the β-D configuration II.[2] To test the validity of this assignment, we

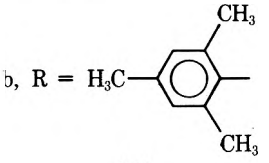


I

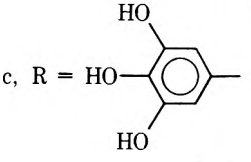


II

a, R = n-$C_{15}H_{31}$



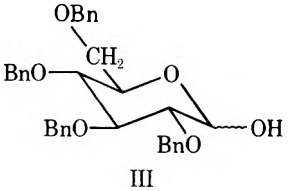
b, R = H_3C—



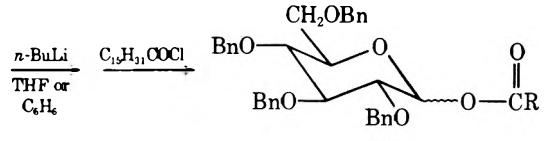
c, R = HO—

set out to synthesize anomerically pure derivatives I and II containing long-chain fatty acid ester moieties.

In this paper we report the results of a study in which we have been able to control successfully the stereochemistry of 1-O-acylation of appropriately protected D-glucose to produce, selectively, in high yield (85–90%), α- and β-D-glucose esters Ia and IIa, respectively. Metalation of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (TBG), III (5.40 g, 0.01 mol), in 125 ml of tetrahydrofuran (THF) at −30 to −40 °C using 1.1 equiv of n-butyllithium (1.6 M in hexane) followed by acylation with hexadecanoyl chloride produces a mixture of α- and β-D-anomeric esters IVa and IVb (noncrystalline mixture) in a



III



IV

a, α anomer
b, β anomer

Bn = benzyl

Table I. Stereochemical Distribution of Anomeric 1-*O*-Hexadecanoyl-D-TBG as a Function of Temperature and Solvent

Solvent	α	β	Temp, °C	Rotation
THF	90	10 (via ^{1}H NMR)	−30 to −40	+45.9 (CH_2Cl_2)
THF	70	30	25	+39.2
THF	70	30	45	
Benzene	50	50	0–5	+27.8
Benzene	26	74	40–45	+20.6
Benzene	11	89	62	+14.9

Table II. Anomeric Composition and ^{13}C Chemical Shifts, δ (ppm, Me_4Si), of TBG and TBG$^-$Li$^+$ in Benzene and THF at 35 °C

	δ (benzene)		δ (THF)		% α	% α
	α	β	α	β	(benzene)	(THF)
TBG	91.3	98.2	91.6	98.6	61	67
TBG$^-$Li$^+$	89.1	95.9	88.8	96.1	50	52

ratio of 9:1, respectively, in chromatographically purified yields exceeding 95%. Other esters which we have prepared include benzoate, acetate, *cis*-9,10-octadecenoate, and octadecanoate; however, in this report we use the hexadecanoate as an illustrative example. Stereochemical assignment and relative amounts of IVa and IVb were readily determined by the measurement of the respective anomeric proton resonances at δ 6.65 (d, J = 2.62 Hz) and 5.85 (d, J = 6.75 Hz) in CCl_4 relative to internal standard Me_4Si.[3] Increasing the temperature in the metalation and acylation reactions in THF changes somewhat the α:β ratio, but the α-D anomer, IVa, still predominates, e.g., at 45 °C the ratio is 2–2.5:1 (Table I). In studying the parameters which influence the stereochemical course of this reaction, we observed that a dramatic inversion in product ratio could be effected by changing the reaction medium. Thus, reaction of III in benzene at 60 °C produces a 1:8 ratio of IVa and IVb, respectively. Compound IVb was isolated from this reaction mixture by crystallization from absolute ethanol, mp 52–53 °C, $[\alpha]^{25}$D +9.1° (c 1.0, CH_2Cl_2). At lower temperatures, intermediate ratios are noted; however, IVb still predominates above 5 °C in benzene (Table I).

At first, interpretation of these data in terms of a solvent and temperature dependent equilibration of metalated anomeric TBG (α-TBG$^+$Li$^-$ and β-TBG$^-$Li$^+$) seemed attractive.[4] Optical rotations of THF and benzene solutions containing TBG$^-$Li$^+$ were +31.6 and +33.4, respectively. These readings were relatively invariant with temperature change from 25 to 56 °C. Rotations obtained for the acetic acid quenched solutions of TBG$^-$Li$^+$ in THF and benzene were +36.8 and +37.0 whereas those of TBG were +46.8 and +53.6, respectively.[5] Presumably, metalation of TBG has only a minor effect on the anomeric equilibrium position seen in a slight shift toward β-D-anomer formation. This is confirmed by ^{13}C NMR spectroscopy which clearly shows the composition of the TBG and TBG$^-$Li$^+$ in benzene and THF. Table II lists the percentage of the α forms for both TBG and TBG$^-$Li$^+$ (generated with an equivalent amount of n-butyllithium) in benzene and THF determined by measurement of the corresponding α and β carbon resonances. Notice that both anomeric carbon shifts

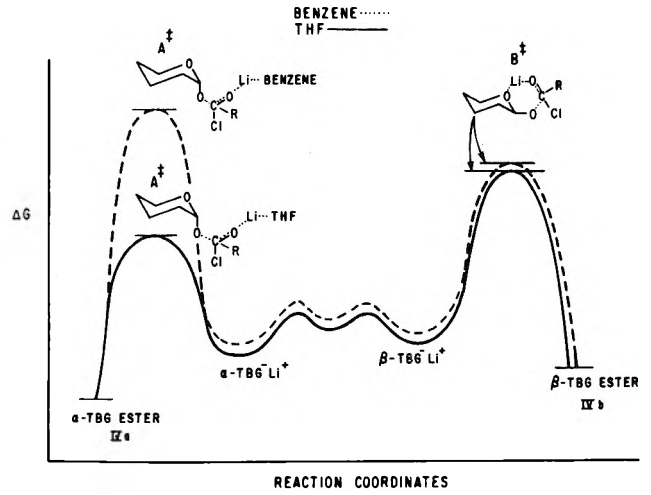


Figure 1. Pathway for the reaction of α and β TBG salts with acid chlorides.

are observed at higher fields in their salt forms, reminiscent of ionization. This result is in sharp contrast with the downfield shifts observed by deWit[4] for D-glucose in D_2O. Furthermore, after metalation and quenching, the anomeric ratios appear to be approximately the same for both solvents (50:50). These findings lead us to believe that the stereochemical control of acylation occurs further along the reaction coordinate, i.e., through the agency of the activated complexes $A^{\ddagger}$ (α form) and $B^{\ddagger}$ (β form) (Figure 1). In THF solution, the lower energy pathway provided by THF-solvated $A^{\ddagger}$ relative to the higher pathway given by intramolecularly bonded $B^{\ddagger}$ leads to a predominance of product IVa. Conversely, in benzene intramolecular coordination in $B^{\ddagger}$ becomes more important since it offers greater stabilization relative to the stabilization imparted to $A^{\ddagger}$ by the relatively nonpolar, poorly solvating benzene. Thus in benzene, product IVb predominates.[6]

Glucosyl esters, especially the α-D anomers, have not been of easy access in the past. Only the gallate, Ic, has been prepared in 5% yield by the procedure of Schmidt[7] and the mesitoate, Ib, in 17% yield by the procedure of Fletcher.[8] Furthermore, Fletcher could not extend either procedure to less hindered systems because of the lack of stereospecificity in the acylation procedure employed[8] and loss of desired product through rapid migration of the unhindered ester function from C-1 to C-2 under the nonneutral deblocking conditions.[9]

Hydrogenolysis of chromatographically purified (90% isomeric purity) IVa and isomerically pure IVb in absolute ethanol containing a catalytic amount of Pd black produced Ia and IIa in yields exceeding 90% (recrystallized from $CHCl_3$).

This synthetic sequence represents the first single pathway to pure, 1-α- and -β-D anomeric esters and the first general, high-yield route to pure unrearranged aliphatic 1-*O*-acyl-α-D-glucopyranoses Ia.

Experimental Section

Melting points are uncorrected. ^{13}C NMR spectra were determined on a Bruker[10] WH-90 spectrometer at 22.63 MHz. ^1H NMR spectra were determined on JEOL C-60H and Varian HA220 spectrometers. All chemical shifts are reported relative to internal Me_4Si. Ir spectra were recorded on a Perkin-Elmer 457 spectrometer. Rotational measurements were made on a Perkin-Elmer Model 141 polarimeter. GLC analyses of all glucose esters were performed on the corresponding trimethylsilyl derivatives prepared from Tri Sil Z reagent. The gas chromatograph used was a Hewlett-Packard Model 5750 equipped with flame ionization detection. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (TBG) was purchased from Pfanstiehl Chemical Co., mp 152–153 °C.

All reported compounds gave satisfactory elemental analyses.

General Procedure for the Preparation of 2,3,4,6-Tetra-*O*-benzyl-1-*O*-acyl-α-D-glucopyranose IVa. For this procedure we have chosen the hexadecanoyl ester as a representative example. Into a dry 250-ml three-neck flask, flushed with N_2, was placed 125 ml of freshly distilled anhydrous THF and 5.40 g (0.010 mol) of dry 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (TBG). The solution was magnetically stirred and the TBG was thoroughly dissolved within a few minutes at room temperature. The solution was then cooled to −30 to −40 °C and 6.8 ml (0.011 mol) of 1.6 M *n*-butyllithium in hexane was added. The homogeneous reaction mixture was stirred at this temperature for 3 min whereupon 3.0 g (0.011 mol) of hexadecanoyl chloride was added and the reaction continued for 20 min. The solution was then allowed to warm to room temperature, quenched with a saturated solution of ammonium chloride, and extracted with methylene chloride. The methylene chloride extracts were dried over sodium sulfate and the solvent removed to yield 7.8 g of crude ester (100%). The crude ester was eluted through an 18 × 0.75 in. column of Florisil with 50:50 methylene chloride–petroleum ether to give 7.7 g (97%) of a glassy solid. Attempts to crystallize this material failed. ^1H NMR in $CDCl_3$ showed the characteristic α and β anomeric proton resonances at δ 6.65 (d, J = 2.62 Hz) and 5.85 (d, J = 6.75 Hz) in the ratio of 9:1, respectively. The ratio of the sum of the α and β anomeric proton resonances to the 2-position methylene resonances of the aliphatic chain at δ 2.5 was 1:2, indicating monoesterification. Ir (neat film) C=O, 1745 cm^{-1}; $[\alpha]^{25}D$ +45.9° (*c* 1.0, CH_2Cl_2).

Preparation of 2,3,4,6-Tetra-*O*-benzyl-1-hexadecanoyl-β-D-glucopyranoses IVb. The preparation of the β-anomeric ester was similar to the above except that the reaction was carried out in anhydrous benzene. Metalation and solubilization of the TBG was carried out at 0 °C. Acylation was then effected at 62 °C for 20 min. Workup was essentially the same as above. Examination of the reaction mixture before crystallization by ^1H NMR indicated a ratio of α:β anomers of 11:89. The yield of crude ester was 95%. Crystallization of the product from absolute ethanol gave pure β anomer, mp 52–53 °C, in 85% yield. ^1H NMR in $CDCl_3$ showed the characteristic β-anomeric proton resonance at δ 5.85 (1 H, d, J = 6.75 Hz), 2.5 (2 H, t, J = 6.75 Hz, the 2 position CH_2 of the fatty acid chain); ir (neat film) C=O 1750 cm^{-1}; $[\alpha]^{25}D$ +9.1° (*c* 1.0, CH_2Cl_2).

Hydrogenolysis of IVa and IVb. IVa (90% α and 10% β) or compound IVb (100% β) (2 g, 0.0025 mol) were dissolved in 20 ml of absolute ethanol containing 75 mg of Pd black. The solutions were shaken on a Parr hydrogenator at room temperature for 8 h at 40 psi. Ia crystallized out of solution following hydrogenolysis of IVa in 92% yield. Recrystallization from $CHCl_3$ gave a solid which rearranged on melting, mp 98–108 °C, $[\alpha]^{25}D$ +66.9° (*c* 0.9, MeOH). ^1H NMR (CD_3OD), taken at 60 °C in a sealed tube because of the compounds' insolubility, showed resonances at δ 6.45 (1 H, d, J = 3.0 Hz, anomeric proton), 2.50 (2 H, t, J = 6.75 Hz, 2-position CH_2 protons of the aliphatic chain); ir (KBr pellet) C=O at 1740 cm^{-1}.

IIa was isolated in 96% yield after recrystallization from ethyl acetate: mp 108, 170–175 °C (double melting point); $[\alpha]^{25}D$ −1.17° (*c* 1.2, MeOH); ^1H NMR (CD_3OD) at 60 °C δ, 5.62 (1 H, d, J = 6.75 Hz, anomeric proton), 2.50 (2 H, t, J = 6.75 Hz, 2-position CH_2 protons of the aliphatic chain); ir (KBr pellet) shows three C=O peaks at 1760, 1750, and 1740 cm^{-1}.

The isomeric purity of Ia and IIa was confirmed by GLC analysis of the corresponding Me_4Si derivatives. Separation of these was made on a 6 ft × 0.25 in. glass column packed with 3% SP2100 and programmed from 180 to 250 °C, 6 °C/min. Under these conditions Ia and IIa have retention times of 12.0 and 12.5 min, respectively.

Acknowledgment. We thank Ms. M. S. Dougherty for her able assistance. ^1H NMR spectra (220 MHz) were taken at the Middle Atlantic Regional NMR facility, which is supported by NIH Grant RR542 at the University of Pennsylvania. Our thanks to G. McDonald for his assistance.

Registry No.—Ia, 59473-41-5; IIa, 39848-71-0; α-III, 6564-72-3; β-III, 59531-24-7; α-III Li, 59473-42-6; β-III Li, 59531-25-8; IVa, 59473-43-7; IVb, 59473-44-8; hexadecanoyl chloride, 112-67-4.

References and Notes

(1) Agricultural Research Service, U.S. Department of Agriculture.
(2) N. Mandava and J. W. Mitchell, *Chem. Ind. (London)*, 930 (1972).
(3) Further verification of assignment of IVa was made through comparison with the material prepared by the alternative route of esterification of TBG in CH_2Cl_2–pyridine. G. P. J. Glaudemans and H. G. Fletcher, Jr., *Methods Carbohydr. Chem.*, **6**, 373 (1972). Structure of IVb was confirmed through its debenzylated product Vb which was identical with the sample obtained

through the 4,6-O-benzylidene-D-glucopyranose acylation, deblocking route. H. G. Fletcher, Jr., *ibid.*, 231 (1963).
(4) A similar anionic equilibration has recently been observed for glucose: G. deWit, A. P. G. Kiekoom, and H. vanBekkum, *Tetrahedron Lett.*, 3943 (1975).
(5) The composition of TBG, e.g., the commercially available mp 149–150 °C material, in both benzene and THF has been determined by 220-MHz ^{1}H NMR to be approximately a 60:40 mixture of α and β anomeric forms. This ratio appears to remain approximately the same in the temperature range 17–56 °C.
(6) Note that addition of 4% HMPA to benzene v/v increases the solvating power of the medium enough to reverse the α:β product ratio to 2.3:1.
(7) O. T. Schmidt and J. Herok, *Justus Liebigs Ann. Chem.*, **587**, 63 (1954).
(8) C. Pedersen and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **82**, 3215 (1960).
(9) H. B. Wood, Jr., and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **78**, 2849 (1956).
(10) Reference to brand or firm name does not constitute endorsement by the U.S. Department of Agriculture over others of a similar nature not mentioned.

A Synthesis of (*Z*)-6-Heneicosen-11-one. The Sex Pheromone of the Douglas Fir Tussock Moth[1]

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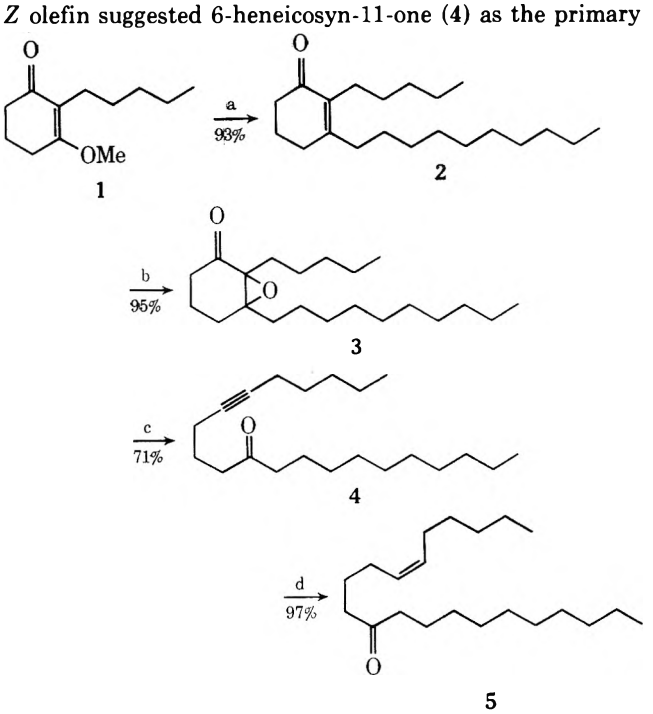
The sex pheromone of the Douglas fir tussock moth *Orgyia pseudotsugata* (McDunnough) has recently been identified as (*Z*)-6-heneicosen-11-one (**5**),[2] which is unusual in that most lepidopterous sex pheromones thus far identified are monoene or diene fatty alcohols or acetates of C_{12} or C_{14} chain length.[3] The structure and stereochemistry of **5** have been corroborated by unambiguous total synthesis.[4] The Douglas fir tussock moth is a severe defoliator of fir forests in western North America; consequently, considerable interest attends the use of the sex pheromone for purposes of bioassay and population control. Since traps baited with synthetic **5** have been shown to be highly attractive to males in field tests,[2] we have explored an alternate synthesis of **5** which is presented in the scheme below.

The high stereoselectivity and chemical yield anticipated for the reduction of an acetylenic bond to the corresponding *Z* olefin suggested 6-heneicosyn-11-one (**4**) as the primary synthetic goal.[5] The 21-carbon chain with the requisite 1,5 relationship between the ketone and acetylene functions in **4** was introduced in one step by the Eschenmoser cleavage[6] of the epoxy ketone **3** in 71% yield. The synthesis of the epoxy ketone **3** was achieved in two steps from the enol ether **1**[7] as shown in the scheme.



a, n-$C_{10}H_{21}MgBr/Et_2O$, H_3O^+; b, H_2O_2–NaOH/MeOH; c, p-$TsNHNH_2/CH_2Cl_2$–HOAc; d, H_2–Pd/$BaSO_4$, MeOH–pyridine.

To complete the synthesis, the acetylenic bond of **4** was semihydrogenated over Lindlar catalyst poisoned with 5 equiv of pyridine to give the *Z* olefin **5** in 97% yield (60% overall from **1**). The MS, ir, and NMR spectra of synthetic **5** were in complete accord with the published data for the natural pheromone.

Experimental Section

Infrared spectra were recorded with a Perkin-Elmer 457 spectrometer as ~5% solutions in CCl_4; NMR spectra were obtained with a Varian HA-100 instrument in CCl_4 solution using Me_4Si as an internal standard. Mass spectra were obtained on a Du Pont 29-491B spectrometer. All yields are based on pure, isolated products.

2-*n*-Pentyl-3-*n*-decylcyclohex-2-en-1-one (2). A solution of *n*-decylmagnesium bromide was prepared from 1.77 g (8.00 mmol) of *n*-decyl bromide and 0.19 g (8.25 g-atoms) of Mg in 35 ml of ether. To the magnetically stirred Grignard reagent was added dropwise 1.00 g (5.10 mmol) of 2-*n*-pentyl-3-methoxycyclohex-2-en-1-one (**1**) in 5.0 ml of ether at 0 °C. After addition was complete, the mixture was stirred at 0 °C for 30 min and at ambient temperature for 3 h. The reaction mixture was poured into 15 ml of iced 1 N HCl and the ether layer separated, washed with 2 × 10 ml of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo to a pale yellow oil. Kugelrohr distillation afforded 1.40 g (93%) of pure **2** as a colorless oil which crystallized on refrigeration: bp 125 °C (bath, 0.18 mm); ir (CCl_4) 1665, 1618 cm^{-1}; NMR (CCl_4) δ 2.1–2.4 (m, 6 H), 1.8–2.1 (m, 2 H), 1.1–1.8 (m, 24 H), 0.8–1.1 (overlapping distorted triplets, 6 H); mass spectrum (70 eV) *m/e* 306 (60, M^+), 165 [100, $(M - C_{10}H_{21})\cdot^+$]; uv (95% EtOH) 245 nm (ϵ 17 200).

2-*n*-Pentyl-3-*n*-decyl-2,3-epoxycyclohexan-1-one (3). To a solution of 0.590 g (1.93 mmol) of enone **2** in 14 ml of MeOH was added 1.00 ml (11.6 mmol) of 30% H_2O_2 and 0.15 ml of 6 N NaOH. The reaction mixture was allowed to stir at ambient temperature for 24 h after which the MeOH solution was diluted with 35 ml of H_2O and extracted with 2 × 15 ml of ether. The combined ether layers were washed with 2 × 10 ml of H_2O, dried over $MgSO_4$, and concentrated in vacuo to a colorless oil which was distilled via Kugelrohr to afford 0.588 g (95%) of the epoxy ketone **3**: bp 120 °C (bath, 0.15 mm); ir (CCl_4) 1710 cm^{-1}; NMR (CCl_4) δ 1.8–2.2 (m, 2 H), 1.1–1.8 (m, 30 H), 0.9 (overlapping distorted triplets, 6 H).

6-Heneicosyn-11-one (4).[4] To a magnetically stirred solution of 0.588 g (1.83 mmol) of the epoxy ketone **3** in 4.0 ml of CH_2Cl_2 and 2.0 ml of HOAc at 0 °C was added 0.340 g (1.83 mmol) of *p*-toluenesulfonylhydrazide in one portion. After stirring at 0 °C for 3 h followed by 3 h at ambient temperature, the mixture was poured into 10 ml of water and extracted with 3 × 10 ml of hexane. The combined hexane layers were washed with 3 × 5 ml of water followed by 5 ml of saturated $NaHCO_3$. The mixture was dried over $MgSO_4$ and concentrated in vacuo to give 0.512 g of a pale yellow oil which consisted of two products by TLC on silica gel ($CHCl_3$ eluent, phosphomolybdic acid development). The major component, the desired acetylenic ketone **4** (R_f 0.6), was separated from a single major contaminant of unidentified structure (R_f 0.5) by column chromatography on 15 g of silica gel packed in hexane. The desired product was eluted with 5% ether in hexane to give 0.396 g (71%) of **4** as a colorless oil after distillation via Kugelrohr [bp 125 °C (bath) at 0.35 mm]. The product crystallized on standing: mp 26–27 °C; ir (CCl_4) 1718 cm^{-1}; NMR (CCl_4) δ 2.00–2.20 (m, 4 H), 1.1–1.8 (m, 24 H), 0.8–1.1 (overlapping distorted triplets, 6 H); mass spectrum (70 eV) *m/e* 306 (100, $M\cdot^+$), 169 [74 $(M - C_{10}H_{17})\cdot^+$], 165 [20, $(M - C_{10}H_{21})\cdot^+$], 122 [42, $(C_5H_{11}C{\equiv}C{-}CH{=}CH_2)\cdot^+$].

(*Z*)-6-Heneicosen-11-one (5). A solution of 0.361 g (1.18 mmol) of the acetylene **4** in 5 ml of MeOH containing 100 μl of pyridine was stirred under a slight positive pressure of H_2 over 35 mg of 5% Pd on $BaSO_4$. The progress of the reduction was followed by TLC on silica gel (5% ether in hexane as eluent, phosphomolybdic acid development). When the reaction was complete (~1 h) the catalyst was removed by filtration and the product (0.353 g, 97%) isolated via Kugelrohr distillation as a colorless oil which crystallized on refrigeration: bp 118 °C (bath, 0.4 mm); ir (CCl_4) 1718 cm^{-1}; NMR (CCl_4) δ 5.1–5.5 (m, 2 H), 2.3 (t, 4 H), 1.8–2.2 (m, 4 H), 1.1–1.8 (m, 24 H), 0.8–1.1 (overlapping distorted triplets, 6 H); mass spectrum (70 eV) *m/e* 308

(5, $M^{\cdot+}$), 167 (23, $C_{10}H_{19}C{\equiv}O^{\cdot+}$), 124 [100, $(C_5H_{11}CH{=}CHCH{=}CH_2{-})^{\cdot+}$].

Acknowledgments. We would like to express our gratitude to the SUNY Research Foundation for financial support and to Dr. Bruce Norcross and Mr. Jon Stickles for technical assistance. We would also like to acknowledge the assistance of Mr. Michael Kushner in the preparation of some intermediates.

Registry No.—**1**, 59434-06-9; **2**, 59434-07-0; **3**, 59434-08-1; **4**, 54844-69-8; **5**, 54844-65-4; *n*-decyl bromide, 112-29-8.

References and Notes

(1) Part 2 of a series on pheromone synthesis. For part 1 see P. J. Kocienski and R. W. Ostrow, *J. Org. Chem.*, **41**, 398 (1976).
(2) R. G. Smith, G. E. Daterman, and G. D. Daves, *Science*, **188**, 63 (1975).
(3) K. Eiter, *Fortschr. Chem. Org. Naturst.*, **28**, 204 (1970); M. Jacobson, "Insect Sex Pheromones", Academic Press, New York, N.Y., 1972; J. G. McConnell and R. M. Silverstein, *Angew. Chem., Int. Ed. Engl.*, **12**, 644 (1973); D. A. Evans and C. L. Green, *Chem. Soc. Rev.*, **2**, 75 (1973).
(4) R. G. Smith, G. D. Daves, and G. E. Daterman, *J. Org. Chem.*, **40**, 1593 (1975).
(5) A more practical reason for choosing **4** as a key intermediate is the fact that reduction to the *E* olefin using Na/NH_3 is more amenable to large scale synthesis than alternative procedures for effecting reduction to the *Z* olefin. Smith and co-workers (see ref 2) have shown that the *E* isomer is also highly attractive.
(6) R. K. Miller, D. Felix, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **53**, 1479 (1970), and references cited therein.
(7) The enol ether **1** was prepared by reaction of 2-*n*-pentylcyclohexane-1-3-dione [K. W. Rosenmund and H. Bach, *Chem. Ber.*, **94**, 2394 (1961)] with MeOH-H_2SO_4: ir (CCl_4) 1655, 1620 cm^{-1}; NMR (CCl_4) δ 3.8 (s, 3 H), 2.55 (t, 2 H), 1.7–2.3 (m, 6 H), 1.25 (br, 6 H), 0.9 (distorted t, 3 H).

Hydrogenation of Cyclic Unsaturated Oxyphosphoranes. A Novel Method for Reduction of α Diketones to Ketones

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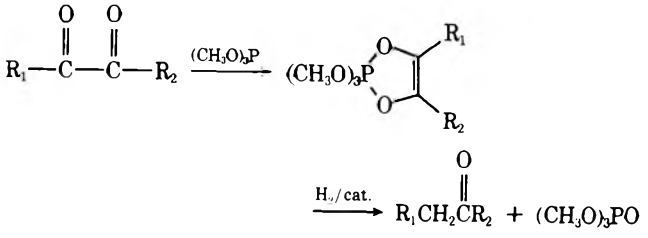
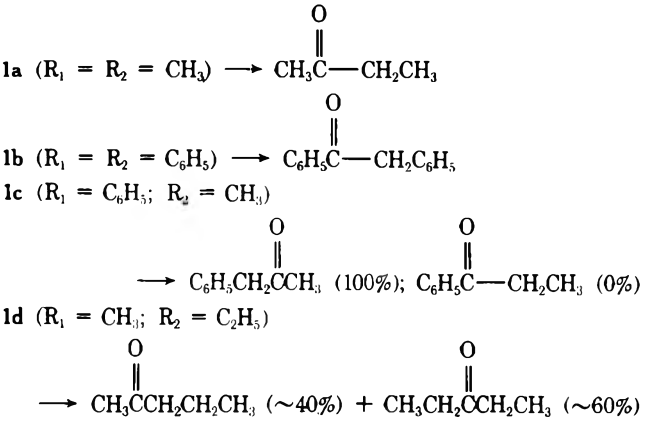
We wish to report that catalytic hydrogenation of unsaturated oxyphosphoranes such as **1** leads directly to high yields of phosphate and monoketone. Cycloadducts are obtained conveniently from diketones and phosphites.[1] Since diketones



are, in turn, available from simple monoketones, the reaction sequence shown above represents a potential solution of a difficult synthetic problem, that of ketone transposition. The procedure also offers an alternative to standard procedures for converting acyloin condensation products to monoketones.

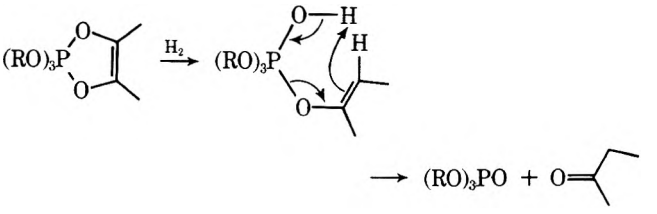
Uptake of hydrogen and yields of ketone are essentially quantitative in this reaction. Where both electronic and steric factors are contributing (example **1c**) high selectivity toward a single product is shown. In example **1d** where much lower discrimination would be expected, only a slight preference for reduction at the less hindered site is found.

This reaction appears to have little precedence in the literature. Indeed, we initiated the study with the intention of designing a method for producing stereochemically pure



erythro 1,2-diols. Alternate syntheses of the cyclic *saturated* oxyphosphoranes[3] expected from **1a** confirmed that these compounds were stable at room temperature, and, further, could be recovered unchanged after prolonged treatment under catalytic hydrogenation conditions. Therefore the saturated compound evidently does not intervene in the process to produce ketone. In earlier work it had been demonstrated by Denney[4] et al. that these cyclic saturated compounds decompose (above 100 °C) and generally yield epoxides as predominant products.

Several mechanistic rationalizations of this reaction which do not involve double bond hydrogenation may be envisaged, but they are highly speculative at this time. A simple possibility involves hydrogenolysis of the vinyl carbon–oxygen



bond, followed by the 1,5 hydrogen shift shown above. Such hydrogenolysis is documented for vinyl[5] and phenyl[6] *phosphates*, and provides precedence for the present proposal.

Experimental Section

Diketones. All diketones were available from Aldrich Chemical Co. and were purified by distillation or crystallization. Selenium dioxide oxidation of propiophenone was also employed to obtain 1-phenyl-1,2-propanedione in 60% yield.[7]

Trimethyl phosphite was distilled before each use.

Cyclic unsaturated oxyphosphoranes (1a–d) were prepared by mixing molar equivalents of trimethyl phosphite and diketone at room temperature as described by Ramirez and Desai.[1] These products were distilled or crystallized before use: **1a**, bp 36 °C (0.5 mm); **1b**, mp 48–50 °C; **1c**, bp 116–119 °C (0.9 mm); **1d**, bp 85–88 ° (10 mm).

Hydrogenations were accomplished at 1 atm H_2 over reduced PtO_2. Cyclohexane, ethyl acetate, or benzene, 5–10% in oxyphosphorane, were used as solvents. The samples typically absorb 1 molar equiv of H_2 within 2–6 h,[8] at which time H_2 uptake had slowed substantially. Hydrogenation was terminated at this point. The reaction mixtures were filtered to remove catalyst. In the case of **1a** NMR examination showed only 2-butanone and trimethyl phosphate from **1a**; **1d** showed 2- and 3-pentanone plus trimethyl phosphate. These products and product ratios were further quantified by VPC analysis. The yields were quantitative with no other products detectable. Similar analyses were performed for the products from **1b** and **1c**. The products could also be isolated by column chromatography over silica gel with ether eluent.

Saturated oxyphosphoranes were prepared from both *meso*- and *dl*-2,3-butanediol by exchange of these diols with pentaethoxyphosphorane. These procedures are described by Denney and Jones.[3] These saturated compounds could be recovered unchanged after prolonged exposure to H_2/Pt in ethyl acetate or cyclohexane.

Acknowledgment. The authors acknowledge helpful dis-

cussions with W. S. Johnson. This work was supported in part by NSF Grant MPS-75-17816.

Registry No.—**1a**, 1665-79-8; **1b**, 4850-55-9; **1c**, 1566-72-9; **1d**, 52938-47-3; 2,3-butanedione, 431-03-8; diphenylethanedione, 134-81-6; 1-phenyl-1,2-propanedione, 579-07-7; 2,3-pentanedione, 600-14-6; trimethyl phosphite, 121-45-9; 2-butanone, 78-93-3; 1,2-diphenylethanone, 451-40-1; 1-phenyl-2-propanone, 103-79-7; 2-pentanone, 107-87-9; 3-pentanone, 96-22-0.

References and Notes

(1) F. Ramirez and N. B. Desai, *J. Am. Chem. Soc.*, **82**, 2652 (1960).
(2) H. L. Riley, *J. Chem. Soc.*, 1875 (1932).
(3) For synthetic details see D. B. Denney and D. Jones, *J. Am. Chem. Soc.*, **91**, 5825 (1969).
(4) D. B. Denney et al., *J. Am. Chem. Soc.*, **93**, 4004 (1971).
(5) A. Jung and R. Engel, *J. Org. Chem.*, **40**, 3652 (1975).
(6) A. Jung and R. Engel, *J. Org. Chem.*, **40**, 244 (1975).
(7) N. Rabjohn, *Org. React.*, **5**, 331 (1949).
(8) If the diketone–phosphite adduct is not purified, hydrogenation frequently fails. We believe that this is due to contamination by phosphite which poisons the catalyst surface.
(9) Camille and Henry Dreyfus Teacher-Scholar, Alfred P. Sloan Foundation Fellow. Case Western Reserve University.

Chemiluminescent Oxidations of 4- and 7-Aminophthalide

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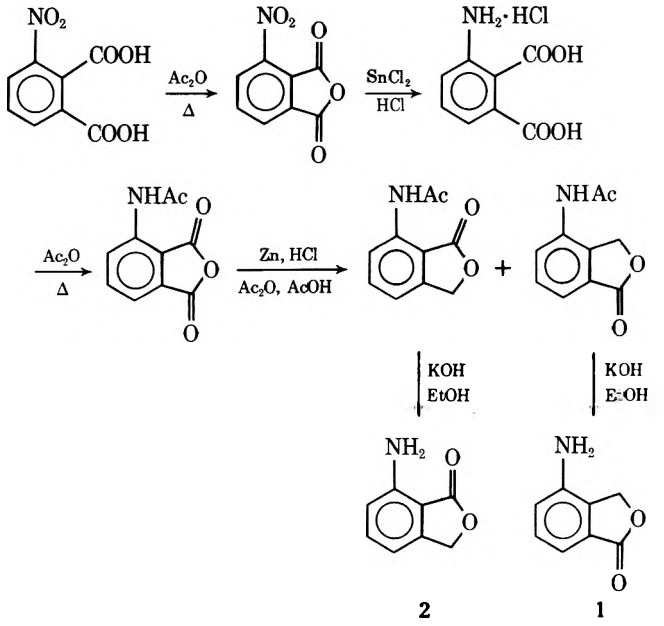
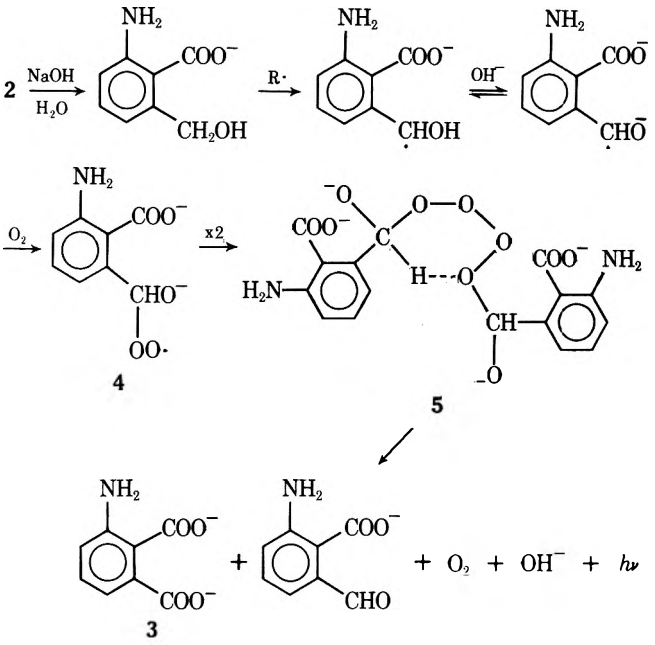
A large variety of organic compounds undergo oxidation with chemiluminescence. Acyl hydrazides are one important class of chemiluminescent substrates, with luminol (5-amino-2,3-dihydrophthalazine-1,4-dione) probably the most notable example.[2] Radical autoxidation of hydrocarbons can also lead to chemiluminescence, by disproportionation of peroxy radicals via a tetroxide intermediate.[3,4] Recently, it has been proposed that a tetroxide intermediate could play a significant role in the chemiluminescent oxidation of luminol.[5]

We have synthesized 4- and 7-aminophthalide (**1** and **2**, respectively; see Scheme I) and subjected them to free-radical autoxidation and other oxidation conditions. The aminophthalides would be expected to be oxidized to 3-aminophthalate (**3**), which has been demonstrated to be the oxidation product and the emitting species in luminol chemiluminescence.[6] The expected oxidation mechanism for the aminophthalides would be that of radical autoxidation, consistent with the mechanism established for hydrocarbon oxidations[3,4] (Scheme II). Thus, we expected to generate an independent route to the intermediates (**4** and **5**) which were suggested for the mechanism of luminol chemiluminescence.[5]

Scheme I. Synthesis of the Aminophthalides



Scheme II. Oxidation of the Aminophthalides



The 4- and 7-aminophthalides were dissolved in basic aqueous solution, which opens the lactone ring, and they were subjected to a variety of oxidants: (a) oxygen with peroxydisulfate as radical initiator; (b) hydrogen peroxide with a catalytic amount of hemin; (c) calcium hypochlorite; (d) sodium hypochlorite. In all cases, the red-brown product solution was shown by paper chromatography to be equivalent to the product mixture obtained by subjecting luminol or authentic 3-aminophthalic acid to the same conditions. We were unable to specifically isolate 3-aminophthalic acid from the reaction mixtures, however, or conclusively prove its presence. The very mild oxidation conditions necessary to isolate 3-aminophthalic acid from luminol oxidations in aqueous solution[2] were ineffective toward the aminophthalides; furthermore, the aminophthalides were unreactive in Me_2SO toward simply O_2 and base (n-$Bu_4N^+OH^-$), which is an effective procedure for isolation of aminophthalic acid in nonaqueous luminol oxidations.[2]

When either of the aminophthalides was oxidized by peroxydisulfate or H_2O_2–hemin (radical oxidants), weak chemiluninescence was observed, detected by photon counting. Treatment of either of the aminophthalides with sodium or calcium hypochlorite (ionic oxidants) led to oxidation but did not lead to any detectable chemiluminescence. Figure 1 shows the chemiluminescence yields from the aminophthalides as a function of their concentration. Steady-state analysis indicates that the chemiluminescence intensity should be proportional to concentration.[7] Maximum chemiluminescence efficiencies, which are proportional to concentration, are observed at low concentrations; these are indicated by the lines on the figure, the slopes of which are the quantum yields. Pronounced curvature was observed at higher concentrations, probably owing to absorption of some chemiluminescence by

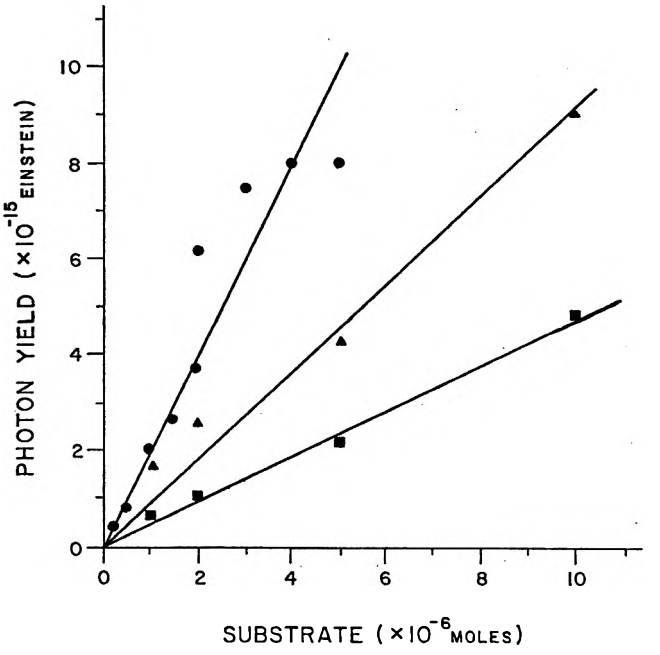


Figure 1. Chemiluminescence yields (H_2O_2–hemin oxidant): ●, 4-aminophthalide (1), $\Phi = 2 \times 10^{-9}$; ■, 7-aminophthalide (2), $\Phi = 5 \times 10^{-10}$; ▲, dimedone, $\Phi = 9 \times 10^{-10}$ (based upon luminol standard,[8] $\Phi = 1.1 \times 10^{-2}$).

the dark-colored oxidation products. The corresponding data for the chemiluminescence of dimedone (5,5-dimethyl-1,3-cyclohexanedione)[7] are also shown in Figure 1.

The quantum yields shown in Figure 1 were based upon the chemiluminescence yield from luminol under standardized conditions which permit calibration of our apparatus with respect to absolute photon yields (quantum yield = 1.1×10^{-2} einstein/mol).[8] That this calibration is still valid at these low intensities is indicated by our measured quantum yield for dimedone chemiluminescence of 9×10^{-10} einstein/mol, compared to the reported value of 2.5×10^{-10} einstein/mol (under somewhat different conditions).[7] Quantum yields for chemiluminescence from 1 and 2 were measured to be 2×10^{-9} and 5×10^{-10} einstein/mol, respectively. The fourfold greater efficiency of chemiluminescence from 1 compared to 2 indicates the significance of the neighboring amino group in determining chemiluminescence efficiency, an effect which has been noted in the chemiluminescence of luminol and its derivatives.[9] In this case, proximity of the amino group to the center undergoing oxidation enhances the efficiency of chemiluminescence.

The substantial difference in the chemiluminescence efficiency of luminol as compared to 1 or 2 suggests that the intermediates in the oxidation of 1 and 2 (i.e., peroxy radical 4 and tetroxide 5) are not the key intermediates which lead to the efficient chemiluminescence of luminol, as has been suggested.[5] The conditions of our experiments were designed to be those conditions which lead to efficient chemiluminescence of luminol.[8] Thus if peroxy radical 4 and tetroxide 5 were intermediates in the normal chemiluminescent oxidation of luminol, they should lead to chemiluminescence as effectively when produced from 2 as from luminol itself. Furthermore, dimedone was subjected to these oxidation conditions and was observed to chemiluminesce with approximately the yield reported.[7] Since dimedone reportedly undergoes chemiluminescent oxidation via the peroxy radical–tetroxide mechanism, this indicates that an authentic peroxy radical reaction works very well under these conditions, both in terms of formation of the peroxy radical and its ultimate chemiluminescence. We therefore conclude that peroxy radical intermediates are not involved in the major light-producing pathway of luminol oxidation. Since it has been reported that luminol can undergo oxidation through several different pathways,[10] the peroxy radical pathway could be one oxidation pathway for luminol; however, our data indicate that it could not be the pathway which leads to the majority of the chemiluminescence.

Experimental Section

Materials. Luminol (5-amino-2,3-dihydro-1,4-phthalazinedione) was obtained from Aldrich Chemical Co. 3-Aminophthalic acid was obtained from Alfred Bader Rare Chemicals (Aldrich). Dimedone (5,5-dimethyl-1,3-cyclohexanedione) was obtained from Matheson Coleman and Bell.

Aminophthalides. The isomeric 4- and 7-aminophthalides (1 and 2, respectively) were prepared from 3-nitrophthalic acid via 3-acetaminophthalic anhydride[11] according to the procedure of Tirouflet[12] (Scheme I). Recrystallized 4-aminophthalide had mp 150–153 °C (lit. 158 °C)[12] and gave ir and NMR spectra identical with those shown in the Sadtler Catalog (ir 19325K, NMR 10075M). Recrystallized 7-aminophthalide had mp 113–117 °C (lit. 121–123 °C)[12] and gave ir and NMR spectra identical with those shown in the Sadtler Catalog (ir 19326K, NMR 10076M).

Oxidation Procedures. Luminol, dimedone, and each of the aminophthalides were oxidized under each of the following conditions: (a) substrate dissolved in 10% aqueous NaOH maintained at 55–75 °C, saturated with O_2 by bubbling, with addition of potassium peroxydisulfate as radical initiator; (b) substrate dissolved in 10% aqueous NaOH with addition of a solution of 1×10^{-4} M hemin followed by addition of 1×10^{-1} M H_2O_2; (c) substrate dissolved in 10% aqueous NaOH with addition of an aqueous solution of 5×10^{-2} M $Ca(OCl)_2$; (d) substrate dissolved in 10% aqueous NaOH with addition of a 5% aqueous solution of NaOCl.

Oxidation product analyses were performed by paper chromatography. Luminol, both aminophthalides, and authentic 3-aminophthalic acid, when subjected to any of the oxidation conditions above, all gave comparable red-brown solutions which analyzed similarly (main component had R_f 0.9 in ether–acetone, with characteristic blue fluorescence under uv light).[2]

Chemiluminescence Measurements. Typical oxidation reactions were carried out on 2 ml of the substrate solution contained in a 1-cm Pyrex square cell in a light-tight compartment.[13] The entire compartment could be controlled in temperature, monitored by thermocouple and a Lewis Engineering Co. pyrometer-potentiometer, calibrated at 0 and 100 °C. Oxidants were added by syringe through a rubber septum without introduction of light. The chemiluminescent emission was detected by a Princeton Applied Research Model 1140A,B photon counter, with an RCA 1P28 phototube. Typical background counts were always less than 300 photons/s. Appropriate blank reactions, with all components but substrate present, always showed negligible emission. After the completion of the chemiluminescence, subsequent addition of oxidant gave no further chemiluminescence. The emission output was recorded on a Heath Model EU-200 recorder, such that either peak emission or total (integrated) emission could be determined. Total photon yields shown in Figure 1 were obtained in the following standardized manner: all photon counter and recorder settings were held constant (photon counter range 10 000 photons/s at 1.3% root mean square deviation; recorder range 1.0 V, chart speed 25 s/cm); the emission vs. time curves thus obtained were cut out and weighed for relative emission yields.

Quantum Yield Determinations. Relative integrated emission yields were converted to absolute photon yields by the method of Lee and Seliger.[8] The quantum yield of luminol chemiluminescence upon oxidation by H_2O_2 and hemin in basic aqueous solution was taken to be 1.1×10^{-2} einstein/mol.[8] The luminol chemiluminescence intensity was proportional to the luminol concentration for the intensity ranges studied; this effectively calibrated our apparatus for conversion of relative intensity to absolute photon yields.

Acknowledgments. We are pleased to acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Corporation for generous financial support of this work.

Registry No.—1, 59434-19-4; 2, 3883-64-5; luminol, 521-31-3; dimedone, 126-81-8.

References and Notes

(1) Visiting Associate Professor, University of Southern California, 1975–1976; address correspondence to this author at California State University, Fullerton.
(2) E. H. White and D. F. Roswell, *Acc. Chem. Res.*, **3**, 54 (1970).
(3) R. E. Kellogg, *J. Am. Chem. Soc.*, **91**, 5433 (1969).
(4) G. A. Russell, *J. Am. Chem. Soc.*, **79**, 3871 (1957).
(5) J. H. Baxendale, *J. Chem. Soc., Faraday Trans.* **69**, 1665 (1973).
(6) P. D. Wildes and E. H. White, *J. Am. Chem. Soc.*, **95**, 2610 (1973).
(7) J. Beutel, *J. Am. Chem. Soc.*, **93**, 2615 (1971).
(8) J. Lee and H. H. Seliger, *Photochem. Photobiol.*, **4**, 1015 (1965); **15**, 227 (1972).
(9) R. B. Brundrett, D. F. Roswell, and E. H. White, *J. Am. Chem. Soc.*, **94**, 7536 (1972).
(10) W. R. Seitz and D. M. Hercules, *J. Am. Chem. Soc.*, **96**, 4094 (1974).
(11) C. H. Wang, R. Isensee, A. M. Griffith, and B. E. Christensen, *J. Am. Chem. Soc.*, **69**, 1909 (1947).
(12) J. Tirouflet, *Bull. Soc. Sci. Bretagne*, **No. 26**, 7 (1951); *Chem. Abstr.*, **47**, 8692*g* (1953).
(13) We are grateful to Mr. Norman Nitzberg for construction of this apparatus.

An Unusual Oxidation–Reduction Reaction of Benzylbis(α-hydroxybenzyl)phosphine Oxide[1a]

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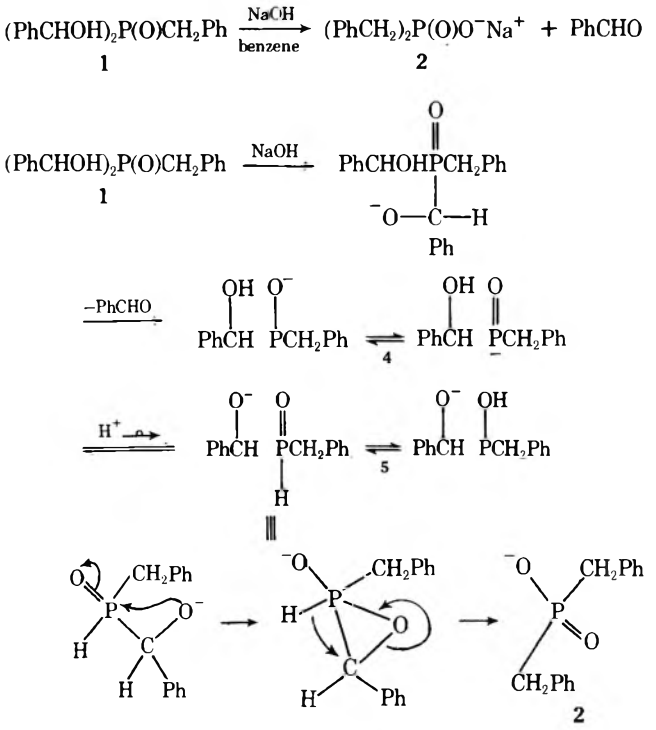
In previous publications[2–4] we have discussed the tendency of benzylbis(α-hydroxybenzyl)phosphine oxide (**1**) to undergo decomposition through the loss of benzaldehyde. Similar decompositions have been reported by other researchers.[5–7] In this work we wish to report an unusual oxidation–reduction reaction which was found to occur when **1** was treated with an equimolar amount of sodium hydroxide in refluxing benzene.

The product of this reaction (93% yield) was identified as the sodium salt of dibenzylphosphinic acid, **2**, from the NMR spectrum and elemental analysis.



Acidification of **2** with HCl caused precipitation of a white solid which was identified as dibenzylphosphinic acid (**3**) by the melting point, ir, and NMR spectra.

Our previous work[2–4] showed that **1** would react with base to eliminate benzaldehyde and form the anion of the secondary phosphine oxide **4**. A proton shift yields **5**, which can rearrange by hydride transfer from phosphorus to carbon by an intramolecular process (as shown, or a similar rearrangement, involving two molecules, which has a six-membered ring intermediate) to yield the dibenzyl phosphinate anion, **2**.

This apparent hydride transfer from phosphorus to carbon is, to our knowledge, the first of its kind in α-hydroxyalkylphosphorus compounds. Hydride transfers from phosphorus to carbon are known, however, to occur during the alkaline hydrolysis of chloromethyl phosphinates.[8] Reductions of hydroxy groups in α-hydroxyalkylphosphorus compounds have been shown to occur but these involve reducing conditions,[9] disproportionations,[10,11] or transfer of hydrogen from oxygen to carbon.[12]

Experimental Section

Reagent grade chemicals and solvents were used without further purification. The ir spectra were taken on a Perkin-Elmer 137[1d] with NaCl optics. Solid samples were run as KBr pellets, using about 1% of the sample. The NMR spectra were taken on a Varian A-60A.[1d] Elemental analyses were performed by Enviro Analytical Laboratory, Knoxville, Tenn. All melting points are uncorrected.

Benzylbis(α-hydroxybenzyl)phosphine oxide (**1**) was prepared as described in an earlier publication.[2]

Reaction of 1 with Sodium Hydroxide. A mixture of 5 mmol of **1**, 5 mmol of sodium hydroxide, and 300 ml of benzene was refluxed for 48 h. On cooling to room temperature, the solid which formed was collected (1.25 g) and washed with ether to remove benzaldehyde, the odor of which was quite noticeable above the reaction mixture. The solid was identified as the sodium salt of dibenzylphosphinic acid (**2**, 93% conversion) from the NMR spectrum and elemental analysis: NMR (D_2O) δ 2.97 (d, J = 16 Hz, 4 H, PCH_2Ph), 7.33 (m, 10 H, aromatics).

Anal. Calcd for $C_{14}H_{14}NaO_2P$: C, 62.69; H, 5.26; P, 11.55. Found: C, 62.45; H, 5.51; P, 11.36.

Acidification of an aqueous solution of **2** with HCl caused precipitation of a white solid which had mp 185–188 °C. Recrystallization from an ethanol (20 ml)–water (5 ml) mixture gave white platelets, **3**, with mp 190–191 °C (lit.[13] 191°C); ir (KBr) 2.88 (OH), 3.28 (aromatic C–H), 3.65–4.8 (broad strong P–OH), 8.5 μ (P=O): NMR (Me_2SO-d_6) δ 3.0 (d, J = 16 Hz, 4 H, PCH_2Ph), 7.22 (m, 10 H, aromatics).

Registry No.—**1**, 36871-68-8; **2**, 13422-04-3; **3**, 7369-51-9; NaOH, 1310-73-2.

References and Notes

(1) (a) Decomposition Reactions of Hydroxyalkylphosphorus Compounds. 4. For parts 1, 2, and 3 see ref 2, 3, and 4. (b) One of the facilities of the Southern Region, Agricultural Research Service, U.S. Department of Agriculture. (c) Formerly Louisiana State University in New Orleans. (d) Mention of companies or commercial products does not imply recommendations or endorsement by the U.S. Department of Agriculture over others not mentioned.
(2) A. B. Pepperman, Jr., and T. H. Siddall, III, *J. Org. Chem.*, **40**, 1373 (1975).
(3) A. B. Pepperman, Jr., and T. H. Siddall, III, *J. Org. Chem.*, **40**, 2053 (1975).
(4) A. B. Pepperman, Jr., G. J. Boudreaux, and T. H. Siddall, III, *J. Org. Chem.*, **40**, 2056 (1975).
(5) R. C. Miller, C. D. Miller, W. Rogers, Jr., and L. A. Hamilton, *J. Am. Chem. Soc.*, **79**, 424 (1957).
(6) V. S. Abramov, L. P. Semenova, and L. G. Semenova, *Dokl. Akad. Nauk SSSR*, **84**, 281 (1952); *Chem. Abstr.*, **47**, 3227 (1953).
(7) W. F. Barthel, B. H. Alexander, P. A. Giang, and S. A. Hall, *J. Am. Chem. Soc.*, **77**, 2424 (1955).
(8) C. E. Griffin, E. H. Uhing, and A. D. F. Toy, *J. Am. Chem. Soc.*, **87**, 4757 (1965).
(9) V. Ettel and J. Horak, *Collect. Czech. Chem. Commun.*, **26**, 1949 (1961).
(10) H. Hellmann, J. Bader, H. Birkner, and O. Schumacher, *Justus Liebigs Ann. Chem.*, **659**, 49 (1962).
(11) S. Trippett, *J. Chem. Soc.*, 2813 (1961).
(12) M. Reuter and C. Beerman, German Patent 2 313 307 (1974).
(13) G. M. Kosolapoff, "Organophosphorus Compounds", Wiley, New York, N.Y., 1950, p 168.

Application of Long-Range Spin–Spin Couplings in Biosynthetic Studies

Summary: The long-range ^{13}C–^{1}H couplings of anthramycin and pyrrolnitrin are utilized to locate the ^{13}C-enriched carbon atoms of the biosynthetically labeled antibiotics which were isolated from feeding experiments with L-[Me-^{13}C]methionine and DL-[alanine-3-^{13}C]tryptophan.

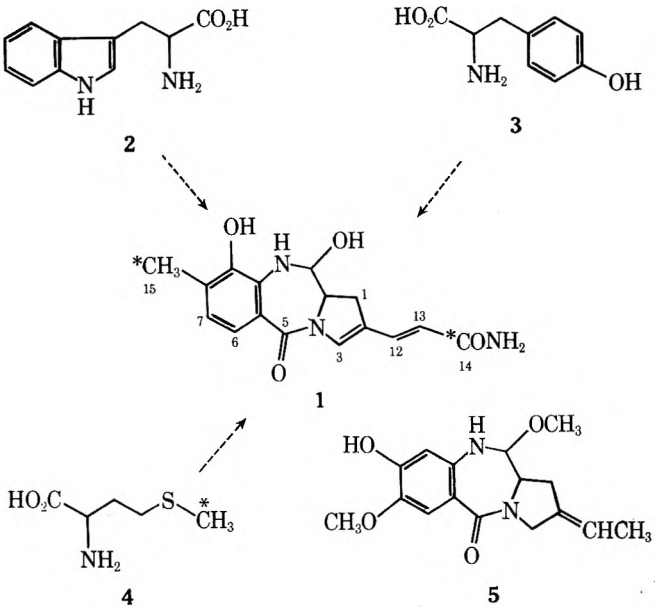
Sir: Stable isotope labeling techniques, such as NMR methods in conjunction with ^{13}C labeling, have attracted much attention as a tool in biosynthetic studies in recent years.[1] The advent of sensitive NMR spectrometers, particularly ones operating in the pulse Fourier transform mode, has provided two elegant methods, the measurement of ^{13}C–^{1}H satellite signals by proton NMR (^{1}H NMR) and ^{13}C-enriched resonance signals by carbon-13 NMR (^{13}C NMR), to detect the labeled carbon atoms. These are especially useful in biosynthetic studies of microbial metabolites because of the ease with which high enrichments can be obtained.

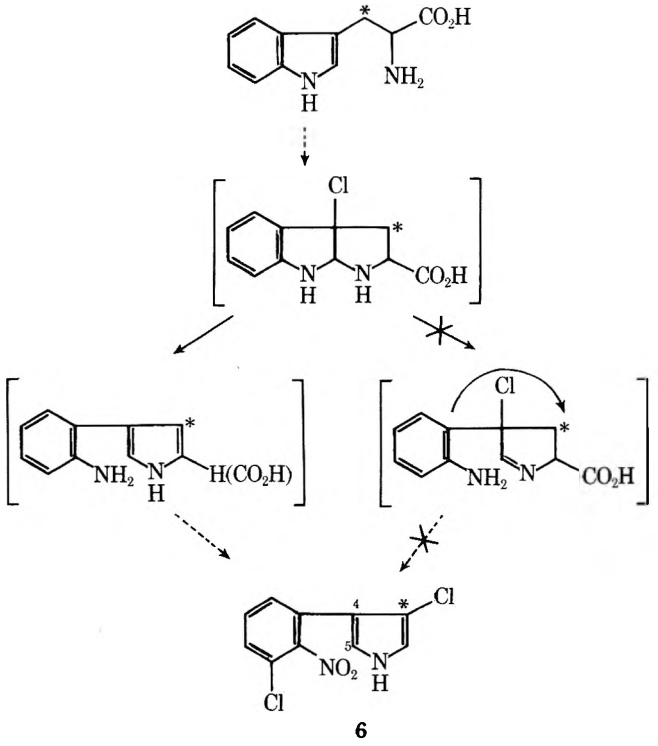
The ^{13}C NMR method generally gives more straightforward information, but access to a highly stable CMR spectrometer is still limited for many researchers and the sensitivity is relatively poor. Therefore, the ^{1}H NMR method is still valuable. On the other hand, it has been noted critically[1] that only carbon atoms with directly attached hydrogens can be analyzed for ^{13}C enrichment by ^{1}H NMR. In this communication, however, we want to illustrate that the presence of a directly attached hydrogen is not a necessary requirement for this type of analysis.

So far the major effort in the analysis of ^{13}C–proton couplings has been directed toward the determination of ^{13}C–^{1}H coupling constants through one bond,[2] which provide the basis for the classical procedure of establishing biosynthetic ^{13}C-labeling patterns by ^{1}H NMR. The ^{13}C–^{1}H long-range interactions have received little attention,[2,3] presumably because of the limited resolution of older NMR spectrometers. By virtue of the gated decoupling technique, we recently have very successfully applied specific ^{13}C–^{1}H long-range coupling information in the spectral analysis of drugs,[4] antibiotics,[5] and other organic molecules.[6] This success has led us to further explore the usefulness of long-range ^{13}C–^{1}H coupling such as in biosynthetic applications.

In a recent publication,[7] we have shown that the antitumor antibiotic anthramycin (**1**) is biosynthetically derived from tryptophan (**2**) and tyrosine (**3**) (Scheme I). Methionine (**4**) was demonstrated to contribute two C-1 units, the aromatic methyl group (C-15) and one of the two amide groups (C-5 or C-14). The ^{1}H NMR spectrum of anthramycin biosynthetically enriched from L-[Me-^{13}C]methionine (Figure 1) clearly indicates the ^{13}C satellite ($J_{C\text{-}15\text{–}H\text{-}15}$ = 126.7 Hz) in agreement with the direct ^{13}C NMR measurement. Using the direct ^{13}C NMR method, there is a possible ambiguity regarding the assignment of the two amide carbonyls which appear at 163.4 and 167.7 ppm. Our original assignment was based upon a comparison with tomaymycin (**5**). However, by means of the indirect ^{1}H NMR method we can now resolve this problem and unequivocally assign the position of the label. Comparing the ^{1}H NMR spectrum of the ^{13}C-enriched sample with that of the unenriched one, it is noticed that the H-12 signal intensity is significantly reduced relative to the H-6 signal intensity. This reduction in intensity can be ascribed to the line-broadening effect which results from the ^{13}C–^{1}H long-range coupling (^{3}J(C-14–H-12)).[8] A similar intensity reduction or line-broadening effect can also be detected in the H-13 and H-7 signals, due to the two-bond coupling between C-14 and H-13, and three-bond coupling between C-15 and H-7, respectively.[6,8] None of these long-range couplings can be measured accurately because of the limited resolution. These spectral data firmly verify our earlier ^{13}C chemical shift assignments[7] and validate the conclusion that the enriched carbon atom is located at the terminal amide group (C-14). Another illustration of this new ^{1}H NMR method is the analysis of biosynthetically ^{13}C-labeled pyrrolnitrin (**6**), an antifungal antibiotic. Previous investigations have shown that pyrrolnitrin is derived from tryptophan,[9] and that no 1,2-aryl rearrangement is involved in its biosynthesis[10] (Scheme II).

Scheme I





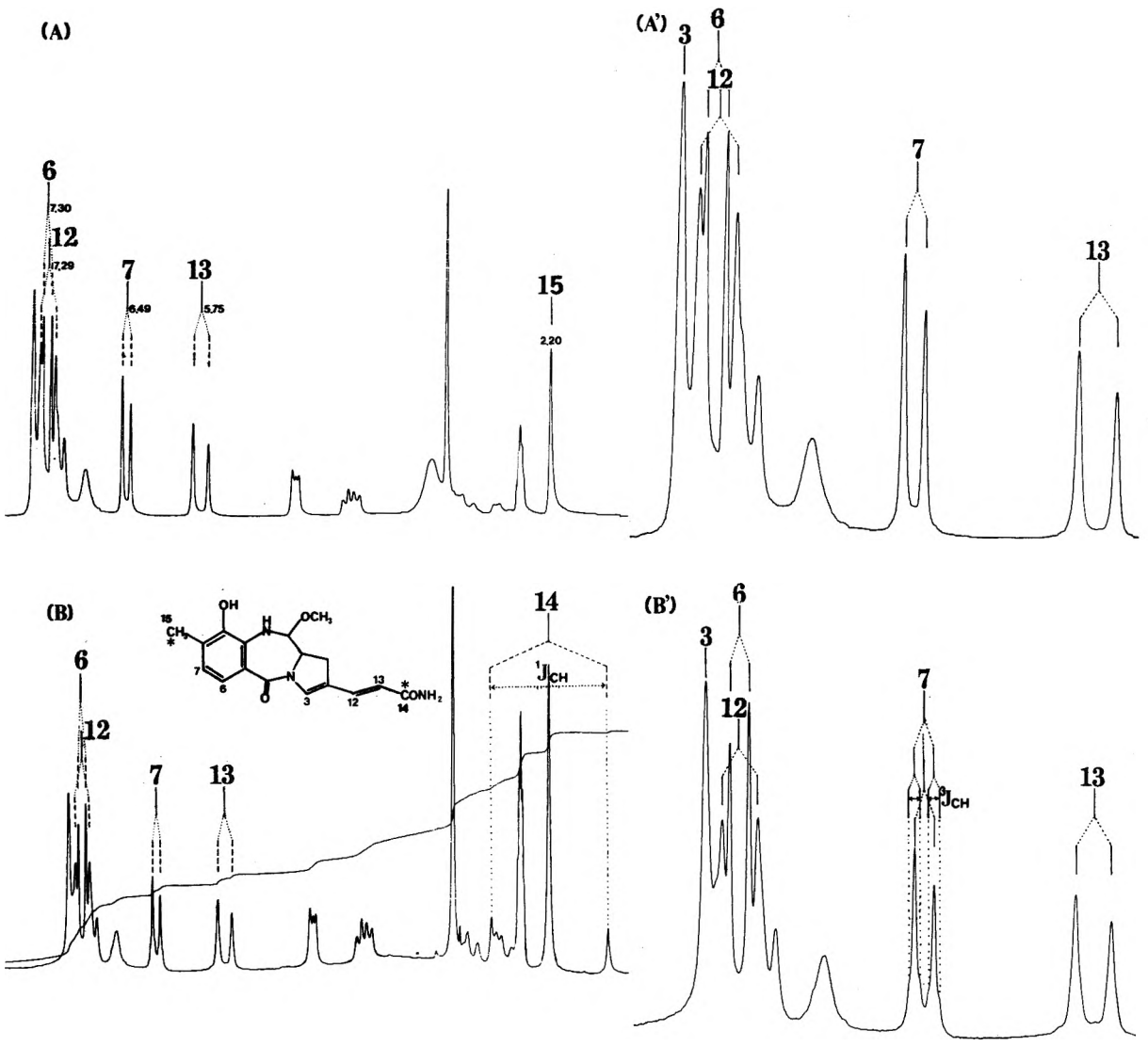


Figure 1. Proton magnetic resonance spectrum of anthramycin methyl ether in deuteriodimethyl sulfoxide solution: (A) normal sample; (A′) expanded downfield portion of (A); (B) biosynthetically ^{13}C-enriched sample; (B′) expanded downfield portion of (B).

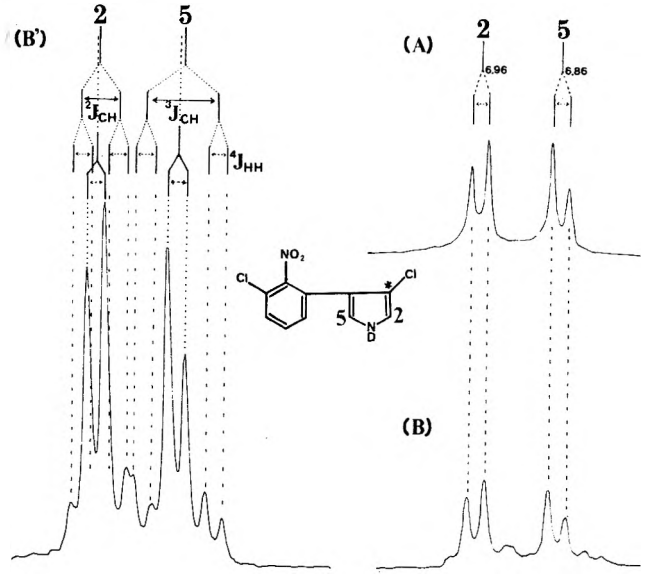


Figure 2. Proton magnetic resonance spectrum of pyrrolnitrin in deuterioacetone solution. Only the H_2 and H_5 signals are shown: (A) normal sample; (B) biosynthetically ^{13}C-enriched sample, 28.5 atom % excess ^{13}C; (B′) expanded portion of (B).

In the ^1H NMR spectrum of the pyrrolnitrin isolated from a feeding experiment with DL-[alanine-3-^{13}C]tryptophan, the H-2 and H-5 signals of the pyrrole ring display extra side bands (Figure 2) which arise from the two-bond [^2J(C-3–H-2) = 5.3 ± 0.3 Hz] and three-bond [^3J(C-3–H-5) = 9.0 ± 0.3 Hz] couplings. The assignments of the H-2 and H-5 chemical shifts are based on specific deuteration experiments.[11] Obviously, the location of the ^{13}C-enriched quaternary carbon can therefore be determined.

These results indicate that the analysis of ^{13}C–^1H long-range coupling can be very useful in biosynthetic studies. It extends the applicability of ^1H NMR spectroscopy for the determination of ^{13}C labeling patterns from only protonated carbon atoms to most nonprotonated ones. In view of the much higher sensitivity of detection of the hydrogen nucleus, this can be particularly important when only very minute amounts of enriched compound are available. We believe that other long-range couplings, for example, those of ^{15}N–^1H and ^{15}N–^{13}C, can also be profitably applied in biosynthetic studies.

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References and Notes

(1) (a) H. G. Floss, *Lloydia*, **35** 399 (1972); (b) U. Sequin and A. I. Scott, *Science*, **186**, 101 (1974); (c) A. G. McInnes and J. L. C. Wright, *Acc. Chem. Res.*, **8**, 313 (1975), and other references therein.
(2) (a) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1971; (b) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972.
(3) J. L. Marshall, D. E. Miller, S. A. Conn, R. Seiwell, and A. M. Ihrig, *Acc. Chem. Res.*, **7**, 333 (1974).
(4) (a) C. Chang, H. G. Floss, and G. E. Peck, *J. Med. Chem.*, **18**, 505 (1975); (b) C. Chang and G. E. Peck, *J. Pharm. Sci.*, **64**, in press.
(5) C. Chang, S. L. Hem, U. Hornemann, and P. Heinstein, unpublished results.
(6) (a) C. Chang, *J. Org. Chem.*, **41**, 1881 (1976); (b) C. Chang, *J. Am. Chem. Soc.*, submitted for publication; (c) C. Chang, T.-L. N. Shieh, and H. G. Floss, *J. Med. Chem.*, submitted for publication.
(7) L. H. Hurley, M. Zmijewski, and C. Chang, *J. Am. Chem. Soc.*, **97**, 4372 (1975).
(8) J. L. Marshall and R. Seiwell, *J. Magn. Reson.*, **15**, 150 (1974).
(9) (a) D. H. Lively, M. Gorman, M. E. Haney, and J. A. Mabe, *Antimicrob. Agents Chemother.*, 462 (1966); (b) R. Hamill, R. Elander, J. A. Mabe, and M. Gorman, *ibid.*, 388 (1967); (c) H. G. Floss, P. E. Manni, R. L. Hamill, and J. A. Mabe, *Biochem. Biophys. Res. Commun.*, **45**, 781 (1971).
(10) L. L. Martin, C. Chang, H. G. Floss, J. A. Mabe, E. W. Hagaman, and E. Wenkert, *J. Am. Chem. Soc.*, **94**, 8942 (1972).
(11) K. Schroder and H. G. Floss, unpublished results.

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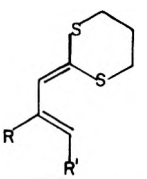
Conjugate and Diels–Alder Reactions of an Activated Allylidenedithiane

Summary: Peterson olefination of 2-methoxyacrolein and 2-lithio-2-trimethylsilyl-1,3-dithiane gives 2-(2-methoxy)-allylidene-1,3-dithiane; this compound reacts in a Michael sense with some electron-deficient unsaturated systems and in a Diels–Alder process with others.

Sir: We have been studying the preparation and utilization of extensively functionalized dienes which might impart to their cycloaddition products relatively complex oxygenation and unsaturation patterns. This facet of the Diels–Alder reaction appears not to have received the degree of study commensurate with its potentialities in organic synthesis.[1-3]

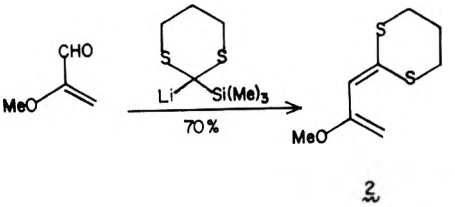
Carey and Court[4] reported the preparation of alkylated allylidenedithianes and their study as potential enophiles. For instance, compound **1a** reacts with tetracyanoethylene and



1a R = R' = Me
1b R = R' = H

with maleic anhydride to give Diels–Alder adducts. However, it does not appear to react with weaker dienophiles.

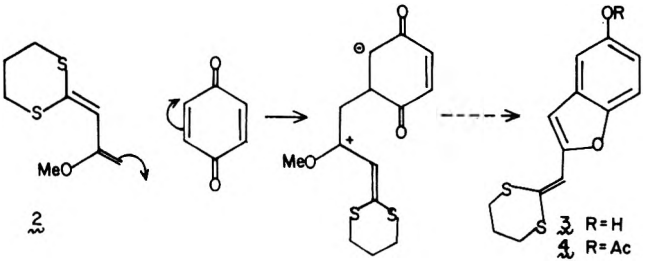
We reasoned that greater reactivity might be achieved if the terminal carbon of the allylidene group were unsubstituted, and if an additional electron-donating group were introduced at the 3 position of the diene. The synergism of such a group with the electron-donating capabilities of the sulfur atoms might be particularly helpful in promoting cycloadditions with electron-deficient dienophiles. Our precise objective thus became compound **2**.



2

In practice, Peterson olefination[5] of 2-methoxyacrolein[6] with 2-lithio-2-trimethylsilyl-1,3-dithiane[7] gave a 70% yield (distilled) of virtually[8] pure **2**: $\delta_{ppm}^{CDCl_3}$ 1.8–2.4 (m, 2), 2.8–3.1 (m, 4), 3.58 (s, 3), 4.13 (d, J = 2 Hz, 1), 4.18 (d, J = 2 Hz, 1), 6.18 (s, 1).[9] In the light of the reports of Seebach[10] that the parent compound **1b** was unstable, it was useful to discover that compound **2** can be prepared on a reasonably large scale and can be distilled [bp 92–94 °C (0.07 mm)] without serious decomposition.

Compound **2** reacts with 1,4-benzoquinone at room temperature. After 3 hr, a 62% yield of a crystalline product, mp 92–95 °C, was isolated. Its formula, $C_{13}H_{12}O_2S_2$, shows it to be a 1:1 adduct minus CH_3OH. Its infrared spectrum ($\lambda_{max}^{CHCl_3}$ 2.85 μm) suggests the presence of a hydroxyl group but lacks absorptions which are characteristic of a carbonyl group. Acetylation with pyridine and acetic anhydride gives a monoacetate, mp 95–96 °C, $\lambda_{max}^{CHCl_3}$ 5.70 μm. The NMR spectrum of this compound measured at 250 MHz [$\lambda_{ppm}^{CDCl_3}$ 2.05–2.20 (m, 2), 2.23 (s, 3), 2.85–3.05 (m, 4), 6.69 (s, 1), 6.83 (s, 1), 6.91 (d, d, J_1 = 8.0 Hz, J_2 = 2.5 Hz, 1), 7.20 (d, J = 2.5 Hz, 1), 7.35 (d, J = 8 Hz, 1)] defines its structure to be **4**.[9]



2 **3** R = H **4** R = Ac

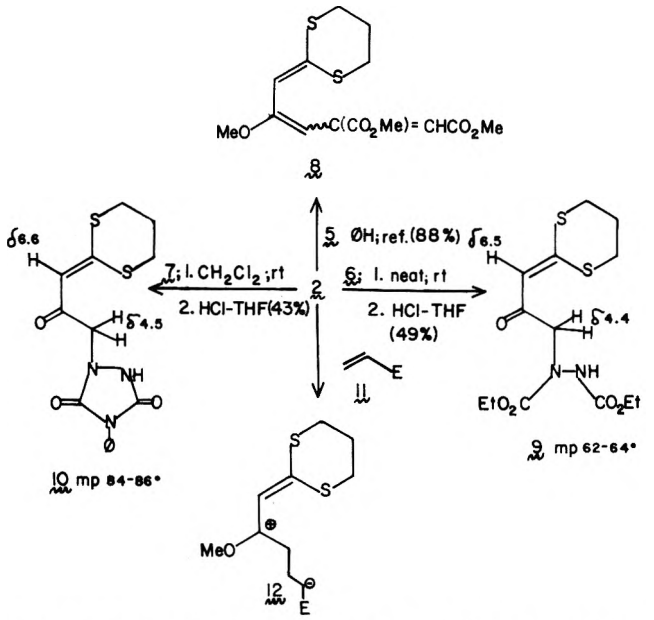
The formation of benzofuran **3** corresponds to Michael addition of diene **2** to the quinone followed by cyclization (with elimination of methanol) and tautomerization in unspecified order. Such a sequence finds analogy in the reaction of ketene acetals with quinones.[11]

The tendency of compound **2** to participate in Michael-type processes was also exhibited in its reactions with dimethyl acetylenedicarboxylate (**5**), diethyl azodicarboxylate (**6**), and 4-phenyl-2,4-triazoline-3,5-dione (**7**)[12] to give **8**,[9] **9**,[9] and **10**,[9] in the yields shown in Scheme I. In the latter two cases, homogeneous products were obtained as the ketones after hydrolysis of the intermediate enol ethers with dilute acid. Though full accounting of the reaction course was not achieved owing to the formation of complex products,[13] we found no evidence for the formation of any [4 + 2] cycloaddition adducts from these reactions.

These results may be understood in terms of the strongly nucleophilic character of diene **2** which is attacked by highly reactive unsaturated electrophiles (cf. **11**) in orientational arrangements which are not suitable for concerted cycloaddition. Dipolar structures of the type **12** which are produced find other pathways for charge dissipation which are of lower energy than cyclization.

On the basis of the arguments cited above, it seemed possible that *less reactive electrophiles might be more prone to give Diels–Alder products.* It was hoped that cycloaddition, which presumably requires more exacting orientational ar-

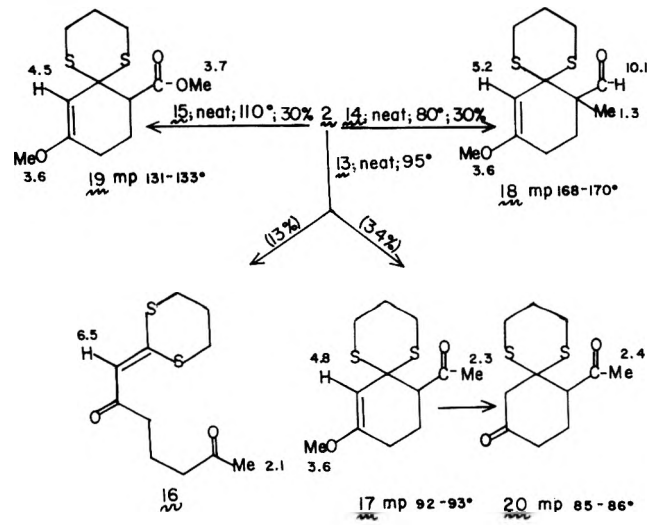
Scheme I



rangements in the alignment of the diene and the dienophile,[14] could be possible if the "electrophile" is of insufficient energy to react via a conjugate addition (one-bond) pathway. The latter process, while less entropically demanding, does, of course, require the sustenance of charged (or radical) intermediates.

While the reasoning advanced above must be regarded as conjectural, in practice *compound 2 does participate in Diels–Alder reactions with methyl vinyl ketone (13), methacrolein (14), and methyl acrylate (15).* In the case of the reaction of 2 + 13, a 13% yield of Michael-type product **16** was obtained along with the cycloaddition compound, **17.** In the reactions of 14 and 15 no Michael products were detected, though the complexity of the reaction mixtures[13] rules out a definite statement in this regard. The structures of compounds **16–19**[9] are rigorously proven by their infrared, NMR, and mass spectra. Pertinent reaction conditions and yields, as well as diagnostically valuable NMR chemical shifts (as $\delta_{ppm}^{CDCl_3}$ from tetramethylsilane) are given in Scheme II. Though

Scheme II



of limited scope, diene 3 may be regarded as a synthetic equivalent of $^{+}C(O)CH_2C(O)C^{-}H_2$.[15] It will be noted that, in products **17, 18,** and **19,** three carbonyl systems are produced in varying, but differentiated, states of exposure. While the synthetic value of such systems remains to be demonstrated, we note already that compound **17** reacts with aqueous HCl in THF, to give the specifically monoprotected 1,3,5 triketone **20** in 87% yield.

Studies involving the utilization of such systems as well as the exploration of new highly functionalized dienes are in progress and will be described in due course.

Acknowledgments. This research was supported by PHS Grant CA-12107-12. NMR spectra were obtained on instrumentation supported by R.R.-00296-06. Mass spectral measurements were made by Mr. Glen Herman. An unrestricted Award from the CIBA-GEIGY Corporation is gratefully acknowledged.

Supplemental Material Available. Experimental procedures for these reactions (4 pages). Ordering information is given on any current masthead.

References and Notes

(1) S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96,** 7807 (1974).
(2) S. Danishefsky and T. Kitahara, *J. Org. Chem.*, **40,** 538 (1975).
(3) For the synthesis of vernolepin, largely based on this concept, see S. Danishefsky, T. Kitahara, P. F. Schuda, and S. J. Etheredge, *J. Am. Chem. Soc.*, **98,** 3028 (1976).
(4) F. A. Carey and A. J. Court, *J. Org. Chem.*, **37,** 4474 (1972).
(5) D. J. Peterson, *J. Org. Chem.*, **33,** 780 (1968).
(6) G. A. Russell and M. Ballenegger, *Synthesis,* 104 (1973).
(7) (a) F. A. Carey and A. S. Court, *J. Org. Chem.*, **37,** 1926 (1972); (b) D. Seebach, B. Th. Grobel, M. Braun, and K. H. Geiss, *Angew. Chem., Int. Ed. Engl.*, **11,** 443 (1972); (c) F. Jones and M. F. Lappert, *J. Chem. Soc., Chem. Commun.*, 526 (1972).
(8) The NMR spectrum indicates a few percent of impurity containing a trimethylsilyl group.
(9) The structure of this compound is in accord with its infrared, NMR, and high resolution mass spectra.
(10) D. Seebach, M. Kolb, and B.-Th. Grobel, *Angew. Chem., Int. Ed. Engl.*, **12,** 69 (1973).
(11) (a) S. M. McElvain and E. L. Engelhardt, *J. Am. Chem. Soc.*, **66,** 1077 (1944); (b) S. M. McElvain, E. R. Degginger, and J. D. Behun, *ibid.*, **76,** 5736 (1954); (c) J. Banville, J. L. Grandmaison, G. Long, and P. Brassard, *Can. J. Chem.*, **52,** 80 (1974).
(12) R. C. Cookson, S. S. H. Gilani and I. D. R. Stevens, *Tetrahedron Lett.*, 615 (1962).
(13) Many of the reactions of compound **2** with electrophiles are characterized by the formation of intense colors and apparently high molecular weight products. The possibility of direct electron transfer from **2** to give cation and anion radical intermediates and extensive polymerization seems likely.
(14) For a recent discussion, see K. N. Houk, *Acc. Chem. Res.*, **8,** 371 (1975). We thank Professor Houk for a useful exchange of correspondence on our work.
(15) Compound **2** appears to be the first 3-oxygenated vinylketene equivalent for Diels–Alder reactions. For simple vinylketene equivalents in Diels–Alder reactions, see (a) E. J. Corey and A. P. Kozikowski, *Tetrahedron Lett.*, 2389 (1975); (b) E. Sonveaux and L. Ghosez, *J. Am. Chem. Soc.*, **95,** 5417 (1973).

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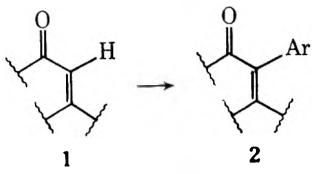
α-Arylation of α,β-Unsaturated Ketones. Utilization of the α-Epoxytosylhydrazone Functional Group as a Δ^2-Enonium Synthon

Summary: The sequential reaction of α-epoxytosylhydrazones (easily available in two steps from α,β-unsaturated ketones) with *n*-butyllithium (1.0 equiv) followed by phenylcopper (1.2 equiv) yields α-aryl-β-hydroxytosylhydrazones which may be dehydrated and hydrolyzed to produce α-aryl α,β-unsaturated ketones.

Sir: In connection with a synthetic project, we required methodology for the α-arylation of α,β-unsaturated ketones (**1** → **2**).[1,2]



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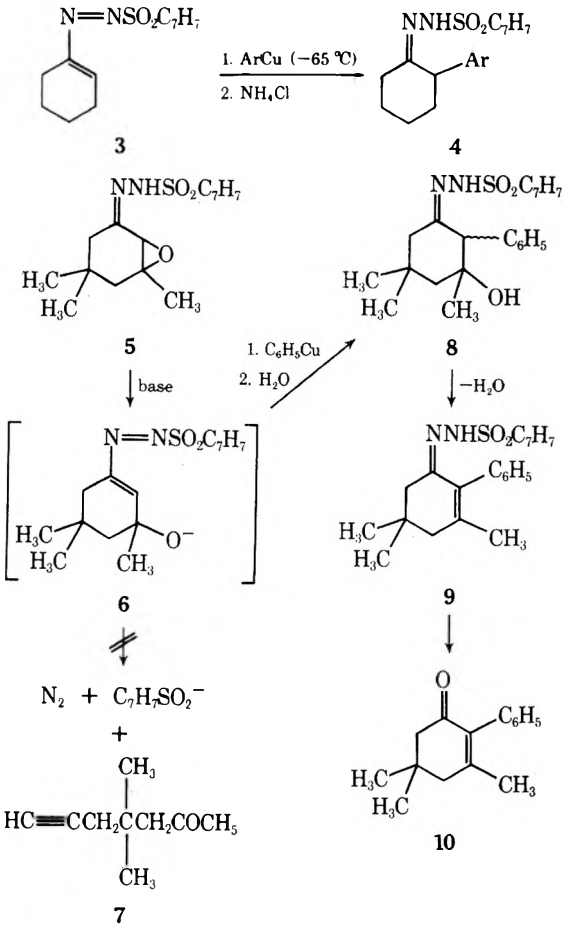
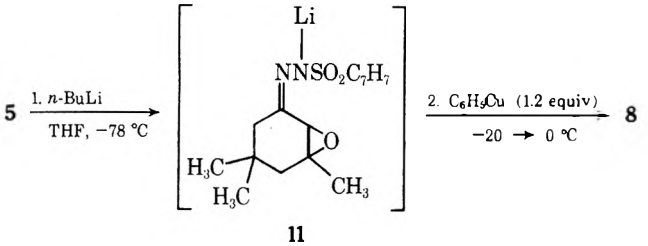
Our previous observation that the reaction of arylcopper reagents with tosylazoenes (**3**) resulted in a facile synthesis of α-aryltosylhydrazones (**4**) suggested a possible solution to



this problem.[3] It is well known that the base- (and acid-) catalyzed fragmentation reaction of α-epoxytosylhydrazones (**5** → **7**) proceeds via an azoene intermediate (**6**);[4,5] therefore, if azoene intermediates could be generated *in the presence* of an arylcopper reagent, they should be smoothly intercepted to yield an α-aryl-β-hydroxytosylhydrazone (**8**). Dehydration (to **9**) and hydrolysis should, in turn, produce the desired enone **10**.

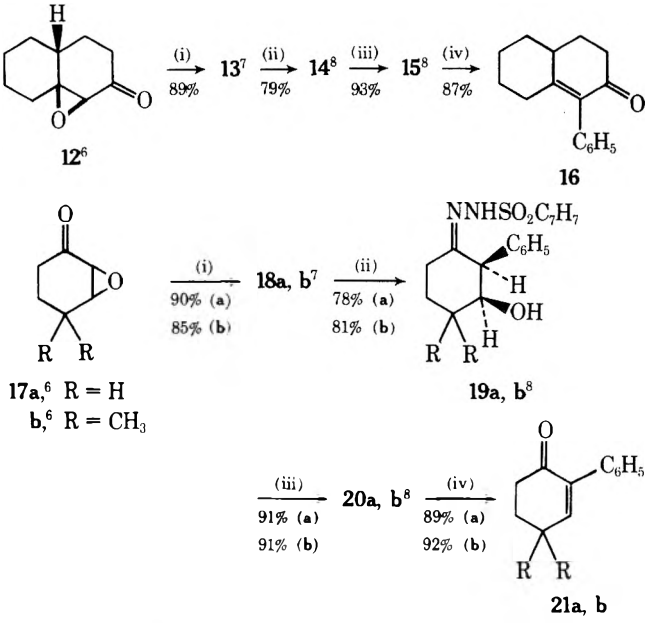
We are pleased to report that this is indeed the case. Reaction of isophorone oxide[6] with a suspension of tosylhydrazine (18 h, room temperature) in ether produces the insoluble crystaline α-epoxytosylhydrazone **5**[7] (95%). Addition of **5** to



11

a tetrahydrofuran (THF) solution of phenylcopper (2.5 equiv, solubilized as its diisopropyl sulfide complex) at −20 °C, followed by warming to 0 °C (over 1.5 h), produces the α-phenyl-β-hydroxytosylhydrazone **8** (80%).[8] Since this procedure has the attendant disadvantage of being wasteful with respect to the phenylcopper reagent and since our eventual application demands the use of a more highly functionalized arylcopper species, we required an alternate procedure (see Experimental). α-Epoxytosylhydrazone **5** (THF, −78 °C) is treated with *n*-butyllithium (1.0 equiv, dipyridyl indicator[9]) to produce a solution of the α-epoxytosylhydrazone anion **11** (−78 °C). The soluble phenylcopper reagent is added to this solution (−78 °C) and the reaction is allowed to warm to 0 °C (−20 → 0 °C, 1.5 h)[10] in order to again produce the phenylated product **8** (85%). Dehydration of **8** (C_6H_6, reflux, 0.5 h) produces α,β-unsaturated tosylhydrazone **9**[8] (95%) which can be smoothly converted to enone **10**[11] (94%) via carbonyl exchange.[12,13]

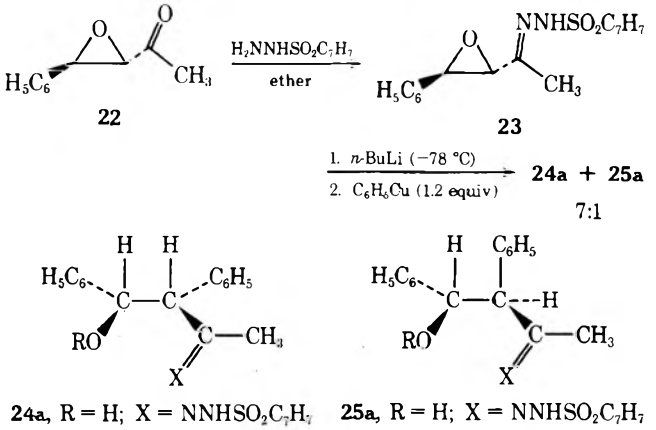
Epoxy ketones **12**, **17a**, and **17b** are also easily transformed to α-arylenones **16**, **21a**, and **21b** by application of the above methodology. The α-phenyl-β-hydroxytosylhydrazones (**8**, **14**, **19a**, **19b**) are all isolated as a single isomer in the four cases



Reagents: (i) $H_2NNHSO_2C_7H_7$/ether; (ii) (1) *n*-BuLi (−78 °C), (2) C_6H_5Cu (1.2 equiv), −20 °C; (iii) C_6H_6, Δ; (iv) $BF_3{\cdot}Et_2O$, H_2O, $(CH_3)_2CO$.

examined. Although the stereochemistry of **8** or **14** has not yet been established, **19a** and **19b** appear to have the hydroxyl and phenyl groups in a cis relationship ($J_{2,3}$ = 2.5 Hz).[14]

The chemistry of an acyclic example further documents the utility of this arylation reaction. Although acyclic α-epoxytosylhydrazones cannot be prepared in polar solvents owing to intramolecular pyrazoline formation,[7b] the conversion of **22** to **23**[7c] using ether/tosylhydrazine[7a] presents no difficulties

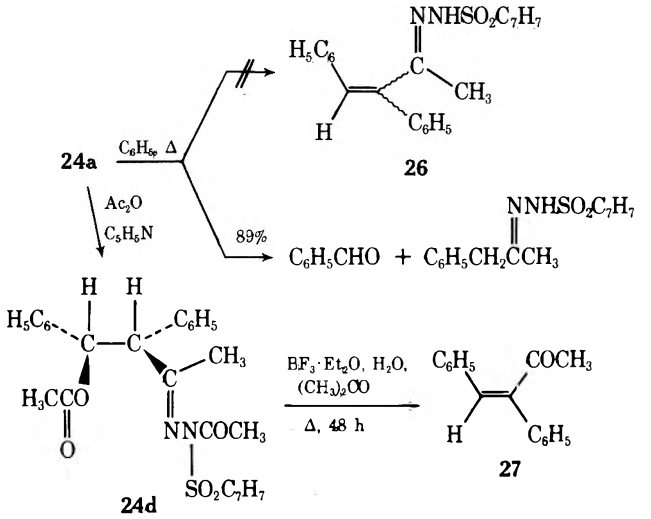


24a, R = H; X = $NNHSO_2C_7H_7$
b, R = H; X = O
c, R = $COCH_3$; X = O

25a, R = H; X = $NNHSO_2C_7H_7$
b, R = H; X = O
c, R = $COCH_3$; X = O

(85%). Sequential reaction of **23** with *n*-butyllithium and phenylcopper provides *erythro*-α-phenyl-β-hydroxytosylhydrazone (**24a**,[8] 60%). Hydrolysis[12] of **24a** provides *erythro*-β-hydroxy ketone **24b**[8,15] (60%), which can be converted to acetate **24c**[8] [$(CH_3CO)_2O/C_5H_5N$, 98%] for the purpose of spectral assignment.[16] The isomeric *threo*-tosylhydrazone **25a** has not been directly isolated from this reaction, but its presence (~10%[17]) has been inferred by isolation of *threo*-β-hydroxy ketone **25b**[8] (6%) by hydrolysis[12] and chromatography of the **24a** reaction residues (7% **24b** also isolated). This places the value of the **24a:25a** ratio for the phenylation reaction at ~7:1.

An additional complication exists with the acyclic example. Attempted dehydration of **24a** (C_6H_6, reflux, 6 h) produces no unsaturated tosylhydrazone (**26**), but, instead, **24a**



undergoes retro-aldol reaction. This difficulty is overcome by conversion of **24a** to the bisacetyl derivative **27d**[7] ($(CH_3CO)_2O/C_5H_5N$, 98%) which, in turn, can be converted to the thermodynamically more stable enone **27** by a single-step hydrolysis–elimination reaction (80%).[18]

Although the primary goal of this investigation was to provide methodology for the α-arylation of α,β-unsaturated ketones, the α-aryl-β-hydroxytosylhydrazones and α,β-unsaturated tosylhydrazones produced via the azoene route should serve equally well as precursors for previously established tosylhydrazone transformations.[19]

Acknowledgment. I wish to thank Eli Lilly and Co. for a Young Faculty Grant.

Supplementary Material Available. General experimental, characterization information, and spectral data (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) A recent paper details a method for the α-alkylation of α,β-unsaturated ketones via the reaction of lithium dialkylcuprates (5 equiv) with α-epoxy oximes: E. J. Corey, L. S. Melvin, Jr., and M. F. Haslanger, *Tetrahedron Lett.*, 3117 (1975).

(2) (a) Another method for the α-arylation (and alkylation) of enones is based on the reaction of Grignard reagents with α-epoxydimethylhydrazones: G. Stork and A. Ponaras, *J. Org. Chem.*, following paper in this issue. (b) See also A. Ponaras, *Diss. Abstr.*, **34**, 145 (1973). (c) We are very grateful to Dr. Stork and Dr. Ponaras for providing us these results prior to publication.

(3) C. E. Sacks and P. L. Fuchs, *J. Am. Chem. Soc.*, **97**, 7372 (1975).

(4) (a) A. Eschenmoser, D. Felix, and G. Ohloff, *Helv. Chim. Acta*, **50**, 708 (1967); (b) J. Schreiber, D. Felix, A. Eschenmoser, M. Winter, F. Gautschi, K. H. Schulte-Elte, E. Sundt, G. Ohloff, J. Kalvoda, M. Kaufmann, P. Wieland, and G. Anner, *ibid.*, **50**, 2101 (1967); (c) P Wieland, H. Kaufmann, and A. Eschenmoser, *ibid.*, **50**, 2108 (1967); (d) M. Tanabe, D. F. Crowe, R. L. Dehn, and G. Detre, *Tetrahedron Lett.*, 3739 (1967); (e) M. Tanabe, D. F. Crowe, and R. L. Dehn, *ibid.*, 3943 (1967); (f) D. Felix, J. Schreiber, G. Ohloff, and A. Eschenmoser, *Helv. Chim. Acta*, **54**, 2896 (1971); (g) E. J. Corey and H. S. Sachdev, *J. Org. Chem.*, **40**, 579 (1975).

(5) Addition (and base-catalyzed) reactions of lithium reagents with azoenes generated from *N,N*-ditosylhydrazones have been previously reported: J. F. W. Keana, D. P. Dolata, and J. Ollerenshaw, *J. Org. Chem.*, **38**, 3815 (1973).

(6) Prepared from the corresponding enone by the method of R. L. Wasson and H. O. House, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 552.

(7) (a) This mild procedure appears to be generally applicable for the preparation of high-purity α-epoxytosylhydrazones in excellent yields. Difficulties associated with preparation of this compound class in polar solvents or in the presence of acid catalysts are well documented.[4,7b] α-Epoxytosylhydrazones are best kept in the freezer for extended storage. (b) A. Padwa, *J. Org. Chem.*, **30**, 1274 (1965). (c) Melting points (°C, all with decomposition, $-N_2$): **5**, 90–91; **12**, 86–87; **17a**, 117–118.5; **17b**, 89–90; **23**, 123–125.

(8) (a) This material exhibits spectra (ir, NMR) and analysis (CHNS or CH) in accord with its assigned structure. (b) Melting point and TLC R_f values for these compounds can be found in the microfilm version.

(9) S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

(10) The solution of anion **11** appears to be stable at temperatures below *ca.* −30 °C (TLC analysis). The temperature (−20 °C) at which the phenylation reaction proceeds appears to be the same temperature at which epoxide fragmentation occurs *in the absence of phenylcopper*. This observation is consistent with the epoxide fragmentation being the rate-determining step for the overall process. (Simpler azoenes are phenylated within 1 min at −65 °C[3].)

(11) (a) This material exhibits spectra (ir, NMR, mass) and analysis (exact mass) in accord with its assigned structure. (b) Melting points (°C): **2**, 86–87; **16**, 77–78; **21a**, 94–95 (lit.[11c] 94–95); **21b**, oil (lit.[11c] oil); **27**, 54–55 (lit.[11d] 55–556). (c) H. Born, R. Pappo, and J. Szmuszkovicz, *J. Chem. Soc.*, 1779 (1953). (d) H. E. Zimmerman, L. Singer, and B. S. Thyagarajan, *J. Am. Chem. Soc.*, **81**, 108 (1959).

(12) C. E. Sacks and P. L. Fuchs, *Synthesis*, in press.

(13) Direct hydrolysis[12] of **8** is less satisfactory. Several other minor uncharacterized products contaminate a mixture of β-hydroxy ketone and enone **10**.

(14) The Corey[1] and Stork[2] procedures give products of trans stereochemistry. The synthetic and mechanistic consequences of this observation are under further investigation.

(15) Benzaldehyde and phenylacetone (20–25% each) are also produced in this reaction.

(16) See supplimentary material for the spectral assignments.

(17) This estimation is based on the assumption that the hydrolysis reaction[12] is equally efficient (~60%) for both isomers.

(18) If this reaction is conducted for shorter periods of time or at a lower temperature, significant amounts (40–50%) of acetate **24c** may be isolated in addition to enone **27**.

(19) (a) For example, tosylhydrazones **9** and **15** serve as excellent substrates for the Dauben–Shapiro diene synthesis.[19b] Treatment of **9** and **15** (in THF, −78 °C) with lithium diisopropylamide[19c,d] (2.5 equv), followed by warming to room temperature (1.5 h), produces 2-phenyl-1,5,5-trimethyl-1,3-cyclohexadiene (90%) and 1-phenyl-4,4a,5,6,7,8-hexahydronaphthalene (85%), respectively. (b) W. G. Dauben, M. E. Lorber, N. D. Vietmeyer, R. H. Shapiro, J. H. Duncan, and K. Tomer, *J. Am. Chem. Soc.*, **90**, 4762 (1968). (c) G. E. Gream, L. R. Smith, and J. Meinwald, *J. Org. Chem.*, **39**, 3461 (1974). (d) E. Vedejs and R. A. Shepherd, *J. Org. Chem.*, **41**, 742 (1976).

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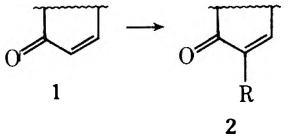
α-Alkylation and Arylation of α,β-Unsaturated Ketones

Summary: The *N,N*-dimethylhydrazones of α,β-epoxy ketones react with aryl and alkyl Gringnard reagents to produce intermediates β-hydroxyhydrazones which are dehydrated to α-aryl or α-alkyl enones; the scheme represents a method for the introduction of alkyl and aryl groups on the α carbon of an α,β-unsaturated ketone.

Sir: The introduction of carbon substituents on the α carbon of an α,β-unsaturated ketone, with preservation of the α,β unsaturation (**1** → **2**), can often be carried out by formation

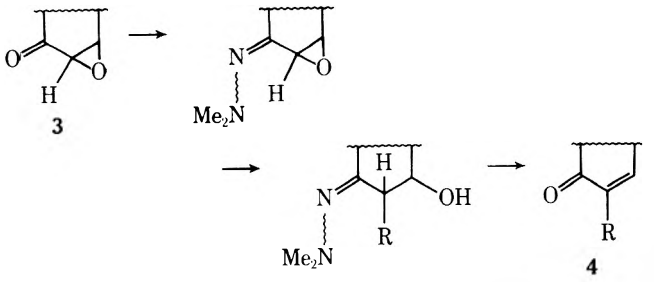


1 2

of the thermodynamic enolate ion, followed by treatment with an alkyl halide.[1] The method is not applicable, however, inter alia, (a) when the α,β-unsaturated ketone is incapable of

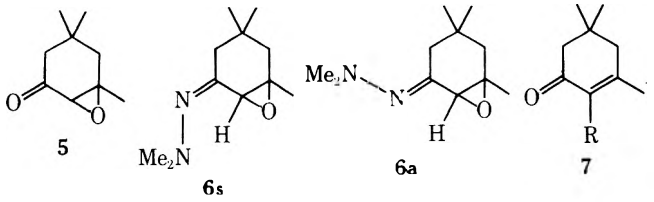
enolization toward the γ carbon, (b) when the equilibration conditions are incompatible with sensitive functions in the molecule, and (c) when the desired α substituent is an aryl group.[2]

We now describe a solution to this problem.[3] Treatment of the *N,N*-dimethylhydrazone of the epoxy ketone corresponding to the initial α,β-unsaturated ketone with a primary alkyl or aryl Grignard reagent leads, after hydrolysis, to the desired α-alkylated or arylated enone. The sequence is shown in **3** → **4**.[4]



We illustrate tlhe process in detail with isophorone oxide[5] **5**: treatment of **5** with 2 equiv of *N,N*-dimethylhydrazine and 0.5 equiv of propionic acid (ethyl acetate, 0 °C, 40 min)[6] and work-up (10% aqueous sodium carbonate) gave the *N,N*-dimethylhydrazone **6** in 95% yield, as a 1:1 mixture of syn and anti isomers [δ 0.84 (s, 3 H), 0.93, 0.95 (2 s, ratio 45:55, 3 H), 1.32 (s, 3 H), 1.4–2.2 (m, 4 H), 2.38, 2.44 (2 s, ratio 1:1, 6 H), 3.14, 3.89 (2 s, ratio 1:1, 1 H);[7] mass spectrum *m/e* 196.1561]. Assignment of the δ 3.89 resonance to the syn isomer **6s** was made by irradiation at δ 2.41 which produced nuclear Overhauser effect enhancement of the δ 3.89, but not the 3.14, resonance.

Reaction of the epoxyhydrazone **6** with 1.5 equiv of phenylmagnesium bromide (tetrahydrofuran, 0 °C → room temperature, 1.5 h), followed by hydrolysis of the crude product by refluxing with 3 M hydrochloric acid in 50% aqueous ethanol for 1 h, gave (77% yield)[8] 2-phenylisophorone **7** (R =

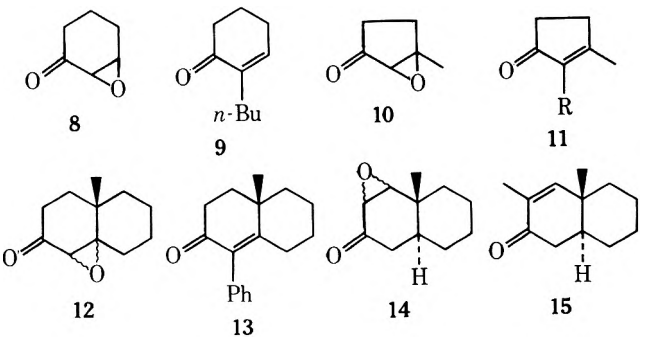


phenyl) [mp 85.5–87 °C, ir (film) 5.98, 6.11 μm; δ 1.09 (s, 6 H), 1.78 (s, 3 H), 2.26 (s, 2 H), 2.29 (br s, 2 H), 6.80–7.30 (m, 5 H); mass spectrum *m/e* 214.1353].

The dimethylhydrazone group can also be removed via ozonolysis (methylene chloride, 0 °C) and the resulting β-hydroxy ketone dehydrated with either acid or base. Alternatively, treatment of the crude Grignard reaction product with methyl iodide in acetonitrile at room temperature, followed by evaporation of solvent and hydrolysis of the residual quaternary salt in refluxing 90% aqueous 2-methoxyethanol containing a weak inorganic base (e.g., formate), gives the α,β-unsaturated ketone.[9] Yields via these procedures were comparable with those obtained using direct acid hydrolysis.

The synthesis of **7** (R = methyl,[10] butyl,[11] and 3-methoxyphenethyl) was carried out via the corresponding Grignard reagents to give **7** in yields of 63, 65, and 61%. respectively,[8] from the epoxy ketone **5**.

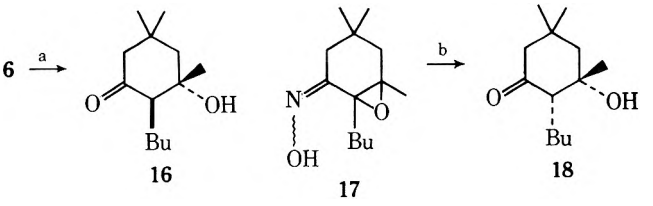
Cyclohexenone oxide (**8**) was transformed into 2-butylcyclohexenone (**9**) in 45% yield; there was no evidence of attack of the Grignard reagent on the epoxide at the β position. The epoxide **10** from 3-methylcyclopentenone was transformed



by the same process into 3-methyl-2-phenylcyclopentenone (**11**, R = phenyl) in 53% yield, and also into the known dihydrojasmone[12] (**11**, R = n-C_5H_{11}) in 51% yield.

The two epoxides, **12**, from 10-methyl-$\Delta^{1,9}$-2-octalone[13] were separately converted in a similar sequence to the 1-phenyl derivative **13**, mp 80–82 °C. The yield was higher (63%) from the dimethylhydrazone of the β-oxide than that from the more slowly reacting α-oxide (47%). The two epoxides, **14**, were separately converted to the known[14] *trans*-3,10-dimethyl-Δ^3-2-octalone (**15**), in 53% overall yield from the α-oxide[15] and 40% overall yield from the β-oxide.[19]

We have made some attempts to determine the mechanism of the reaction and have established that, at least in the isophorone series, the initial opening leads stereospecifically to inversion at the α carbon of the epoxyhydrazone. This was demonstrated by comparing the two (different) β-hydroxy ketones **16** and **18** obtained, respectively, by (a) ozonolysis of



the reaction product of the dimethylhydrazone of isophorone oxide with butylmagnesium bromide and (b) by sodium borohydride reduction, followed by ceric ion cleavage,[21] of the oxime of 2-butylisophorone oxide (**17**).[22] The two substances were clearly isomeric [*m/e* 212 (M^+)],[23] and both gave 2-butylisophorone (**7**, R = butyl) on acid-catalyzed dehydration.

These facts are compatible with direct displacement on the epoxide although they do not rule out an a priori possible elimination–addition mechanism.[24]

Acknowledgment. We thank the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this work.

References and Notes

(1) Cf. J. M. Conia, *Rec. Chem. Prog.*, **24**, 43 (1963); H. O. House, "Modern Synthetic Reactions", second ed, W. A. Benjamin, New York, N.Y., 1972, Chapter 9.

(2) For an alternative sequence which, however, should have fairly strict conformational requirements, cf. S. Julia and C. Moutonnier, *Bull. Soc. Chim. Fr.*, 321 (1964). A different method which proceeds from α,β-epoxy ketones involves alkylation of the enolate from calcium–ammonia reduction: J. D. McChesney and H. F. Wycpalek, *J. Chem. Soc., Chem. Commun.*, 542 (1971). This method is obviously not readily applicable to α-arylation.

(3) A. A. Ponaras, *Diss. Abstr.*, **34**, 145 (1973); *Chem. Abstr.*, **79**, 105038 (1973).

(4) The reaction is not useful with secondary Grignard reagents or when the α carbon of the α,β-epoxy ketone bears no hydrogen. Enone is eventually recovered in these cases (elimination–dehydration?).

(5) H. O. House and R. L. Wasson, *J. Am. Chem. Soc.*, **79**, 1488 (1957). In some cases, e.g., **10**, better yields were obtained using dipotassium hydrogen phosphate, rather than sodium hydroxide, for the epoxidation.

(6) The dimethylhydrazones of certain epoxy ketones, e.g., **14**, are unstable, and are best prepared at about −35 °C over several hours using only 0.1 equiv of propionic acid.
(7) NMR spectra were taken in carbon tetrachloride.
(8) Small amounts (usually <10%) of the unalkylated enone were also obtained in these reactions. The mechanism of this reduction is not clear; see A. A. Ponaras, Ph.D. Dissertation, Columbia University, New York, N.Y. 1972.
(9) Cf. M. Avaro, J. Levisalles, and H. Rudler, *J. Chem. Soc., Chem. Commun.*, 445 (1969). We were unable to effect hydrolysis of the dimethylhydrazone group using the published reaction conditions. For other possible cleavage methods, see J. R. Maynez, *J. Org. Chem.*, **40**, 3302 (1975); J. E. McMurry, *ibid.*, **40**, 1502 (1975); and, especially, E. J. Corey and D. Enders, *Tetrahedron Lett.*, 3 (1976).
(10) K. Eiter and H. Oediger, *Justus Liebigs Ann. Chem.*, **682**, 62 (1965).
(11) Identical with an authentic sample prepared by the method of G. Stork and J. Ben Aim, *J. Am. Chem. Soc.*, **93**, 5938 (1971).
(12) Identical with an authentic sample: G. Stork and R. Borch, *J. Am Chem. Soc.*, **86**, 935 (1964).
(13) J. T. Edward and J. M. Ferland, *Can. J. Chem.*, **44**, 1317 (1966).
(14) R. Futaki, *J. Org. Chem.*, **23**, 451 (1958).
(15) Prepared by reaction of *trans*-10-methyl-Δ^3-2-octalone[16] with alkaline hydrogen peroxide. The α configuration of the epoxide was confirmed via Wharton reaction[17] to give the allylic alcohol, mp 60.5–62.5 °C, followed by catalytic hydrogenation to *trans,trans*-1-hydroxy-9-methyldecalin, mp 59–61 °C (reported[18] mp 56–57 °C).
(16) C. Djerassi and D. Marshall, *J. Am. Chem. Soc.*, **80**, 3986 (1958).
(17) P. S. Wharton and D. S. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961).
(18) S. H. Grover and J. B. Stothers, *Can. J. Chem.*, **52**, 870 (1974).
(19) Obtained as a low-melting solid via (1) reduction of *trans*-10-methyl-Δ^3-2-octalone with aluminum hydride to the β-alcohol, (2) epoxidation[20] with 3-chloroperbenzoic acid in chloroform to give a 2:1 mixture of β and α epoxides, (3) Jones oxidation, (4) chromatography.
(20) Cf. H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957); J. W. Bird and D. G. M. Diaper, *Can. J. Chem.*, **47**, 145 (1969).
(21) This method of making β-hydroxy ketones appears to be quite general (A. A. Ponaras, unpublished observations). For another use of oximes of epoxy ketones in an alkylation sequence closely related to our own work, see E. J. Corey, L. S. Melvin, Jr., and M. F. Haslanger, *Tetrahedron Lett.*, 3117 (1975).
(22) The stereochemistry shown in **18** is based on the presence of two separated singlets for the *gem*-dimethyl group at δ 1.00 and 1.11, corresponding to the equatorial and axial methyls of (essentially) a single chair conformation. In contrast, the *gem*-dimethyls of **16** appear as a six-proton singlet at δ 1.05, representing the average of two conformations of very close energy.
(23) For instance, acid-catalyzed opening of certain epoxyhydrazones in protic media is clearly nonconcerted: inter alia, B. Ellis, S. P. Hall, and S. Waddington-Feather, *J. Chem. Soc.*, 4111 (1961).
(24) Introduction of a phenyl substituent on the α carbon of an α,β-unsaturated ketone can also be achieved via reaction of arylcopper reagents with the tosylhydrazones of α,β-epoxy ketones: P. L. Fuchs, *J. Org. Chem.*, preceding paper in this issue.

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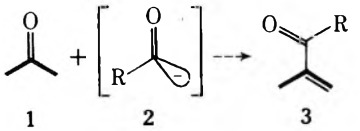
A Synthesis of α,β-Unsaturated Ketones from α,β-Unsaturated Nitriles

Summary: An effective sequence for the synthesis of α,β-unsaturated ketones involves (1) the Horner–Emmons modification of the Wittig reaction to synthesize α,β-unsaturated nitriles, $R_2CH_2(R_1)C{=}C(R_3)CN$, from carbonyl compounds, $R_2CH_2COR_1$, and (2) the oxidative decyanation of the α,β-unsaturated nitriles to afford α,β-unsaturated ketones, $R_2CH{=}C(R_1)COR_3$, by sequential treatment with lithium diisopropylamide, oxygen gas, sodium sulfite, and sodium hydroxide.

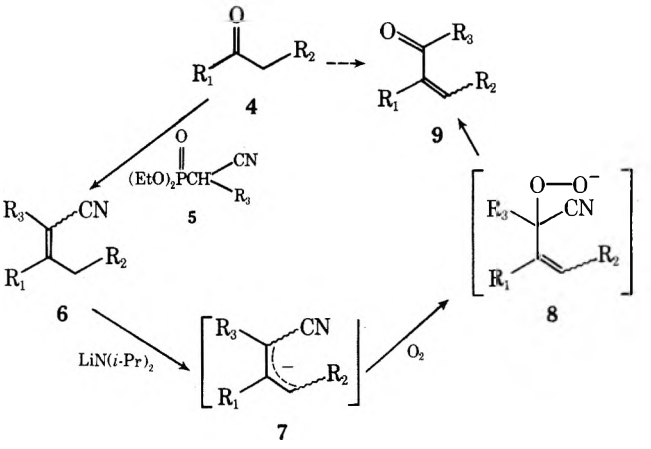
Sir: The condensation–dehydration reaction of a carbonyl compound **1** with an acyl carbanion equivalent **2** would provide an α,β-unsaturated ketone **3** in which the carbonyl carbon



1 **2** **3**

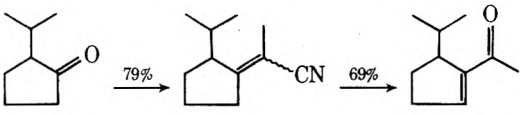
of **1** was incorporated as the α carbon of **3**. We required methodology of this type in order to effect the homologation of 17-keto steroids to 20-keto-Δ^{16} steroids.[1] Unfortunately, the classic Rupe rearrangement[2] of 17β-hydroxy-17α-ethynyl steroids derived from 17-keto steroids fails to effect the desired transformation.[3] We now wish to report that the oxidative decyanation[4] of α,β-unsaturated nitriles provides a convenient synthesis of certain α,β-unsaturated ketones including 20-keto-Δ^{16} steroids. In this case, the nitrile group serves as the masked carbonyl group in the acyl carbanion equivalent.[5]

The Horner–Emmons modification of the Wittig reaction[6] of aldehydes **4** (R_1 = H) and ketones **4** with the anions of substituted diethyl phosphonoacetonitriles **5** furnishes α,β-unsaturated nitriles **6** in excellent yield. The reaction of **6** with lithium diisopropylamide in 20% HMPA–THF[7] results in the



abstraction of a γ hydrogen from a methylene site to afford the delocalized anion **7**. The introduction of dry oxygen gas results in the regioselective trapping of **7** at the α carbon to produce the hydroperoxide **8**. Reduction of **8** with aqueous sodium sulfite and exposure of the cyanohydrin to sodium hydroxide affords the α,β-unsaturated ketone **9** in good yield (Table I).

In exploring the scope of this oxidative decyanation procedure, we have found that the reaction is well suited for the synthesis of α,β-unsaturated ketones but not α,β-unsaturated aldehydes. In addition, the reaction is limited to the synthesis of α,β-unsaturated ketones **9** which possess only one nonhydrogen β substituent.[8] This apparent limitation can be turned to some advantage, however, in the synthesis of α,β-unsaturated ketones **9** derived from unsymmetrical ketones **4**. For example, 2-isopropylcyclopentanone (**10**) furnished **11** which

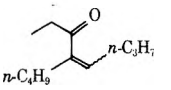
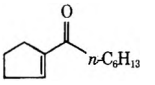
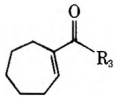
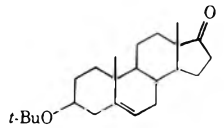
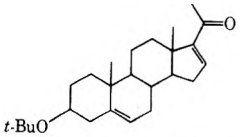
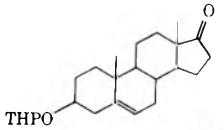
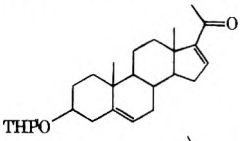
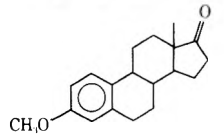
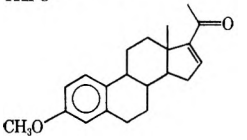


10 **11**

is not otherwise readily accessible. In cases where the yields of **9** were disappointing, we found that a fraction of **6** had been diverted to the production of γ-hydroxy-α,β-unsaturated nitriles. Although the regioselectivity of oxygen trapping at the α or γ sites in **7** varies with structure in a way that is not clearly understood, the oxidative decyanation of α,β-unsaturated nitriles **6** provides a viable solution to the synthesis of an array of α,β-unsaturated ketones **9**.[9]

The following is a typical experimental procedure. To 131 mg (1.3 mmol, 1.3 equiv) of diisopropylamine in 2.0 ml of anhydrous THF under a nitrogen atmosphere at −78 °C was added 0.44 ml of 3.00 M *n*-butyllithium in hexane. To the lithium diisopropylamide solution was added 409 mg (1.0 mmol) of the tetrahydropyranyl ether of 3β-hydroxypregna-5,17(20)-diene-20-carbonitrile in 2.5 ml of 40% HMPA–THF. Oxygen gas was bubbled (250 ml/min) into the solution for 30 min. The reaction was quenched with 2 ml of 1 M sodium sulfite solution, stirred for 1 h at 25 °C, diluted with 25 ml of 20% dichloromethane–ether, washed with 25 ml of 1 M sodium hydroxide solution

Table I. Synthesis of α,β-Unsaturated Ketones 9

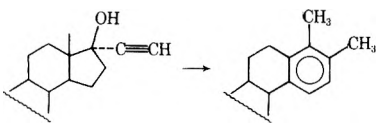
Starting material 4	R_3 in phosphonate 5	Isolated yields, % 6	Isolated yields, % 9	Product
$CH_3(CH_2)_5CHO$	n-C_6H_{13}	73	62	(*E*)- and (*Z*)-8-tetradecen-7-one
$(n$-$C_4H_9)_2C{=}O$	CH_2CH_3	81	44	
Cyclopentanone	n-C_6H_{13}	94	57	
Cyclohexanone	H	74	0	1-Cyclohexene-1-carboxaldehyde
	i-C_3H_7	88	45	1-Isobutyryl-1-cyclohexene
Cycloheptanone	CH_3	89	57	
	CH_2CH_3	90	70	
	i-C_3H_7	35	55	
	n-C_6H_{13}	96	72	
Cyclooctanone	CH_3	82	74	(*E*)-1-Acetyl-1-cyclooctene
Cyclododecanone	CH_3	92	81	1:1 (*E*)- and (*Z*)-1-acetyl-1-cyclododecene
	CH_3	74	74	
	CH_3	77	72	
	CH_3	62	78	

and 25 ml of brine, and dried over anhydrous magnesium sulfate. The product was chromatographed on Merck silica gel F254 in 1:1 ether–hexane to afford 301 mg (76%) of the tetrahydropyranyl ether of 3β-hydroxypregna-5,16-dien-20-one having melting point and spectral data in accord with literature values.[10]

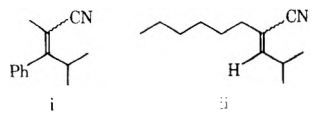
Acknowledgment. We would like to thank the National Institutes of Health (GM-22978-01 and HD-6-2855) for their generous financial support. We also wish to thank G. D. Searle and Co. for a generous gift of steroid intermediates.

References and Notes

(1) J. Fried and J. A. Edwards, "Organic Reactions in Steroid Chemistry", Vol. 2, Van Nostrand-Reinhold, New York, N.Y., 1972, Chapter 11.
(2) S. Swaminathan and K. V. Narayanan, *Chem. Rev.*, **71**, 429 (1971).
(3) (a) M. Dvolaitzky, A.-M. Giroud, and J. Jacques, *Bull. Soc. Chim. Fr.*, 62 (1963); (b) J. Canceill, M. Dvolaitzky, and J. Jacques, *ibid.*, 336 (1963); (c) C. Ouannes, M. Dvolaitzky, and J. Jacques, *ibid.*, 776 (1964); and (d) E. Hardegger and C. Scholz, *Helv. Chim. Acta*, **28**, 1355 (1945).



(4) S. J. Selikson and D. S. Watt, *J. Org. Chem.*, **40**, 267 (1975).
(5) For an alternative approach to 3 using 1,3-dithianes as the acyl carbanion equivalent, see D. Seebach, M. Kolb, and B.-T. Gröbel, *Tetrahedron Lett.*, 3171 (1974).
(6) J. Boutagy and R. Thomas, *Chem. Rev.*, **74**, 87 (1974).
(7) Unlike the oxidative decyanation of secondary nitriles (ref 4), HMPA was required for the successful oxidation decyanation of α,β-unsaturated nitriles.
(8) For example, i and ii afford the corresponding α,β-unsaturated ketones in 0 and 6% yield, respectively.



(9) All compounds had ir, NMR, and mass spectral data in accord with assigned structures.
(10) J. P. Dusza and W. Bergmann, *J. Org. Chem.*, **25**, 79 (1960).

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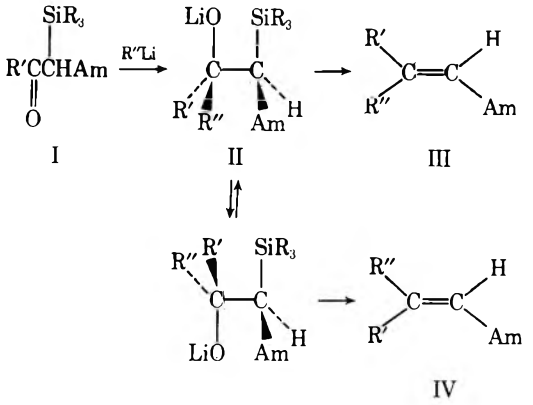
Reaction of β-Ketosilanes with Alkyllithium. A Stereoselective Synthesis of Trisubstituted Ethylenes

Summary: Reaction of β-ketosilanes with alkyllithium reagents afforded predominantly one diastereoisomer of possible two β-hydroxysilanes, which gave trisubstituted ethylenes stereoselectively by acidic or basic workup.

Sir: Recent progress in organic synthesis via silicon compounds has disclosed novel procedures for the synthesis of 1,2-disubstituted ethylenes with rigorous stereochemistry.[1-7] We describe herein a novel procedure for the stereoselective synthesis of trisubstituted ethylenes via reaction of β-ketosilanes with alkyllithium reagents followed by syn-elimination under basic conditions or by anti-elimination on acid treatment.[8,9]

Treatment of 5-trimethylsilyl-4-decanone (Ia)[10] with methyllithium at −78 °C afforded a reaction mixture containing IIa[11] whose corresponding alcohol was obtained in 80% yield by hydrolytic workup. Treatment of the reaction mixture with potassium *tert*-butoxide afforded (*E*)-4-methyl-4-decene (IIIa)[12] in 74% overall yield (stereoselectivity 91%). When the reaction mixture was treated with glacial acetic acid saturated

with sodium acetate (−15 °C for 30 min and room temperature overnight), the *Z* isomer (IVa) was obtained in 69% overall yield (stereoselectivity 88%).[14] Similar reaction of 5-triethylsilyl-4-decanone (Ic) with methyllithium gave IIIa in 76% yield (stereoselectivity 91%) by treatment with potassium *tert*-butoxide and IVa in 57% overall yield (stereoselectivity 90%) by treatment with glacial acetic acid saturated with sodium acetate.[15]



I II III IV

a, R = Me; R′ = *n*-Pr; R″ = Me
b, R = Me; R′ = Me; R″ = *n*-Pr
c, R = Et; R′ = *n*-Pr; R″ = Me

Further information about the stereoselectivity of this olefin synthesis was obtained from the reaction of 3-trimethylsilyl-2-octanone (Ib) with propyllithium. Treatment of the reaction mixture with potassium *tert*-butoxide gave IVa in 25% yield (stereoselectivity 96%) via IIb.[16]

When methylmagnesium bromide, in place of methyllithium, was treated with β-ketosilane Ia, IVa was obtained in 22% (stereoselectivity 77%) after acidic workup (glacial acid saturated with sodium acetate). Reaction of Ia with phenyllithium gave 4-phenyl-4-decene (52% overall yield, 39/61 *E*/*Z*) after treatment of the reaction mixture with concentrated sulfuric acid.[17]

These data show that β-hydroxysilanes are produced from β-ketosilanes and alkyllithium reagents in high stereoselectivity. The potassium salt of the alcohol produces a trisubstituted ethylene by syn-elimination of trimethylsilyl and hydroxy groups whereas treatment with acid in the presence of nucleophile induces anti-elimination of these two groups.[1-3,6]

Preparation of 4-methyl-4(*E*)-decene (IIIa) and the *Z* isomer (IVa) are representative. A stirred solution of 5-trimethylsilyl-4-decanone (Ia, 0.23 g, 1 mmol) in 5 ml of THF was treated with methyllithium (3 mmol, 3.5 ml of 0.85 M ethereal solution) at −78 °C and the reaction mixture was stirred at room temperature overnight. Addition of 1.0 g (9 mmol) of potassium *tert*-butoxide and refluxing of the reaction mixture for 1 h gave IIIa (74% overall yield, 91/9 *E*/*Z*): NMR (CCl_4) δ 0.6–1.04 (6 H, m), 1.04–1.5 (8 H, m), 1.55 (3 H, br s), 1.70–2.20 (4 H, m), 5.05 (1 H, br t, *J* = 7 Hz). When the reaction mixture from Ia and methyllithium (−78 °C for 15 min, then room temperature for 1 h) was treated with 10 ml of glacial acetic acid saturated with sodium acetate under stirring at −15 °C for 30 min and at room temperature overnight, workup gave IVa (69%, 12/88 *E*/*Z*): NMR (CCl_4) δ 0.88 (6 H, t, *J* = 6 Hz), 1.03–1.57 (8 H, m), 1.63 (3 H, br s), 1.70–2.17 (4 H, m), 5.00 (1 H, t, *J* = 7 Hz); MS *m*/*e* (rel intensity, %), 154 (M^+, 11), 111 (13), 97 (22), 84 (16), 69 (52), 55 (100).

Acknowledgment. The authors wish to thank to the Ministry of Education, Japan, for Grant-in-Aid 911506.

References and Notes

(1) P. F. Hudrlik and D. Peterson, *Tetrahedron Lett.*, 1133 (1974).
(2) P. F. Hudrlik and D. Peterson, *J. Am. Chem. Soc.*, **97**, 1464 (1975).
(3) P. F. Hudrlik, D. Petersom, and R. J. Rona, *J. Org. Chem.*, **40**, 2263 (1975).
(4) K. Utimoto, M. Kitai, and H. Nozaki, *Tetrahedron Lett.*, 2825 (1975).
(5) K. Uchida, K. Utimoto, and H. Nozaki, *J. Org. Chem.*, **41**, 2215 (1976).
(6) P. B. Dervan and M. A. Shippey, *J. Am. Chem. Soc.*, **98**, 1265 (1976).
(7) T. H. Chan, W. Mychajlowskij, B. S. Ong, and D. N. Harpp, *J. Organometal. Chem.*, **107**, CI (1976).
(8) Stereochemistry of olefin-forming reaction from β-hydroxysilanes was studied (ref 1–3).
(9) 1,1-Disubstituted ethylenes were prepared by analogous procedures: (a) P. F. Hudrlik and D. Peterson, *Tetrahedron Lett.*, 1785 (1972); (b) R. A. Ruden and B. L. Gaffney, *Synth. Commun.*, **5**, 15 (1975).
(10) Prepared from trimethylvinylsilane, butyllithium, and butyraldehyde analogously to the reported procedure (ref 2) for the preparation of β-ketosilanes. This ketosilane was also prepared from trimethylvinylsilane, butyllithium, and butyryl chloride in 45% overall yield: bp 110–120 °C (23 mm).
(11) Compound IIa was not isolated. Stereochemistry of IIa as well as its corresponding alcohol could not be determined but estimated from the stereochemistry of olefins prepared by syn- and anti-elimination.
(12) The structure of IIIa and IVa are based on the NMR. The chemical shift of 7-methyl signal in 3-propyl-7-methyl-2(*Z*),6(*E*)-decadien-1-ol is recorded to be at δ 1.57 ppm, whereas that of the 6(*Z*) isomer is recorded to be at 1.66 (ref 13). The observed chemical shift of vinylic methyl of IIIa appeared at δ 1.55 ppm and that of the *Z* isomer (IVa) at 1.63.
(13) (a) S. B. Bowlus and J. A. Katzenellenbogen, *J. Org. Chem.*, **38**, 2733 (1973); *Tetrahedron Lett.*, 1277 (1973); (b) M. P. Cooke, Jr., *Tetrahedron Lett.*, 1281 (1973).
(14) This mixture did not contain other isomers. We could not detect (*Z*)- and (*E*)-4-methyl-3-decene from the product mixture.
(15) Further attempts for preparation of olefins: treatment with thioglycolic acid, 61% yield, 46/54 *E*/*Z*; BF_3·OEt_2, 82, 37/63. Treatment of the reaction mixture with ammonium chloride gave β-hydroxysilane (IIa′, Li = H) which gave IVa: treatment with AcOH saturated with ACONa, 46% yield, 10:90 *E*/*Z*; AcOH–KF, 72, 12/88; H_2SO_4–KF, 84, 18/82; H_2SO_4, 69, 24/76.
(16) Propyllithium may abstract proton from methyl ketone in Ib. This side reaction may lower the overall yield of IVa.
(17) Treatment of the reaction mixture with potassium *tert*-butoxide or glacial acetic acid saturated with sodium acetate did not give any olefin. Sulfuric acid produces a benzyl-type cation which gives 4-phenyl-4-decene by the elimination of trimethylsilyl group.

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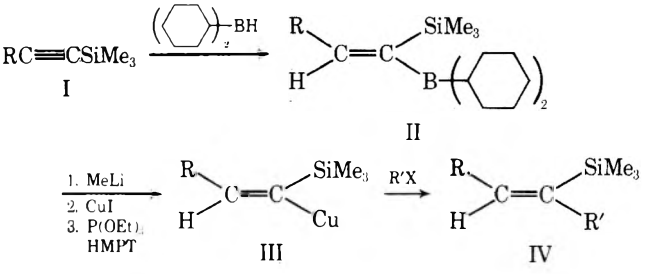
Stereoselective Synthesis of Vinylsilanes from Alkynylsilanes by Reductive Alkylation via Hydroboration and Carbodemetalation

Summary: Hydroboration of 1-trimethylsilyl-1-alkyne with dicyclohexylborane gave 1-trimethylsilylvinylborane regio- and stereoselectively whose successive treatment with methyllithium, cuprous iodide, and alkyl halides afforded 1,2-dialkylvinylsilane with strict geometry.

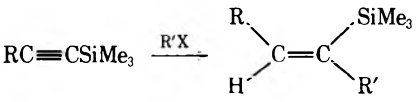
Sir: Organosilicon compounds have attracted much attention as versatile reagents for organic synthesis,[1] for example, vinylsilanes have been shown to be useful precursor for ketones, vinyl halides, and olefins of predictable stereochemistry.[2,3] We wish to describe here a novel stereoselective and generally applicable procedure for the reductive 1,2-dialkylvinylsilanes with fixed configuration, which is based on regioselective hydroboration of 1-alkynylsilane to vinylborane and the following stereoselective transmetalation and carbodemetalation.[4]

Hydroboration of 1-trimethylsilyl-1-octyne (I, R = *n*-C_6H_{13}) with excess dicyclohexylborane gave vinylborane II (R = *n*-C_6H_{13}) regioselectively.[5,6] Excess borane was quenched with 1-butene and the resulting mixture was treated with



I II III IV

Table I. Stereoselective Synthesis of 1,2-Dialkylvinylsilanes (IV)



IV

RC≡CSiMe$_3$, R	R′X	Method[a]	Yield,[b] %	Isomer[c] ratio, % Z
n-C_6H_{13}	CH_3I	B	94 (99)[d]	>99
	CH_2=$CHCH_2Cl$	B	93	>99
	CH_2=$CMeCH_2Cl$	B	87	>99
	CH_2=$CClCH_2Cl$	B	71[e]	99
	CH_3CH_2I	Cu	88	98
	n-C_4H_9I	Cu	81	97
	n-$C_6H_{13}I$	Cu	80	94
	Me_2C=$CHCH_2CH_2I$[f]	Cu	(29)[d]	94
	$CH_3COCH_2CH_2O(CH_2)_3I$[k]	Cu	46	90
	n-C_4H_9OTs[g]	Cu	75	97
$(CH_2)_4OTHP$	CH_2=$CHCH_2Cl$	B	81	95[h]
	CH_3CH_2I	Cu	85	95[h]
	Me_2C=$CHCH_2CH_2I$[f]	Cu	31[i]	94
CH_2OCMe_2OMe	CH_3I	B	80	>99
	CH_2=$CHCH_2Br$	B	59[j]	>99
	n-C_4H_9I	Cu	41[i]	85

[a] Method B means carbodemetallation via borate and method Cu indicates carbodemetallation via vinylcopper. [b] Isolated yield after column chromatography unless otherwise stated. [c] Analysis by GLC (3 m × 3 mm glass column packed with 20% silicon HVSG or 20% PEG 20M on Chromosorb W-AW). [d] Determined by GLC. [e] Isolated by column chromatography followed by distillation. [f] Prepared according to the modified Julia method: J. P. McCormick and D. L. Barton, *J. Chem. Soc., Chem. Commun.*, 303 (1975). [g] Trimethyl phosphite was used in the place of triethyl phosphite. [h] Determined by NMR. [i] After isolation of the protected alcohol by column chromatography (silica gel or basic alumina), the alcohol was obtained by methanolysis (5 mM TsOH in MeOH, room temperature, 1 h) followed by distillation (Kugelrohr). [j] After removal of the protecting group, the alcohol was purified by column chromatography (silica gel). [k] 2-Methyl-2-(3-iodopropyl)-1,3-dioxolane.

methyllithium (equimolar to used borane and an additional 1 mol) and cuprous iodide affording α-silylated vinylcopper.[7] Treatment with a wide variety of alkyl halides afforded stereoselective 1,2-dialkylvinylsilanes IV in excellent yield. The reactivity toward tosylate and homoallyl halide indicated that the above-described α-silylated vinylcopper was more reactive than the simple vinylcopper.[8] Table I shows the chemical yield and stereoselectivity of the vinylsilanes.

Preparation of 3-trimethylsilyl-3(Z)-decene is representative. To a stirred suspension of dicyclohexylborane in THF, prepared from 6 mmol (5.6 ml of 1.08 M solution of BH_3 in THF) of borane and 0.98 g (12 mmol) of cyclohexene in 4.0 ml of THF at 0 °C, was added 0.55 g (3.0 mmol) of 1-trimethylsilyl-1-octyne under argon. After stirring at room temperature for 5 h, the remaining dicyclohexylborane was quenched with 1-butene at 0 °C and transformed into dicyclohexylbutylborane. The reaction mixture was first treated with 9.0 mmol of methyllithium (6.6 ml of 1.36 M ethereal solution), stirred at room temperature for 20 min, and finally treated with cuprous iodide (0.57 g, 3.0 mmol) at −30 °C for 5 min. The resulting dark brown mixture was added with triethyl phosphite (0.60 g, 3.6 mmol) and hexamethylphosphoric triamide (3 ml) then with ethyl iodide (0.70 g, 4.5 mmol) at −30 °C. The reaction mixture was allowed to warm to room temperature overnight and treated with 4 ml of 3 N NaOH and 8 ml of 30% H_2O_2 at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was extracted with ether, washed, dried, and chromatographed on silica gel (hexane), affording 0.56 g (88%) of IV (R = n-C_6H_{13}; R′ = C_2H_5).

Analogous to the previously reported synthesis of vinylsilane from alanates,[4] intermediary borates, prepared from 1-trimethylsilyl-1-alkyne, dicyclohexylborane, and methyllithium, could react with methyl iodide and allyl halides in excellent yield.[9,10]

The above-described procedures, coupled with the facile exchange of trimethylsilyl into hydrogen,[2b,3] provide highly stereoselective synthesis of olefins from 1-alkyne and are novel additions to the synthetic reactions with organoboron compounds.

Acknowledgment. The authors wish to thank the Ministry of Education, Japan, for Grant-in-Aid 911506.

References and Notes

(1) (a) S. S. Washborn, *J. Organometal. Chem.*, **83**, 155 (1974); (b) I. Fleming, *Chem. Ind. (London)*, 449 (1975).
(2) (a) K. E. Koenig and W. P. Weber, *J. Am. Chem. Soc.*, **95**, 3416 (1973); (b) K. Utimoto, M. Kitai, and H. Nozaki, *Tetrahedron Lett.*, 2825 (1975), and references cited therein; (c) B. Miller and T. Reichenbach, *ibid.*, 543 (1974); (d) I. Fleming and A. Pearce, *J. Chem. Soc., Chem. Commun.*, 633 (1975); (e) G. Stork, M. E. Jung, E. Colvin, Y. Noel, *J. Am. Chem. Soc.*, **96**, 3684 (1974).
(3) Vinylsilanes were prepared from 1-trimethylsilylvinyllithium. Recent report in this field: T. H. Chan, W. Mychajlowskij, B. S. Ong, and D. N. Harpp, *J. Organometal Chem.*, **107**, CI (1976), and references cited therein.
(4) Analogous carbodemetalation affording vinylsilanes from 1-trimethylsilylvinylalanates has been published: (a) J. J. Eisch and G. A. Damasevitz, *J. Org. Chem.*, **41**, 2214 (1976); (b) K. Uchida, K. Utimoto, and H. Nozaki, *ibid.*, **41**, 2215 (1976).
(5) Hydroboration and successive treatment with acetic acid was reported to produce (Z)-vinylsilane from 1-trimethylsilyl-1-alkyne (ref 2c), but regioselectivity of hydroboration has not been described.
(6) NMR of the crude product showed a single olefinic proton (CCl_4, Me_4Si as internal standard, δ 5.48 ppm, t, J = 7 Hz). This observation as well as the yield of carbodemetalation product suggested that 1-trimethylsilylvinylborane II is the sole product.
(7) The formation of α-silylated vinylcopper upon treatment with cuprous iodide was suggested by the characteristic brown color of the reaction mixture.
(8) J. F. Normant, G. Cahiez, C. Chuit, and J. Villieras, *J. Organometal. Chem.*, **77**, 269 (1974), and references cited therein.
(9) Under similar reaction conditions, ethyl iodide gave the corresponding ethylated product in 10% yield.
(10) This would be the first example of intermolecular carbodemetalation of the α,β-unsaturated boron ate complex, whose reaction with electrophiles usually gives rearranged product (ref 11). Similar intermolecular reaction was reported by E. Negishi's group for the case of phenylborates (ref 12).
(11) (a) G. Zweifel, H. Arzoumanian, and C. C. Whitney, *J. Am. Chem. Soc.*, **89**, 3652 (1967); (b) G. Zweifel, R. P. Fisher, J. T. Snow, and C. C. Whitney, *ibid.*, **93**, 6309 (1971); **94**, 6560 (1972); (c) K. Utimoto, K. Uchida, and H. Nozaki, *Tetrahedron Lett.*, 4527 (1973); *Chem. Lett.*, 1493 (1974).
(12) E. Negishi, A. Abramovitch, and R. E. Merill, *J. Chem. Soc., Chem. Commun.*, 138 (1975).

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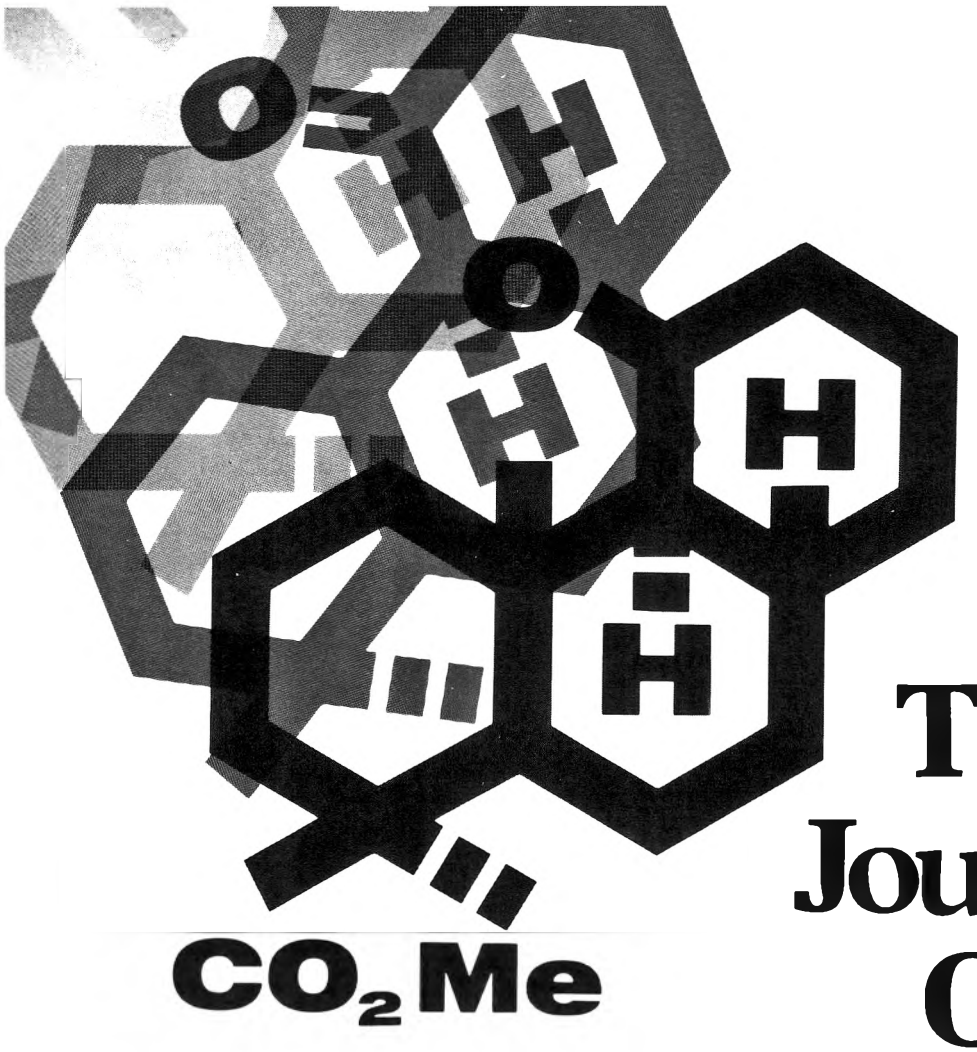

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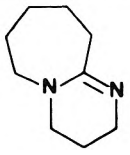
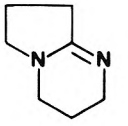
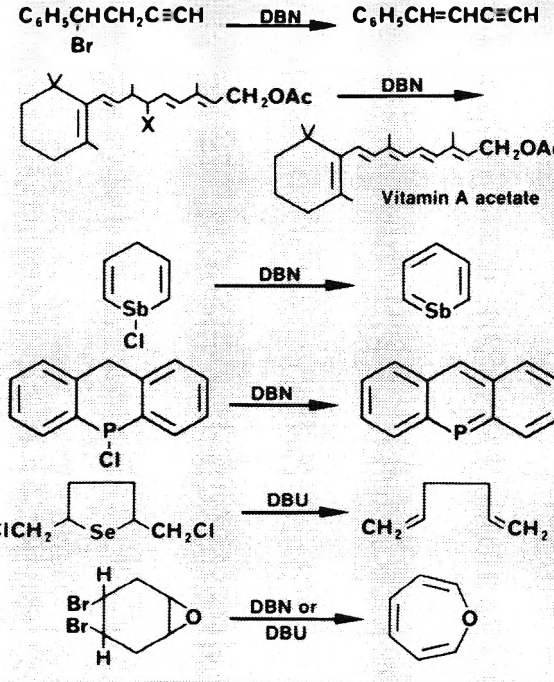
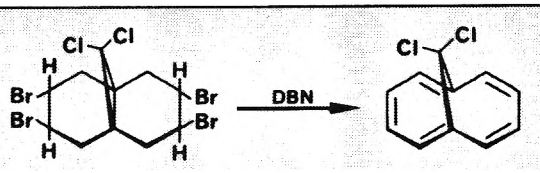
DBU and DBN: Reagents of choice for dehydrohalogenation





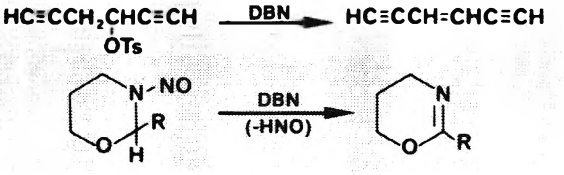
1,5-Diazabicyclo[5.4.0]undec-5-ene (DBU) and **1,5-diazabicyclo[4.3.0]non-5-ene (DBN)** are of particular interest as reagents in synthetic organic chemistry[1-3] since they have been shown to be extremely versatile dehydrohalogenating agents,[4-7] being more reactive than the amines generally used. As a result, much milder reaction conditions can be employed and even generally unstable compounds such as α,β-unsaturated terminal acetylenes can be prepared. **DBN** has been used in the preparation of Vitamin A acetate,[6] where other tertiary amines such as pyridine, *N*-methylmorpholine and *N,N*-dimethylaniline have failed. A large number of examples of dehydrohalogenation for the introduction of single or multiple double bonds have been reviewed.[3] Some interesting examples are highlighted below:



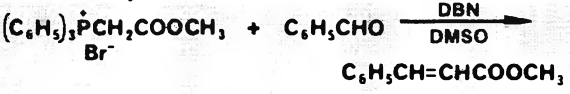


A comparison of the relative dehydrohalogenation activities of **DBU** and **DBN** using 4- and 2-bromoheptanes showed that **DBU** gave higher yields of the heptenes.[7]

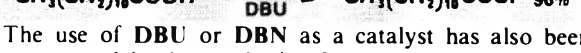
The use of **DBU** and **DBN** has been extended to the elimination of sulfonic acid and hyponitrous acid.[3]



DBN has also been used in Wittig reactions with alkali-sensitive aldehydes.[6]



An interesting application of **DBU** as a catalyst in the preparation of acid chlorides has been patented.[8]



The use of **DBU** or **DBN** as a catalyst has also been demonstrated in the synthesis of macromolecules such as polyurethanes and polyaryl ethers.[9]

References:

1) L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Wiley and Sons, New York, N.Y., 1967, 1969 and 1974.
2) K. Yamakawa, *Yuki Gosei Kagaku Kyokai Shi*, **29**, 429 (1971).
3) H. Oediger, F. Moller, and K. Eiter, *Synthesis*, 591 (1972).
4) E. Truscheit and K. Eiter, *Ann. Chem.*, **658**, 65 (1962).
5) K. Eiter and H. Oediger, *ibid.*, **682**, 62 (1965).
6) H. Oediger *et al.*, *Chem. Ber.*, **99**, 2012 (1966).
7) H. Oediger and F. Moller, *Angew. Chem.*, **79**, 53 (1967).
8) C.F. Hansen, German Patent 1,931,074 (1970) [*Chem. Abstr.*, 72, 78472 (1970)].
9) H. Weiden and U. Bahr, German Patent 595,609; British Patent 1,134,613 [*Chem. Abstr.*, 70, 29589 (1969)].

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