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THE JOURNAL OF Organic Chemistry®

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Phenyl Group Migration during Pyrolytic and Photolytic Deazotizations of 1,2-Bis[2-(phenylated 2,5-dihydrofuranyl)]hydrazines to β,γ-Unsaturated Ketones[1-3a-c,4a]

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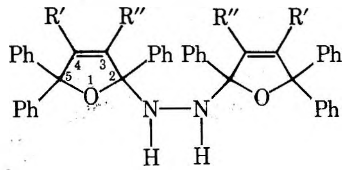
Received June 3, 1974

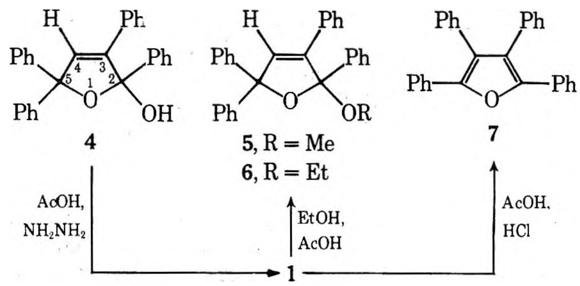
Chemistry related to 1,2-bis[2-(phenylated 2,5-dihydrofuranyl)]hydrazines is detailed. Pyrolytic and photolytic deazotizations converted the 2,3,5,5-tetraphenylated derivative into 1,3,4,4-tetraphenyl-3-butenone with migration of a 5-phenyl, but pyrolysis in decalin also gave some isomeric 1,2,4,4-tetraphenyl ketone without phenyl migration. These results were corroborated by ^{14}C-phenyl tracing. Fusion pyrolysis and photolysis of the 2,4,5,5-tetraphenyl isomer gave mainly the 1,3,4,4-tetraphenyl unsaturated ketone without phenyl migration, but pyrolysis in decalin produced also a small amount of isomeric 1,2,4,4-tetraphenyl ketone with phenyl migration. Pyrolysis of the bis(2,3,4,5,5-pentaphenyl) analog gave 1,2,3,4,4-pentaphenyl-3-buten-1-one, 2,3,4,5,5-pentaphenyl-2,3-dihydrofuran, and tetraphenylfuran. ^{14}C tracing showed that ketone formation involved some 5- to 2-phenyl migration and that the furan resulted from elimination of a 5-phenyl. Photolysis gave the unsaturated ketone, the dihydrofuran, and 1-benzoyl-1,2,2,3-tetraphenylcyclopropane. Mechanisms are considered. Synthesis, chemistry, and aryl migrations in the 2,3,5,5-tetraphenyl-2,5-dihydrofuranol series, p-MeO or p-CF_3 labeled in one of the 5,5-diphenyl positions, establish a foundation for further work.

It has been shown[3a,b,4a] that the product of reaction of 2,3,5,5-tetraphenyl-2,5-dihydrofuranol-2 (4) with hydrazine,[4b] namely 1,2-bis[2-(2,3,5,5-tetraphenyl-2,5-dihydrofuranyl)]hydrazine[4a] (1), undergoes pyrolytic deazotization to the 1,3,4,4-tetraphenyl β,γ-unsaturated ketone 14[4d,5] and empirically involves 5 to 2 transannular migration of a 5-phenyl (1,4-cis migration relative to the acyclic tautomeric forms). Related examples of phenyl migrations are known,[6] but there appears to be no exact precedent for the type described in our previous preliminary report.[4a] This report contains the details of the study on 1 and extends the investigation to include the 2,4,5,5-tetraphenyl and 2,3,4,5,5-pentaphenyl analogs 2 and 3.



1, R′ = H; R″ = Ph
2, R′ = Ph; R″ = H
3, R′ = R″ = Ph

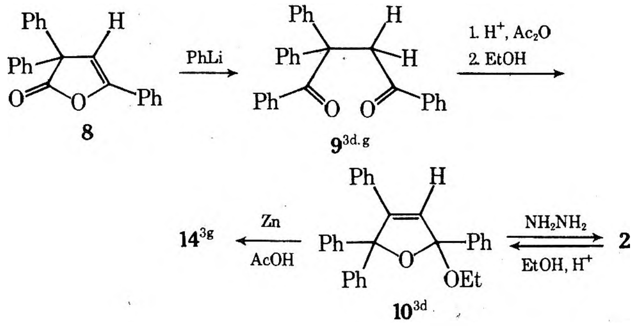
1,2-Bis[2-(2,3,5,5-tetraphenyldihydrofuranyl)]hydrazine (1)[4a] and its precursor, 2,3,5,5-tetraphenyldihydrofuranol-2 (4),[4c] undergo facile acid-catalyzed alcoholyses to 2-alkoxydihydrofurans 5 and 6 and dehydrative furanization to 7 with 5- to 4-phenyl group migration.



The *vic*-1,2-bis(dihydrofuranyl)hydrazine structures 1–3 (rather than the gem-1,1-bis structures), with intramolecular hydrogen bonding (32), are supported by ir spectra[4a,7a] and analogy to 1,2-bis(organosilyl)hydrazines where preference for forming 1,2-bis types increases with increasing steric bulk of the organo groups[8] and where the two types have been distinguished by the effect of coupling interaction of the N–H stretching modes to give in-phase and out-of-phase stretching bands of different frequencies (for H–N–H of the 1,1 isomers the band separations were 76–88 cm^{-1}, but for H–N–N–H of the 1,2 isomers they did not exceed 23 cm^{-1}). The ir spectra of 1–3 obtained in CCl_4[7b] showed sharp single bands at 3555, 3260, and 3240 cm^{-1}, respectively, with lower frequency shoulders which represent peak separations on the order of 10–20 cm^{-1}, and the latter correspond to the small peak separations for 1,2-bishydrazines.[8]

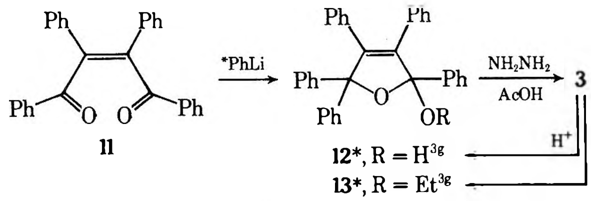
1,2-Bis[2-(2,4,5,5-tetraphenyldihydrofuranyl)]hydrazine (2), the positional isomer of 1, was prepared by reaction of hydrazine in AcOH with 2-ethoxydihydrofuran (10), using the sequence 8[4g] → 9[3d,g] → 10 → 2. Acid-catalyzed ethanolysis of 2 gave cyclic ketal 10 which underwent

Zn–AcOH conjugate reduction to the β,γ-unsaturated ketone 14,[3g] with proton acquisition at position 3 and without 5- to 4-phenyl migration.



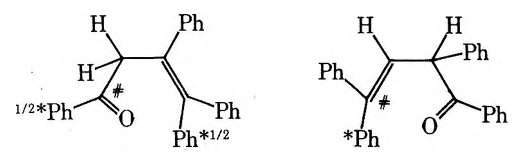
8, 9[3d,g], 10[3d], 14[3g]

1,2-Bis[2-(2,3,4,5,5-pentaphenyldihydrofuranyl)]hydrazine (3) was obtained by the reaction of hydrazine with dihydrofuranol (12) which had been made by addition of PhLi to *cis*-dibenzoylstilbene (11).[3a,g] Acid-catalyzed hydrolysis of 3 gave 12, and ethanolysis with or without added H^+ gave ketal 13.



11; 12*, R = H[3g]; 13*, R = Et[3g]

Deazotization of 1,2-Bis[2-(2,3,5,5-tetraphenyldihydrofuranyl)]hydrazine (1). Pyrolysis by fusion (220°), in decalin (160°) or in DMF (153°), and photolysis[9] in benzene gave N_2 and β,γ-unsaturated ketone 14[4d] in yields of 68, 58, 40, and 50%, respectively. In 1 the 5,5-diphenyls

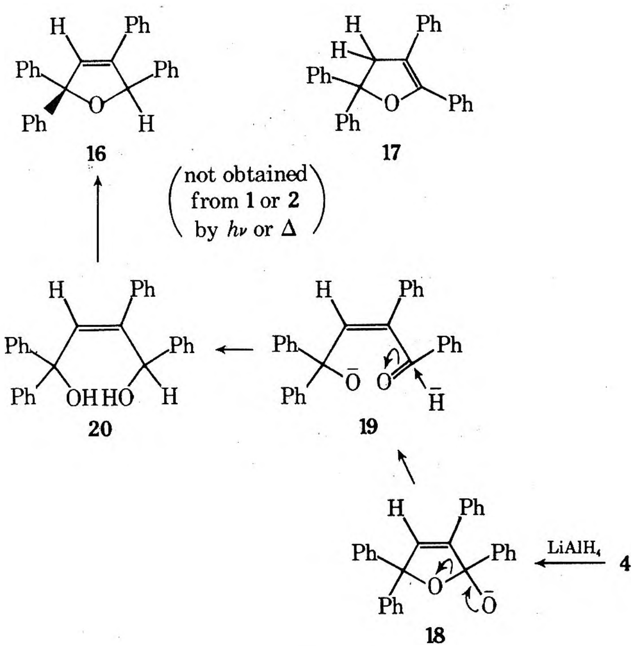


14 15

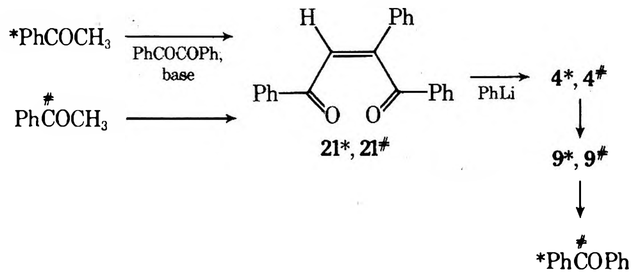
* or # = ^{14}C label

were two carbons removed from the one nonterminal 3-phenyl, and in product 14 they are adjacent to that phenyl. Therefore, 5 to 2 transannular (or cis-1,4) phenyl migration must have occurred. In only one of these four experiments, pyrolysis in the relatively nonpolar decalin, was the isomeric ketone 15[4i] also obtained, *without* phenyl migration (total ketone yield 82%, 14:15 = 58:24%). In no case was there formed either 2,5- or the 4,5-dihydrofuran 16 or 17. That the 2,5 isomer 16 was not an intermediate in the reactions was shown by its preparation from dihydrofuranol (4) by $LiAlH_4$ reduction to 1,4-glycol 20 and cyclodehydration, and by the distinctive behavior of both isomers 16 and 17 under the deazotizing conditions in giving products, none of which were isolated in the deazotizations of 1.

Although it is certain from the structure of ketone 14 that phenyl migration did occur in the deazotization of 1, this was corroborated by ^{14}C tracings which also gave pertinent information limiting the mechanistic possibilities. Two samples, 1* and 1#, ^{14}C-labeled respectively in the *gem*-diphenyls and at carbon-5, were prepared through dibenzoylstyrenes 21* and 21# and dihydrofuranols 4* and 4#, starting from samples of acetophenone ^{14}C-labeled respectively in the phenyl and at the carbonyl carbon. To show that in 1* the *gem*-diphenyls contained all of the original ^{14}C label, and thereby to preclude the possibility of rearrangement during deazotizations or oxidations, a sample was oxidized by CrO_3 to Ph_2CO which within experimental error contained all of the original ^{14}C (98%).



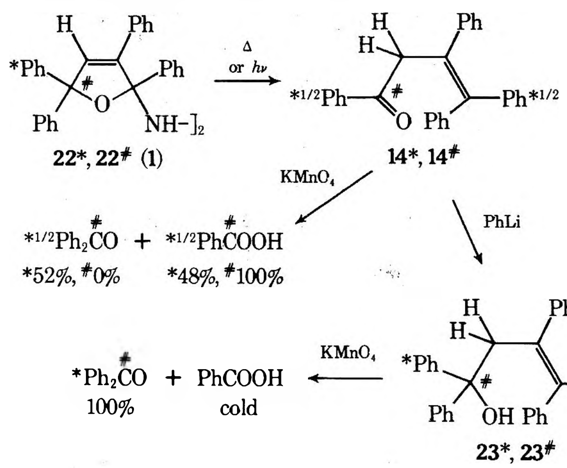
16, 17, 20, 19, 18



21*, 21#; 4*, 4#; 9*, 9#

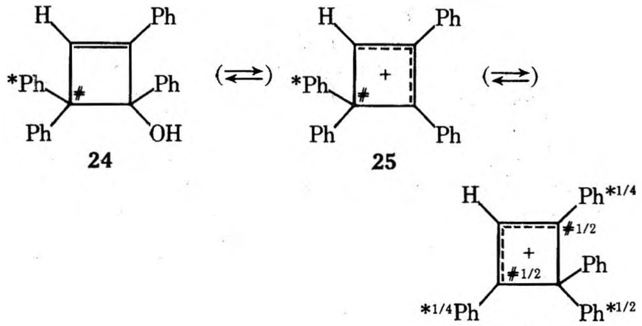
* or # = ^{14}C label

In the tracing experiments outlined below, oxidations of unsaturated ketone 14* obtained from pyrolysis and photolysis of 22* (1) gave benzophenone and benzoic acid containing respectively 48 and 52% of the original ^{14}C activity, thus demonstrating phenyl migration (otherwise ^{14}C activities would have been 100 and 0%).



22*, 22# (1); 14*, 14#; 23*, 23#

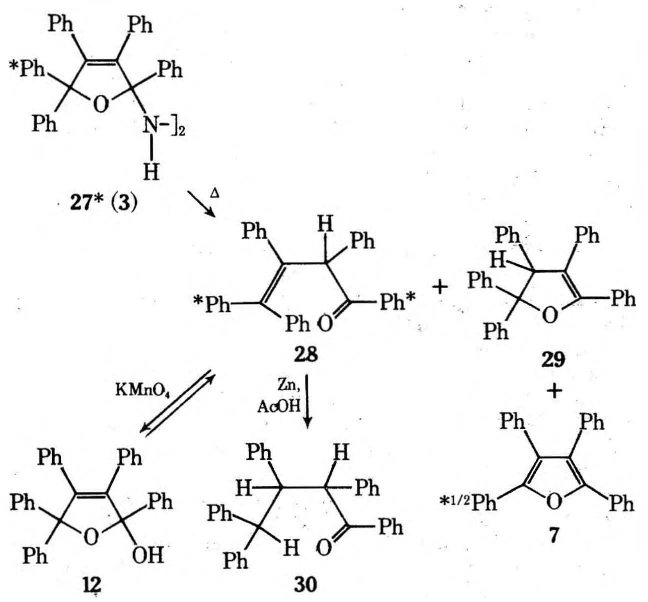
The noninvolvement in the above reactions of the 3-phenyl and carbon-3 of 22* and 22# (1) was demonstrated by additions of PhLi to the unsaturated ketones 14* and 14# and by oxidation of the resulting unsaturated alcohols 23* and 23# to benzophenone containing practically all of the original ^{14}C and benzoic acid containing none. These experiments show that orderly and extensive *irreversible* 5- to 2-phenyl migration had been involved; they preclude scrambling of ^{14}C-phenyls between positions 5 and 2; and they preclude total scrambling of the ^{14}C-phenyls *via* cyclobutenyl intermediates such as **24–26**.


24 **25** **26**

To complete proof that phenyl migration or skeletal rearrangement had occurred neither during formation of the minor product **15** nor in the oxidations of **14** and **15**, **22*** (**1**) was pyrolyzed and the resulting ketones **14*** and **15*** were then oxidized; **15*** gave benzophenone containing all of the original ^{14}C and cold benzoic acid, whereas **14*** gave benzophenone and benzoic acid each containing half of the original ^{14}C.

Deazotization of 1,2-Bis[2-(2,4,5,5-tetraphenyl-2,5-dihydrofuranyl)]hydrazine (2).[3c] From fusion pyrolysis (210°), and from photolysis in benzene,[9] only β,γ-unsaturated ketone **14** was isolated, without phenyl migration. Pyrolysis in refluxing decalin, however, gave a mixture of ketones **14** (32%) and **15** (5.7%), the latter involving 5- to 2-phenyl migration; and the ratio of migration to nonmigration was in the direction opposite that in the comparable pyrolysis of **1**, a point of limited significance, however, because of the low total ketone yield (38%).

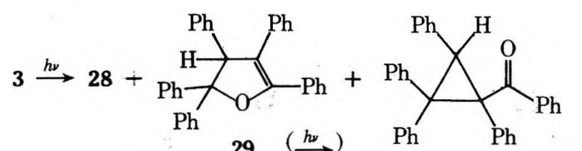
Deazotization of 1,2-Bis[2-(2,3,4,5,5-pentaphenyl-dihydrofuranyl)]hydrazine (3).[3c] Pyrolysis by fusion (280°) or in decalin (190°) gave the expected β,γ-unsaturated ketone **28** and two additional products, 2,3,4,5,5-pentaphenyl-4,5-dihydrofuran (**29**) and tetraphenylfuran (**7**). In DMF (153°) no reaction occurred (as did with **1**).


27* (**3**) **28** **29** **12** **30** **7**

It is significant that $KMnO_4$ oxidation of unsaturated ketone **28** to benzophenone and benzoic acid was very slow and that upon interruption it gave a considerable amount of presumably intermediate dihydrofuranol **12**, a type of reaction possible but not observed in oxidations of the tetraphenyl unsaturated ketones **14** and **15**. This oxidation is the reverse of conjugate reductions of dihydrofuranol **12** → **28** (and of **10** → **14**); and doubtless steric and resonance-stabilized cyclic radical intermediates are involved. Prolonged Zn–AcOH reduction of dihydrofuranol (**12**) carried the reduction beyond **28** to saturated ketone **30**.

It is not known from the foregoing whether ketone **28** produced in the pyrolysis of unlabeled **3** had been formed with or without phenyl migration because in either event the result would be the same. To determine this, **3*** ^{14}C-labeled in the *gem*-diphenyl was synthesized by addition–cyclization of *cis*-dibenzoylstilbene (**11**)[3g] by ^{14}C-labeled *PhLi and treatment of the resulting pentaphenyldihydrofuranol **12*** with hydrazine. Two of the products of fusion pyrolysis of **3***, namely **7*** and **28***, were oxidized by $KMnO_4$. Benzoic acid obtained from the furan **7** contained half of the original ^{14}C, showing that one of the 5,5-diphenyls had been expelled and that little if any prior 5- to 2-phenyl migration had occurred (otherwise ^{14}C activity in the furan would have been higher than 50%). Benzophenone obtained from oxidation of unsaturated ketone **28** contained 78.6% of the original ^{14}C, proving that phenyl migration actually had occurred to a considerable extent. This result is to be considered in relation to the 50, 67, and 75% expected if competitive mechanisms involved irreversibility of migration at all stages, 5 to 2 scrambling through reversibility at some intermediate stage, and irreversible degeneration from a symmetrical intermediate such as **40**.

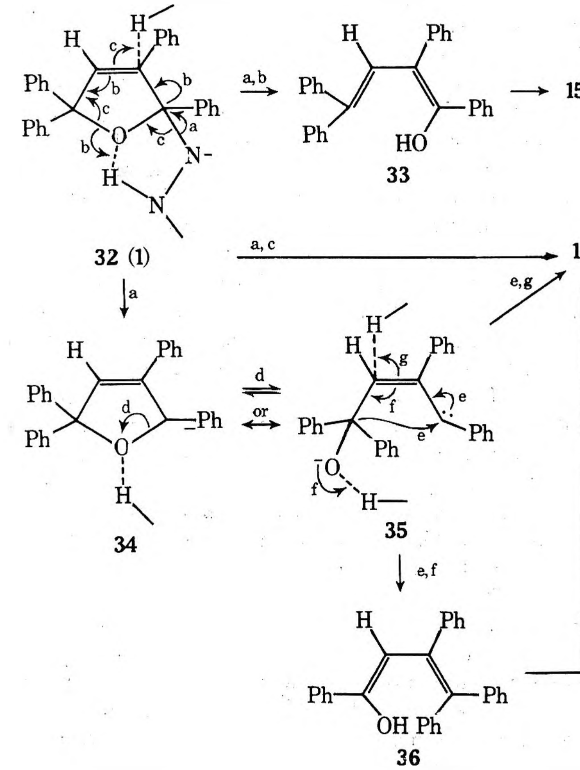
The photolysis[9] of **3** in benzene yielded unsaturated ketone **28**, the 4,5-dihydrofuran **29** (involving proton transfer to position 2), and 1-benzoyl-1,2,2,3-tetraphenylcyclopropane (**31**). It had previously been shown[4b] that under these conditions ketone **28** is relatively stable but that dihydrofuran **29** is converted into **31**. Thus, **28** and **29** are the primary photolytic products, and cyclopropyl ketone **31** results from photolysis of **29**.


29 **31**

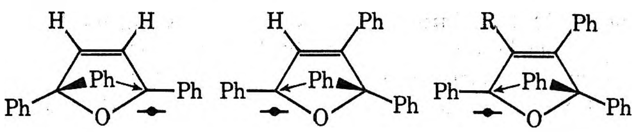
Discussion

2,3,5,5-Tetraphenyldihydrofuranol types **1**, **4**, and **5** undergo acid-catalyzed furanization easily with facile 5- to 4-phenyl migration clearing the way. The isomeric compounds **2** and **10** with the nonterminal phenyl at position 4, however, do not furanize because of obvious mechanistic difficulty in the required phenyl migration. The pentaphenyl compounds **3**, **12**, and **13** cannot furanize readily because expulsion of a molecule of benzene would be required, but it does happen to a small extent in pyrolysis of **3**. The various deazotization products cannot furanize directly because their lower oxidation state constitutes a barrier to be surmounted by some form of oxidation.

The deazotizations of **1** and **2**, with or without phenyl migration, involve overall intramolecular oxidation–reduction, in which the hydrazine nitrogens become oxidized to molecular nitrogen (perhaps through diimide or its equivalent) and in which the dihydrofuryl moieties become reduced. The reactions may be concerted with hydrogen bonding playing a role (*e.g.*, **32**). Initial cleavage may be heterolytic, **32** (a); giving ketone **15**, without phenyl migration, through **32** (b) and dienol **33**, or directly by **32** (c); and giving ketone **14** through carbenoid anion[10] **34–35** where position 2 becomes receptor for the migrating phenyl, through **35** (e,f) and enol **36**, or directly by **35** (e,g).



Or the initial cleavage may be homolytic, giving steric and resonance-stabilized intermediate radicals, *e.g.*, **37–40**.



37 (from **1**) **38** (from **2**) **39**, R = H (from **1**, **2**) **40**, R = Ph (from **3**)

—•— = radical or anion radical

Relative yields of ketones **14** and **15** are a measure of phenyl migration aptitudes in **1** and **2** (through **37** and **38**), and they show that **1** ≫ **2**. In **2** (and **38**) steric buttressing stresses on the 5,5-diphenyl group by the 4-phenyl, and minimization of steric interference at the receptor site 2 through absence of phenyl at position 3, call for opposite migrational aptitudes of **1** ≪ **2**. Activation energies for intramolecular reaction, however, would be higher for **1** than for **2** because the 1–4 allyloxy system of intermediate **37** with its 3-phenyl lacks the increment of conjugation stabilization which is furnished in **38** (from **2**) by terminal conjugation with the 4-phenyl. This would account for the observed migration aptitudes **1** ≫ **2**. Although extensive phenyl migration occurs in the deazotization of the pentaphenyl compound **3***, the amount may not be truly measured by the ^{14}C activity of benzophenone obtained on oxidation of the resulting ketone **28*** (as it is in the cases of ketones **14*** and **15***). A low activation energy for reaching the symmetrical pentaphenyl intermediate **40** (relative to that for the tetraphenyl analog **39**) may permit this as a competitive path involving 5- to 2-phenyl migrational interchange. An important extension of this work would be determination of the true extent of migration here and whether or not any 5- to 2-phenyl migration occurs in related reactions such as reductions of **3**, **12**, **13**, and analogs and in pyrolysis and photolysis of 2-alkoxy, 2-carboxy, and related derivatives.

The pyrolyses and photolyses of **1** and **2** appear to be significantly different because product ratios are quite different, but it is not known whether the migrating phenyl is in different states or in the same as would be the case if the photoexcited state underwent internal conversion to the thermally excited state. Initiating work was undertaken in the migration-prone 2,4,5,5-tetraphenyl series to obtain analogs carrying a *p*-MeO or *p*-CF_3 as a label on one of the 5,5-diphenyls toward migrational aptitude and crossover studies which might give pertinent information on the electronic identity of the migrating phenyl and receptor site. Although the few experiments on the reaction of hydrazine with the analogs of **4** and **5** failed to give bis(dihydrofuranyl)hydrazines of type **1**, the results on their precursors **41–59** are of interest *per se* and afford foundation for further study.

Experimental Section[11]

2,3-Diphenyl-5,5-[^{14}C-diphenyl]-2,5-dihydrofuranol-2 (4*).[4b,c] Condensation of benzil with ^{14}C-phenyl labeled acetophenone [from $AcCl^{12}$ + C_6H_6 (30.8 g, 0.1 mCi)] gave *cis*-1,2-diphenyl-4-[^{14}C-phenyl]-2-butene-1,4-dione (**21***, 88%, mp 128–129°[3a,4g]). Of this, 25 g was added (2 min) to stirred PhLi [from Li wire (4.5 g), PhBr (50 g), Et_2O (300 ml), 0°, 5 min]. Hydrolysis (ice–NH_4Cl), extraction (Et_2O), and crystallization (C_6H_6–hexane) gave **4*** [25 g, 80%, mp 140–143° (lit.[4c] 144–146°)].

1,2-Bis[2-(2,3-diphenyl-5,5-[^{14}C-diphenyl]-2,5-dihydrofuranyl)]hydrazine (1*). To a solution of **4*** [6 g, AcOH (75 ml), 50°] was added dropwise 85% hydrazine hydrate [2 ml in AcOH (15 ml), stirring, 2 min]. Cooling gave **1*** (5.0 g, 84%) which was recrystallized (C_6H_6–absolute EtOH): mp 214–218° dec; uv ($\epsilon \times 10^{-3}$) 253.5 nm (28.4); ir (CCl_4)[3b] 3555 (narrow), shoulder at 3575 (NH), 3440 cm^{-1} (br, NH, persisting at increased dilution), no absorption in the 1600-cm^{-1} range assignable to NH_2, C=O, or C=N. *Anal.* Calcd for $C_{56}H_{44}N_2O_2$: C, 86.55; H, 5.71; N, 3.61. Found: C, 86.38; H, 5.88; N, 4.04. Furanization [**1** (0.2 g), AcOH–concentrated HCl (25:1 ml), heating, 1 hr] gave **7** (94%). Alcoholysis [**1** (3 g), absolute EtOH–AcOH (10 ml), reflux, 30 hr] quenching (H_2O), and recrystallization (petroleum ether–hexane) gave 2-ethoxy-2,3-diphenyl-5,5-[^{14}C-diphenyl]-2,5-dihydrofuran (**6***): 1.9 g (60%); mp 112–114° (lit.[4b,c] 116–118°).

Oxidation of **6*** [1.1 g, slurry, AcOH (75 ml), CrO_3 (2 g), 20 min (75°), 20 min (50°), basification (K_2CO_3), steam distillation, and extraction (Et_2O)] gave benzophenone which was chromatographed (Al_2O_3, 1:19–1:9 C_6H_6–petroleum pentane) and converted[13] into the 2,4-dinitrophenylhydrazone [40%, recrystallized (C_6H_6–EtOH), mp 237–239° (lit.[13] 239°)]. Attempted $KMnO_4$ oxidation of **6** failed (**6** recovered).

Deazotizations of 1. (A) Pyrolysis [4 g heated slowly to 225° (→N_2)] and chromatography (Florisil, 30–100% C_6H_6–petroleum ether fractions) gave 1,3,4,4-tetraphenyl-3-buten-1-one [**14**, 2.6 g (68%), mp 192–193° (lit.[4d] 194–195°); no **15** was isolated].

(B) Pyrolysis in decalin (1 g, 10 ml), purification by chromatography (Al_2O_3, 20–40% C_6H_6–petroleum pentane), and fractional crystallizations gave **14** (0.56 g, 58% total) and **15** (0.23 g, 24%), mp 90–92°.[4i]

(C) Pyrolysis in DMF (3 g, 600 ml, reflux, 4 hr, 153°), cooling, quenching (H_2O), and recrystallization (EtOH–benzene) gave **14** (1.15 g, 40%), mp 193–195° (no **15** was isolated). Identification of N_2 was by injection of a DMF solution of **1** into the preheated vpc block (225°) and separation on a 5 ft × ⅛ in. Cu column (molecular sieve 5A, 30°, carrier gas, He, O_2 for reference peak[14]).

(D) Photolysis[9] [2 g, C_6H_6 (800 ml)] and fractional crystallization (absolute EtOH) gave unchanged **1** (1.35 g, 67%, mp 214–218° dec) and **15** [(0.32 g) 50% from **1** consumed, recrystallized (C_6H_6–EtOH), mp 193–194°]. A similar experiment (chromatographing) gave no **15**.

$KMnO_4$ Oxidations of Unsaturated Ketones 14* and 15*. Typically, a mixture of **14** (0.45 g), 60% pyridine–H_2O (350 ml), and $KMnO_4$ (1 g) was refluxed until the purple disappeared and then continued with 1-g additions of $KMnO_4$ to a total of 6 g and persistence of color. Steam distillation gave the pyridine–H_2O azeotrope and then cloudy distillate from which benzophenone was extracted [acidification (HCl), Et_2O] and converted[13] to the 2,4-dinitrophenylhydrazone (0.3 g, 69%). Acidification of the steam distillation residue, reduction ($NaHSO_3$), extractions (Et_2O), and

Table I
^{14}C Activities[a] of Benzophenone[b] and Benzoic Acid from Oxidative[c,d] Degradations of Deazotization Products

Substrate[e]	Reaction[f] (of 1*# or 1# and 3#)	$Ph_2C{=}NNHPh\text{-}(NO_2)_2$[b]	PhCOOH
14*	Pyrolysis, neat	48.2	51.8
14*	Pyrolysis, DMF	48.0	52.8
6*[d]	Ethanolysis	98.2	
23*	Pyrolysis, DMF; then PhLi	98.9	4.6[g]
15*	Pyrolysis, decalin	95.7	10.7[g,h]
14#	Pyrolysis, DMF	2.2	99
14#	Photolysis,[m] benzene	2.2	99.5
21#	Pyrolysis, decalin	103	19[g,h]
23#	Pyrolysis, DMF; then PhLi	102	4.5
23#[d]	Pyrolysis, DMF; then PhLi	100	14.5[g]
23#	Photolysis,[m] DMF; then PhLi	100.6	4.4[g]
28*	Photolysis,[m] neat	78.5[i]	13.5,[j] 9.3[k,l]
7*	Pyrolysis,[m] neat		53.2

[a] Relative to starting materials taken as 100%; 1*, 4*, 17*, and 3* randomly ^{14}C labeled in one of the 5,5-diphenyls and 1= and 25= at ring carbon-5 and chain carbon-1, respectively. Radioactivities were determined by means of a Tracerlab, Inc., Model superscaler, using 100-mg samples in 25-nm stainless steel planchets. Experimental error, 2–3%. [b] Isolated and measured as the 2,4-dinitrophenylhydrazone. [c] $KMnO_4$ except where [d] CrO_3 is specified. [e] Formula number of compounds whose ^{14}C content was being determined. [f] Source of compounds and reactions involved. [g] These high ^{14}C activities can be explained in terms of some oxidative attack on phenyl groups *prior* to carbon chain cleavage, *e.g.*, using the more active CrO_3 or [h] a large excess of $KMnO_4$. This does not vitiate interpretations of results based on ^{14}C activities of the benzophenone moiety which were consistent within experimental error in a number of comparisons of activities at the several stages of synthesis from ^{14}C active bromobenzene and acetophenone-*1*-^{14}C. The benzoic acid ^{14}C activities were determined and considered as secondary checks. [i] The weight of substrate counted (mg): 75; [j] 46; [k] 28. [l] During this oxidation there was loss of *ca.* 18% of the original ^{14}C activity. This was presumed to result from relatively rapid initial attack at the benzylic C–H group of 28 and 1,2 cleavage followed by partial oxidative destruction of the resulting ^{14}C labeled benzoic acid during the long drawn out completion of the oxidation of the relatively stable diphenylchalcone which is doubtless the intermediate in formation of benzophenone. The probable correctness of this interpretation was supported by the results of interruption of a typical oxidation of 28 whereby the ^{14}C activity of the benzoic acid obtained rose to 13.7%, a significantly higher value but one still considerably lower than the stoichiometric 21.4% demanded on the basis of the ^{14}C activity of the benzophenone produced. [m] *Cf.* ref 9.

evaporation gave benzoic acid (1.4 g, 48%) which was recrystallized (H_2O): mp 120–122°.

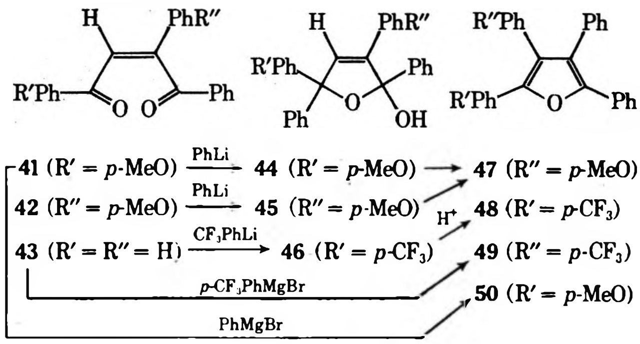
Addition of PhLi to 1,3,4,4-Tetraphenyl-3-buten-1-one (14* and 14#). 1,1,3,4,4-Pentaphenyl-3-buten-1-ol (23* and 23#). To stirred PhLi [from Li (0.23 g) and PhBr (2.51 g), Et_2O (15 ml), −5°], **14*** was added (1.5 g, stirring, 5 min). Hydrolysis (ice–NH_4Cl), extractions (Et_2O), and recrystallization (absolute EtOH) gave **23** (0.95 g, 65%), mp 175–177° (lit[3a] mp 175.5–178°).

Oxidation of **23*** (or **23#**) (0.85 g) by CrO_3 (3.6 g) and AcOH (25 ml), reflux, 3 hr), evaporation, basification (5% K_2CO_3), steam distillation, and extraction (Et_2O) gave benzophenone which was converted into the [^{14}C]-2,5-dinitrophenylhydrazone[13] (75%). Acidification of the steam distillation residue, extraction (Et_2O), and evaporation gave benzoic acid, 0.14 g (61%), which was crystallized (H_2O): mp 120–122° (this had small ^{14}C activity arising presumably from some oxidative degradation of one of the [^{14}C]-*gem*-diphenyl groups prior or subsequent to benzophenone formation). $KMnO_4$ oxidation of **23*** (procedure for **14***) gave benzoic acid with a little ^{14}C activity.

1,2,2,4-Tetraphenylbutane-1,4-dione (*pseudo*-Bidesyl, 9[3d,g]). To PhLi [from Li (0.16 g), PhBr (11.1 g), Et_2O (300 ml), 0°] was added 3,3,5-triphenylcrotolactone [8g[4g] (16 g), stirring, 2 min]. Quenching (ice–NH_4Cl) gave **9** (16.2 g, 82%) which was recrystallized (C_6H_6–EtOH): mp 156–157° (lit.[3d] mp 159–160°); uv (EtOH) 244 nm (ε 21,950); ir 5.95 μ (aromatic C=O). *Anal.*[3d] Calcd for $C_{28}H_{22}O_2$: C, 86.12; H, 5.68. Found: C, 85.92; H, 5.61.

2-Ethoxy-2,4,5,5-tetraphenyl-2,5-dihydrofuran (10).[3d,4d] To **9** (5 g) in AcOH (150 ml) was added concentrated H_2SO_4 (2.5 ml). Stirring until solution, standing (4 hr), quenching (H_2O), extraction (Et_2O), washing (H_2O–$NaHCO_3$), evaporation, and digestion (absolute EtOH) gave **10** (4.6 g, 86%) which was recrystallized (absolute EtOH): mp 148–149° (lit.[3d] mp 149–153°). *Anal.*[3d] Calcd for $C_{30}H_{26}O_2$: C, 86.09; H, 6.26. Found: C, 85.65; H, 6.16. Reduction of **10** [1 g, AcOH (40 ml), Zn dust (2 g), 1 hr] gave **1,3,4,4-tetraphenyl-3-buten-1-one (14)** which was recrystallized (EtOH–AcOH): 39% mp 190–193° (lit.[4d] 193–195.5°).

Synthesis of Analogs of 2,3,5,5-Tetraphenyl-2,5-dihydrofuranol (4) carrying one *p*-MeO or *p*-CF_3 group (**44–46**) utilized the preference of the appropriate diaroylstyrenes (**41**[15]–**43**) for additions of PhLi or *p*-CF_3PhLi to the less hindered carbonyl group and for conjugate additions of PhMgBr and *p*-CF_3PhMgBr β to the less hindered α,β-unsaturated ketone system. In the PhLi reac-

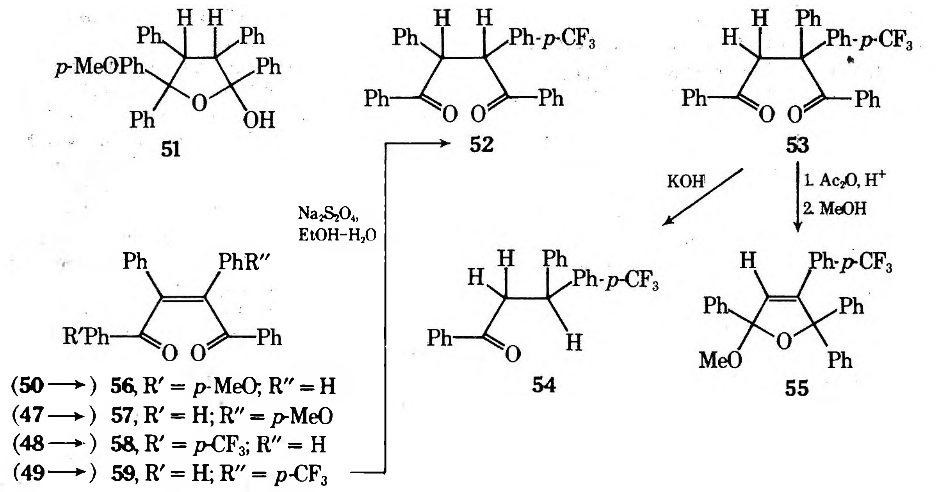


tion with **41** where the *p*-MeOPhCO carbonyl activity is somewhat lessened by *p*-MeO, a significant amount of β addition to the less hindered of the two α,β-unsaturated ketone systems occurs in competition with the 4-carbonyl addition which then follows to give diaddition product **51**.[4d] PhMgBr shows its preference for β addition to the less hindered C=C—C=O of **41**, subsequent dehydration giving furan **50**. *p*-CF_3PhMgBr, while reacting β to the less hindered C=C—C=O of **43** to give saturated diketone **52** and furan **49**, also to a small extent added β to the more hindered C=C—C=O, giving **53**. The structure of **53** was shown by KOH cleavage to **54**, by acid-catalyzed rearrangement with 2 to 1 migration of the 2-Ph rather than the 2-*p*-CF_3Ph, and by methanolysis to **55** whose structure follows by its difference from **46** methyl ether. The 5,5-diaryl-2,5-dihydrofuranols **44–46** were dehydratively rearranged to the expected furans **47** and **48**, *p*-MeOPh consistently migrating in preference to Ph, and Ph migrating in preference to *p*-CF_3Ph. Oxidations of the furans **47–50** by HNO_3–AcOH, and of saturated diketone **52** by DMSO–KOH–O_2, gave the respective diaroylethylenes **56–59**.

4-*p*-Anisyl-1,2-diphenyl-2-butene-1,4-dione (41):[15] mp 182–184° (lit.[15] mp 177°); uv (ε × 10^{-3}) 239, 320 nm (19.7, 2.31); ir 1665, 1640 cm^{-1}; nmr δ 7.4 (m, 15), 3.77 (s, 3).

2-*p*-Anisyl-1,4-diphenylbutene-1,4-dione (42).[15,16] Chromatographing (Florisil, 70–100% benzene–petroleum ether fractions) gave 3.5% which was recrystallized (EtOH): mp 134–136°; uv (ε × 10^{-3}) 247, 344 nm (22.0, 13.7); ir 1645, 1655 cm^{-1}; nmr δ 7.5 (m, 15), 3.77 (s, 3). *Anal.* Calcd for $C_{23}H_{18}O_3$; C, 80.68; H, 5.30. Found: C, 80.48; H, 5.11. It had been supposed (erroneously) that this was the isomer expected from condensation of acetophenone with the more active carbonyl of 4-methoxybenzil;[16] structure **42** was proved by the relationships between **41** and **42**, **44** and **45**, and **47** and **50**. The main product, an oil, which had been discarded, doubtless contained large amounts of the expected and presumably predominent isomer of **42**.

5-*p*-Anisyl-2,3,5-triphenyl-2,5-dihydrofuranol (44, prepared like 4): 76%, mp 167–168°; uv (ε × 10^{-3}) 2.52 nm (18.4); ir (KBr) 2475 cm^{-1}; nmr δ 7.1 (m, 20), 3.76 (s, 3), 3.02 (s, 1, D_2O → 0). *Anal.* Calcd for $C_{29}H_{24}O_3$: C, 82.83; H, 5.75. Found: C, 82.62; H, 5.58.



5-*p*-Anisyl-2,3,4,5-tetrahydrofuranol-2 (51) was isolated as a minor product in one preparation of **44**: 0.35% mp 196–198°; uv ($\epsilon \times 10^{-3}$) 268 nm (4.0); ir 3410 cm^{-1}; nmr δ 7.1 (m, 24), 5.21 (split d, 1, J = 12.5 Hz), 3.73 (split d, 1, J = 12.5, 1.5 Hz, $D_2O \rightarrow$ O), 3.72 (s, 3), 2.58 (split s, 1, J = 1.5 Hz). *Anal.* Calcd for $C_{35}H_{30}O_3$: C, 84.31; H, 6.06. Found: C, 84.37; H, 6.08.

44 methyl cyclic ketal (also the ethyl analog) was prepared from **44** (1 g) by a 30:1 milliliter mixture of absolute MeOH (or EtOH)–AcOH (reflux, 5 min, cooled): 74%; recrystallized from MeOH; mp 165–166°; uv ($\epsilon \times 10^{-3}$) 255 nm (22.0); ir 2960, 2935, 2825 cm^{-1}; nmr δ 7.2 (m, 20), 3.70 (s, 3), 3.13 (s, 3). *Anal.* Calcd for $C_{30}H_{26}O_3$: C, 82.92; H, 6.03. Found: C, 82.66; H, 6.16. **44 ethyl cyclic ketal:** 75%; recrystallized from absolute EtOH; mp 145–146°; uv, ($\epsilon \times 10^{-3}$) 255 nm (22.1); ir 2970, 2925, 2875, 2830 cm^{-1}; nmr δ 7.2 (m, 20), 3.72 (s, 3), 3.27 (q, 2, J = 7 Hz), 1.12 (t, 3, J = 7 Hz). *Anal.* Calcd for $C_{31}H_{28}O_3$: C, 83.01; H, 6.29. Found: C, 82.89; H, 6.24.

3-*p*-Anisyl-2,5,5-triphenyl-2,5-dihydrofuranol-2 (45) was prepared (like **44**) from **42**: 78%; recrystallized from EtOH; mp 134–135°; uv ($\epsilon \times 10^{-3}$) 267 nm (21.2); ir 3420 cm^{-1}; nmr δ 7.2 (m, 20), 3.70 (s, 3), 2.99 (s, 1, $D_2O \rightarrow$ O). *Anal.* Calcd for $C_{29}H_{24}O_3$: C, 82.83; H, 5.75. Found: C, 82.63; H, 5.60. **45 ethyl cyclic ketal** (prepared like **44** analog): 41%; mp 151–152°; uv ($\epsilon \times 10^{-3}$) 271 nm (23.8); ir 2935, 2835 cm^{-1}; nmr δ 7.3 (m, 20), 3.70 (s, 3), 3.33 (q, 2, J = 7 Hz), 1.11 (t, 3, J = 7 Hz). *Anal.* Calcd for $C_{31}H_{28}O_3$: C, 83.10; H, 6.29. Found: C, 82.75; H, 6.29.

5-*p*-Trifluoromethyl-2,3,5-triphenyl-2,5-dihydrofuranol-2 (46, Isolated as Methyl or Ethyl Cyclic Ketal). To BuLi from Li wire [1.04 g + *n*-BuBr (9.8 g), Et_2O, 30 min] was added *p*-CF_3PhBr [16 g, 0°, dropwise (a test sample + Dry Ice gave *p*-CF_3PhCOOH] and then *cis*-dibenzoylstyrene (**43**) (stirring, 5 min) and quenching (H_2O, ice, NH_4Cl), evaporation of Et_2O extracts, chromatography (Florisil), evaporation of the 70–100% benzene–petroleum ether eluent, and crystallization (EtOH) gave 6.3 g (*ca.* 70%) of a mixture of **46** and its ethyl cyclic ketal (ir, nmr) which was converted by EtOH (or MeOH)–AcOH (30:1 ml, reflux 2–5 min) into the cyclic ketal. **46 ethyl cyclic ketal:** 66%; recrystallized from EtOH; mp 63–64°; uv ($\epsilon \times 10^{-3}$) 253 nm (22.1); nmr δ 7.5 (m, 20), 3.35 (q, 2, J = 7.4 Hz), 1.13 (t, 3, J = 7.5 Hz). *Anal.* Calcd for $C_{31}H_{25}F_3O_2$: C, 76.53; H, 5.18. Found: C, 76.32; H, 5.29. **46 methyl cyclic ketal:** 47%; recrystallized from MeOH; mp 141–142°; uv ($\epsilon \times 10^{-3}$) 253 nm (21.7); nmr δ 7.4 (m, 20), 3.13 (s, 3). *Anal.* Calcd for $C_{30}H_{23}F_3O_2$: C, 76.26; H, 4.91; F, 12.06. Found: C, 76.06; H, 4.90; F, 11.89.

Reactions of 44–46 with 85% hydrazine hydrate gave no bishydrazine derivatives (as did **4**, **10**, and **13**). **46** instead underwent dehydrative rearrangement to furan **48**, and the products from **44** and **45** on crystallization (EtOH) gave the ethyl cyclic ketals. Doubtless the analogs of **1** could be obtained under more sophisticated conditions.

3-*p*-Anisyl-2,4,5-triphenylfuran (47) was prepared from **44** by AcOH (reflux, 5 min, 98°) and from **45** (AcOH, trace H^+, 71°) and was recrystallized (AcOH): mp 169–170°; uv ($\epsilon \times 10^{-3}$) 232, 292, 325 nm (28.9, 19.6, 24.1); nmr δ 7.2 (m, 19), 3.74 (s, 3). *Anal.* Calcd for $C_{29}H_{22}O_2$: C, 86.54; H, 5.51. Found: C, 86.31; H, 5.64.

2-*p*-Anisyl-3,4,5-triphenylfuran (50) was prepared by addition of **41** to PhMgBr–Et_2O, treatment with I_2,[3g] and chromatography (Florisil, C_6H_6–petroleum ether): 19%; crystallized from AcOH; mp 142–143°; uv ($\epsilon \times 10^{-3}$) 232, 250, 327 nm (21.0, 19.9, 22.0); nmr δ 7.2 (m, 19), 3.74 (s, 3). *Anal.* Calcd for $C_{29}H_{22}O_2$: C, 86.54; H, 5.51. Found: C, 86.23; H, 5.66.

2-*p*-Trifluoromethylphenyl-3,4,5-triphenylfuran (48). Portions of the mixture of **46** and its ethyl ketal were treated with (a) AcOH–concentrated HCl (10:1 ml, reflux, 5 min) and (b) Et_2O [100 ml + I_2 (1 g), room temperature, 4 hr]: yields 74 and 10%, respectively; recrystallized from EtOH; mp 187–188°; uv ($\epsilon \times 10^{-3}$) 234, 265, 332 nm (25.8, 16.8, 25.6). *Anal.* Calcd for $C_{29}H_{19}F_3O$: C, 79.07; H, 4.35; F, 12.97. Found: C, 79.02, H, 4.39; F, 13.03.

Additions of *p*-CF_3PhMgBr to *cis*-Dibenzoylstyrene (43). 3-*p*-Trifluoromethylphenyl-2,4,5-triphenylfuran (49). To *p*-CF_3PhMgBr [from Mg (1.16 g + crystal of I_2), *p*-CF_3PhBr (12.2 g), and Et_2O (200 ml), 0°] was added **43** (10 g, stirring, 10 min). Hydrolysis, extractions (Et_2O), and chromatography (Florisil, benzene–petroleum ether) followed. The 20–40% fractions gave **49** (6.8 g, 48%): recrystallized from absolute EtOH; mp 144–145°; uv ($\epsilon \times 10^{-3}$) 231, 260 nm (shoulder), 320 (26.9, 18.9, 22.4). *Anal.* Calcd for $C_{29}H_{19}F_3O$: C, 79.07; H, 4.35. Found: C, 79.14; H, 4.48.

2-*p*-Trifluorophenyl-1,3,4-triphenylbutane-1,4-dione (52). The 80–90% benzene fractions (above) gave **52**: 0.58 g (40%); recrystallized from AcOH; mp 216–217°; uv ($\epsilon \times 10^{-3}$) 252 nm (27.3); ir 1665, 1325, 1165, 1130 cm^{-1}; nmr δ 7.5 (m, 19), 6.03 (s, 2). *Anal.* Calcd for $C_{29}H_{21}F_3O_2$: C, 75.97; H, 4.62. Found: C, 75.67; H, 4.26. **52** was also made from **59** by $Na_2S_2O_4$ [88:53 (ml) EtOH–H_2O, reflux, 1 hr]: 93%. It was dehydrated to furan **49** (Ac_2O + trace of concentrated H_2SO_4, reflux, 10 min), hydrolyzed, and chromatographed (Florisil, 10%, C_6H_6–petroleum ether fraction): 50%. Autoxidation[17] of **52** (1% KOH–DMSO, stirring, air) gave **59**: 53%.

2-*p*-Trifluoromethyl-1,2,4-triphenylbutane-1,4-dione (53): from 100% benzene and Et_2O extraction (above); 5 g (34%); recrystallized from AcOH; mp 142–143°; uv ($\epsilon \times 10^{-3}$) 246 nm (24.8); ir 1680 cm^{-1}; nmr δ 7.4 (m, 19), 4.38 (s, 2). *Anal.* Calcd for $C_{29}H_{21}F_3O_2$: C, 75.97; H, 4.62. Found: C, 76.13; H, 4.61.

3-*p*-Trifluoromethylphenyl-1,3-diphenylpropanone (54): from **53** [0.2 g + KOH (0.05 g), warm EtOH (100 ml), 1 hr]; 71%; chromatographed (Florisil, acetone); mp 119–121°; uv ($\epsilon \times 10^{-3}$) 226, 244 nm (17.1, 15.7); ir 1675 cm^{-1}; nmr δ 8.0 (m, 2), 7.4 (m, 12), 4.93 (t, 1, J = 7.5 Hz), 3.79 (d, 2, J = 7.5 Hz). *Anal.* Calcd for $C_{22}H_{17}F_3O$: C, 74.57; H, 4.84. Found: C, 74.26; H, 4.67.

2-Methoxy-4-*p*-trifluoromethylphenyl-2,5,5-triphenyl-2,5-dihydrofuran (55): from **53** (with 4- to 5-Ph migration[3g]) by Ac_2O + concentrated H_2SO_4 (trace) [24 hr, hydrolysis solution, MeOH (48 hr, deep freeze)]; 61%, recrystallized from MeOH; mp 138–139°; uv ($\epsilon \times 10^{-3}$) 256, 265 nm (17.1, 14.8); nmr δ 7.3 (m, 19), 6.57 (s, 1), 3.10 (s, 3). *Anal.* Calcd for $C_{30}H_{23}F_3O_2$: C, 76.26; H, 4.91. Found: C, 76.40, H, 4.92.

***cis*-2-*p*-Anisyl-1,3,4-triphenyl-2-butene-1,4-dione (57):** from furan **47** by AcOH–concentrated H_2SO_4 (2 min, 60°, cooled); 58%; recrystallized from AcOH; mp 208–209°; uv ($\epsilon \times 10^{-3}$) 231, 257 nm (26.2, 28.2); ir 1660 cm^{-1}; nmr δ 7.85 (m, 4), 7.2 (m, 15), 3.7 (s, 3). *Anal.* Calcd for $C_{29}H_{22}O_3$: C, 83.23; H, 5.30. Found: C, 83.08; H, 5.18.

***cis*-1-*p*-Anisyl-2,3,4-triphenyl-2-butene-1,4-dione (56):** from **50**, (a) like **57**, chromatographed (Florisil, C_6H_6–petroleum ether), 80%; (b) by Br_2–Et_2O–H_2O[18] (30 min), 87%; and (c) by CrO_3 (AcOH, 60°, 15 min), 67%. **56** crystallized (MeOH, EtOH, or AcOH) with solvent of crystallization (shown by ir and nmr) and dried *in vacuo:* mp 126–127°; uv ($\epsilon \times 10^{-3}$) 260, 291 nm (23.6, 21.9); ir 1655, 1645 cm^{-1}; nmr δ 7.9 (m, 4), 7.2 (m, 15), 2.76 (s, 3). *Anal.* Calcd for $C_{29}H_{22}O_3$: C, 83.23; H, 5.30. Found: C, 83.06; H, 5.29.

***cis*-1-*p*-Trifluoromethylphenyl-2,3,4-triphenyl-2-butene-1,4-dione (58):** prepared like **57**; 96%; recrystallized from 50% AcOH; mp 140–141°; uv ($\epsilon \times 10^{-3}$) 251.5 nm (27.5); ir 1665, 1654 cm^{-1}. *Anal.* Calcd for $C_{29}H_{19}F_3O_2$: C, 76.30; H, 4.20. Found: C, 76.16; H, 4.41.

2,5-Diethoxy-2-*p*-trifluoromethylphenyl-3,4,5-triphenyl-2,5-dihydrofuran (58 cyclic diethyl ketal[19]): from **58** by absolute EtOH–AcOH (10:1 (ml), reflux, 2 min, cooled); 69%; recrystallized from hexane; mp 160–161°; uv ($\epsilon \times 10^{-3}$) 261 nm (16.5); nmr δ 7.2 (m, 19), 3.75 (q, 4, J = 6.5 Hz), 1.27 (t, 6, J = 6.5 Hz). *Anal.* Calcd for $C_{33}H_{29}F_3O_3$: C, 74.73; H, 5.47. Found: C, 74.51; H, 5.52.

***cis*-2-*p*-Trifluoromethylphenyl-1,3,4-triphenyl-2-butene-1,4-dione (59):** from **49** (like **57**); 87%; recrystallized from MeOH; mp 187–188°; uv ($\epsilon \times 10^{-3}$) 259 nm (28.2); ir 1650, 1670 cm^{-1}; nmr δ 7.9 (m, 4), 7.3 (m, 15). *Anal.* Calcd for $C_{29}H_{19}F_3O_2$: C, 76.30; H, 4.20. Found: C, 76.42; H, 4.37.

1,2-Bis[2-(2,4,5,5-Tetraphenyl-2,5-dihydrofuranyl)]hydrazine (2). To a solution of cyclic ketal **10** (2 g) in AcOH (10 ml, 100°) was added dropwise 85% hydrazine hydrate in AcOH (1:5 ml), followed by stirring (2 min), cooling (**2** crystallizing), and addition of H_2O (second crop): 1.6 g (86%); recrystallized from C_6H_6–absolute EtOH; mp 194–195° dec; uv ($\epsilon \times 10^{-3}$) 254 nm (2.96); ir (CCl_4) 3250, 3270 (shoulder), 3260, 3270 cm^{-1} (shoulder); nmr δ 7.1 (m, 40), 5.97 (s, 2), 3.10 (s, 2). *Anal.* Calcd for $C_{56}H_{44}N_2O_2$: C, 86.57; H, 5.71; N, 3.61. Found: C, 86.62, H, 5.80, N, 3.54.

Deazotizations of 2. (A) Fusion pyrolysis (6 g, heated slowly, N_2 evolution beginning at 197° and ceasing before 212°) and chromatography (Florisil, 60–100% C_6H_6–petroleum pentane) gave **14**[4d] (3.6 g, 62%): mp 156–159°; recrystallized (C_6H_6–EtOH); mp 193–194°.

(B) Pyrolysis in decalin (1 g, 10 ml, reflux, 4 hr), crystallizations (EtOH), and chromatography (Al_2O_3, C_6H_6–petroleum pentane) gave **14** (0.3 g, 32%), mp 176–178°. Crystallization of the residual oil (absolute EtOH) gave 1,2,4,4-tetraphenyl-3-buten-1-one (**15**): 0.055 g (5.7%); mp 86–87° (lit.[4i] 91.5–93°).

(C) Photolysis[9] [3 g, C_6H_6 (500 ml, degassed, N_2), $\rightarrow N_2$, 4 hr], evaporation (*in vacuo*), and digestion of the residue hot hexane (200 ml, 30 min, standing overnight)] returned **2** (1.4 g). From the filtrate chromatography (Florisil, 50–60% C_6H_6–petroleum pentane) gave **14** (0.05 g, 7% from **2** consumed), mp 179–180°. The residue (from 90–100% benzene fraction), with EtOH, gave cyclic ketal **12** (0.29 g, 29%), mp 145–146° (that hydrolysis and ethanolysis occur on the column was demonstrated separately).

2,3,4-Triphenyl-5,5-[^{14}C-diphenyl]-2,5-dihydrofuran-2-ol (12*).[3e,g] To PhLi [from Li (4.5 g), [^{14}C]-PhBr (50 g), Et_2O (300 ml), 1.5 hr] was added portionwise 31 g of *cis*-dibenzoylstilbene (**11**). Stirring (5 min), quenching (ice–NH_4Cl), evaporation of Et_2O extracts, and digestion of the residue (absolute EtOH) gave **12** (35.5 g, 95%): recrystallized from C_6H_6–EtOH; mp 163–164° (lit.[3e,g] 164–165°); uv 250 nm (shoulder, ϵ 12,000); ir 2.8 μ. *Anal.*[3e] Calcd for $C_{34}H_{26}O_2$: C, 87.52; H, 5.62. Found: C, 87.31: H, 5.52. **12** was converted into 2-ethoxy ketal **13** by EtOH (trace H^+): recrystallized from EtOH; mp 157–158° (73%). *Anal.* Calcd for $C_{36}H_{30}O_2$: C, 87.42; H, 6.12. Found: C 87.44; H, 6.12. Hydrolysis of **13** [AcOH–H_2O, 10:1 (ml), reflux 15 min] regenerated **12**.

1,2-Bis[2-(2,3,4-triphenyl-5,5-[^{14}C-diphenyl]-2,5-dihydrofuranyl)]hydrazine (3*). Hydrazine hydrate [85% (3.5 ml), AcOH (25 ml)] was added dropwise (stirring) to **13** (5 g, AcOH, 125 ml, 70°), crystals soon appearing. Cooling gave **3*** (4.3 g, 86%): mp 256–257° dec; recrystallized from C_6H_6–abs EtOH; mp 264–265° dec; uv ($CHCl_3$) nm ($\epsilon \times 10^{-3}$) 250 nm (20.6); ir 3240, 3220 cm^{-1} (shoulder); nmr δ 6.9 (m, 50), 4.59 (s, 2, $D_2O \rightarrow 0$). *Anal.* Calcd for $C_{68}H_{52}N_2O_2$: C, 87.90; H, 5.64; N, 3.01. Found: C, 88.00; H, 5.64; N, 2.94. Ethanolysis of **3** by absolute EtOH–AcOH [30:1 (ml), reflux 5.5 hr] and cooling returned **3** (0.055 g), and quenching (H_2O) gave **13** (97% from **3** consumed), mp 140–145° (lit.[3c] 156–157°). Hydrolysis of **3** by AcOH–concentrated HCl [30:1 (ml), reflux, 1 hr], cooling, quenching (H_2O), chromatographing (Florisil, 50–80% C_6H_6–petroleum ether), and recrystallization (hexane) gave **12**.

Deazotizations of 3. (A) Pyrolysis (4 g), heated slowly to fusion (280°, $\rightarrow N_2$ at 258°), and chromatographing (Florisil, C_6H_6–petroleum pentane) gave tetraphenylfuran (**7**) [0.2 g (62%); recrystallized from AcOH; mp 174–175°], 2,3,4,5,5-pentaphenyl-4,5-dihydrofuran (**29**) [0.6 g (15%); recrystallized from absolute EtOH; mp 143–145° (lit.[3a,e,g] 148–151°)], and 1,2,3,4,4-pentaphenyl-3-buten-1-one (**28**) [2 g (52%); crystallized from C_6H_6–absolute EtOH; mp 185–186° (lit.[3e] 185°)]. **28** and **29** were subjected to the above conditions and were recovered unchanged.

(B) Pyrolysis in decalin (3 g, 15 ml, reflux 12 hr, cooling) gave **28** (1.3 g). Chromatographing the residue (Florisil, 10–80% C_6H_6–petroleum ether) and crystallization (AcOH) gave **7** (0.186 g, 7.7%), **29** (0.288 g, 9.9%), and **28** (bringing its total to 53%, mp 179–180°).

(C) Pyrolysis in DMF (153°) (4 hr, $\rightarrow$30% unchanged) for 14 hr, quenching (H_2O), and chromatographing (Florisil) gave only **12** (50%), mp 153–154° (shown to result from hydrolysis of **3** on the column).

(D) Photolysis[9] in benzene (degassed N_2, 4 hr), evaporation, digestion of the residue (hexane, 100), and cooling returned **3** (87%). Evaporation of the filtrate and chromatographing (Florisil, 40–100% C_6H_6–petroleum ether) gave **29** (8%), **31** (10%), and **28** (10%), calculated from **3** consumed. Furan **7** was recovered upon similar irradiation (80%).

1,2,3,4,4-Pentaphenyl-3-buten-1-one (28[3g]) by Reduction of 2-Ethoxy-2,3,4,5,5-pentaphenyl-2,5-dihydrofuran (13). To **13** (3 g, AcOH, reflux) was added Zn dust (6 g, 15 min, exothermic, color change from red through green to yellow); filtering and cooling gave **28** (1.6 g, 59%) which was recrystallized from absolute EtOH, mp 180–184° (lit.[3g] 185°).

1,2,3,4,4-Pentaphenylbutan-1-one (30). Reduction of **13** (as above but reflux, 80 min) gave **30** (62%), mp 167–169°, which was recrystallized from absolute EtOH: mp 193–194.5°; ir 1675 cm^{-1}; uv ($\epsilon \times 10^{-3}$) 240 nm (14.6); nmr δ 7.3 (m, 25), 5.12 (d, 1, J = 8.0 Hz), 4.55 (m, 2); nmr (C_6H_6) δ 5.29 (d, 1, J = 8.5 Hz), 4.93 (pair of overlapping doublets, 1, J = 8.5 Hz, J' = 9.0 Hz), 4.67 (dd, 1, J' = 9.0 Hz). *Anal.* Calcd for $C_{34}H_{28}O$: C, 90.23; H, 6.24. Found: C, 90.15; H, 6.15.

$KMnO_4$ oxidations of 1,2,3,4,4-pentaphenyl-3-buten-1-one (28 and 28*), carried out as for **14**, gave benzophenone 2,4-dinitrophenylhydrazone (15%*), mp 237–238°. The benzoic acid in the ether extract of the acidified steam distillation residue was removed by 10% NaOH and isolated by acidification, Et_2O extraction, sublimation, and recrystallization (H_2O): mp 121–122°. Evaporation of the remaining Et_2O solution containing dihydrofuranol **12***, chromatographing (Florisil), and crystallizing (absolute EtOH) gave cyclic ketal **13*** (18%), mp 156–157°. A similar oxidation and work-up, but using only 1 equivalent of $KMnO_4$ (1 hr), gave **13***; 35% from **28** was consumed.

Registry No.—**1,** 53449-04-0; **2,** 53466-62-9; **3,** 53466-63-0; **4,** 53449-05-1; **6,** 53449-06-2; **7,** 1056-77-5; **8,** 2313-03-3; **9,** 53449-07-3; **10,** 53449-08-4; **11,** 6313-26-4; **12,** 53449-09-5; **13,** 53449-10-8; **14,** 53449-11-9; **15,** 2491-41-0; **21,** 13249-75-7; **23,** 2491-44-3; **28,** 53448-80-9; **30,** 53448-81-0; **41,** 21449-71-8; **42,** 53448-82-1; **43,** 13249-75-7; **44,** 53448-83-2; **44** methyl cyclic ketal, 53448-84-3; **44** ethyl cyclic ketal, 53448-85-4; **45,** 53448-86-5; **45** ethyl cyclic ketal, 53448-87-6; **46,** 53448-88-7; **46** methyl cyclic ketal, 53448-89-8; **46** ethyl cyclic ketal, 53448-90-1; **47,** 53448-91-2; **48,** 53448-92-3; **49,** 53448-93-4; **50,** 53448-94-5; **52,** 53448-95-6; **53,** 53448-96-7; **54,** 53448-97-8; **55,** 53448-98-9; **56,** 53448-99-0; **57,** 53449-00-6; **58,** 53449-01-7; **58** cyclic diethyl ketal, 53449-02-8; **59,** 53449-03-9; hydrazine hydrate, 7803-57-8; *p*-trifluoromethylphenyl bromide, 402-43-7.

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(3) Ph.D. Dissertations, University of Virginia: (a) J. I. Dale, 1962; (b) D. W. Boykin, Jr., 1965; (c) C. V. Juelke, 1967; (d) R. G. Bass, 1961; (e) C. L. Dickerson, 1954; (f) L. P. Tenney, 1966. (g) *Cf.* unpublished portions of the work of J.I.D., R.G.B., and C.L.D. on methylaryl reduction of, and additions to, *cis*- and *trans*-dibenzoylstilbenes and dibenzoylstyrenes.

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Oxidative Ring Closure of 1-Benzyloxy-3-arylureas to 1-Benzyloxybenzimidazolones[1]

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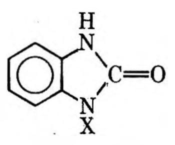
Lead tetraacetate oxidation of 1-benzyloxy-3-arylureas (1) results in intramolecular ring closure to form 1-benzyloxybenzimidazolone (2) or in intermolecular nitrogen to nitrogen coupling to form 1,2-dibenzyloxy-1,2-diphenylcarbamylhydrazines (7). Studies of the oxidation of structures related to 1 establish that the requirements for a ring closure are quite specific. Studies of the influence of substituents show that electron-withdrawing substituents on the aryl group inhibit the ring closure particularly when the substituents are ortho to the urea group. The decomposition of the hydrazines 7 occurs rapidly and aryl isocyanates and benzyl alcohol are first formed.

The finding that *N*-acyl-*O*-alkylhydroxylamines undergo oxidative coupling to *N,N*-diacyl-*N,N*-dialkoxyhydrazines[3] prompted us to study the lead tetraacetate oxidation of 1-benzyloxy-3-phenylurea[4] (1). Instead of the expected hydrazine product, oxidation of 1 with excess lead tetraacetate resulted in a single product, 1-benzyloxybenzimidazolone (**2a**), mp 159–160°, isolated in 85% yield and estimated in 97% yield by spectroscopic measurements. The structure of **2a** was established by catalytic hydrogenolysis to **2b** with palladium on carbon and to the known compound **2c** with Raney nickel. The properties of **2c** were identical with those of a sample of benzimidazolone prepared by the method of Kym.[5]

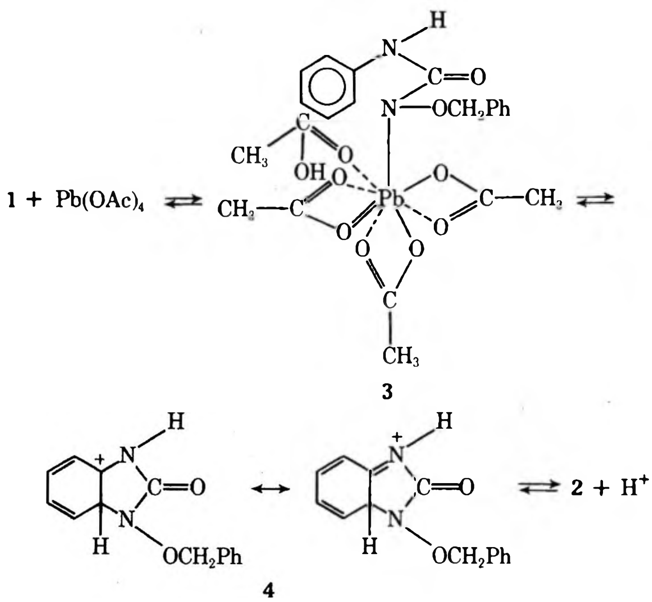
$C_6H_5CH_2ONHCONHC_6H_5$

1



2a, X = $OCH_2C_6H_5$
b, X = OH
c, X = H

Scheme I



Results and Discussion

The proposed scheme for conversion of 1 to 2 is shown in Scheme I

Substituents on the Aryl Ring. The influence of substituents on the aryl ring of 1-benzyloxy-3-arylureas was studied first. Results are presented in Table I. Strongly electron-withdrawing groups decreased the yield of ring closure, and in these cases a competing reaction, nitrogen to nitrogen coupling, was observed (*vide infra*).

Groups in the ortho position markedly affect the ring closure. While a *p*- or *m*-chloro substituent appeared not to diminish the ring closure significantly below the unsubstituted case, no ring closure was observed with the o-chloro substituent. Even when 1-benzyloxy-3-o-chlorophenylurea was slowly added to lead tetraacetate to effect high dilution conditions only a 19% yield of benzimidazolone was realized. Under no conditions, high dilution or otherwise, were we able to affect a ring closure with 1-benzyloxy-3-o-nitrophenylurea.

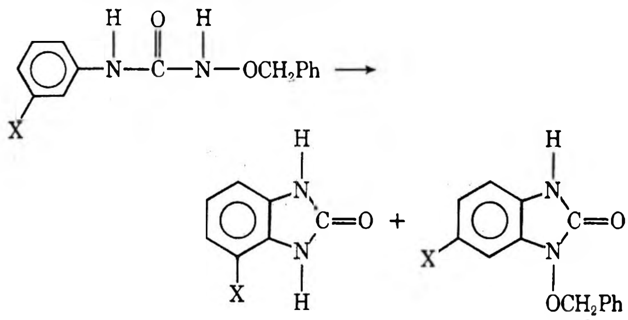
The inhibition of ring closure with the o-fluoro, o-chloro, and o-nitro compounds is probably a combination of inductive and steric effects. In cases where both electron withdrawal and steric repression are important (*e.g.*, the nitro and chloro compounds), the ring closure reaction is strongly inhibited. In cases where steric repulsion is small and the

Table I
Products from Lead Tetraacetate Oxidation of 1-Benzyloxy-3-arylureas in Chloroform Solution[a]

Reaction no.	Aromatic substituent	Registry no.	% benzimidazolone[b]	% carbamate
1	p-CH_3O	51457-93-3	95	0
2	p-CH_3	51457-92-2	100	0
3	p-H	33026-77-6	97	0
4	p-Cl	51457-91-1	94	0
5	p-NO_2	51457-90-0	12	88
6	m-CH_3	51457-96-6	97	0
7	m-Cl	51457-94-4	99	0
8	m-NO_2	51457-95-5	15	84
9	o-CH_3O	51458-01-6	98	0
10	o-CH_3	51458-00-5	96	0
11	o-F	51457-99-9	41	50
12	o-Cl	51457-98-8	0	98
13	o-NO_2	51457-97-7	0	96

[a] All reactions were run with an initial concentration of 5.82×10^{-2} M solutions of 1-benzyloxy-3-arylureas in chloroform containing 5.94×10^{-2} M concentration of lead tetraacetate. [b] Values reported are actual percentage yields of isolated product.

Table II
Ratio of Isomeric Benzimidazolone Products from Lead Tetraacetate Oxidation of Meta-Substituted 1-Benzyloxy-3-arylureas



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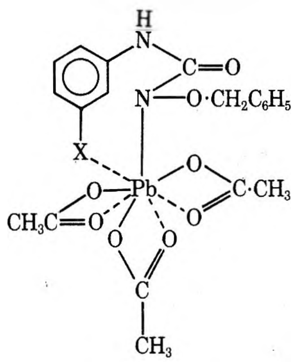
	%	Position of NH in nmr	%	Position of NH in nmr	of/pf
m-Cl	51	11.41	49	11.24	1.04
m-CH_3	45	10.54	55	10.68	0.82
m-NO_2	60	11.86	40	11.68	1.50

inductive influence is large (*e.g.*, fluorine), the ring closure is moderately inhibited. And in the case where the inductive influence is still smaller and the steric interaction is also small (*e.g.*, methoxyl), ring closure is quantitative.

In the case of meta-substituted 1-benzyloxy-3-arylureas two isomeric products are possible depending upon whether ring closure occurs ortho or para to the substituent. The presence of these isomeric products were established by nmr spectra, and they were isolated from the reaction mixture either by fractional crystallization or thin layer chromatography. Structure **6** was established for the higher melting isomer from oxidation of 1-benzyloxy-3-m-chlorophenylurea by hydrogenolysis to 5-chlorobenzimidazolone. The same product was obtained by hydrogenolysis of 1-benzyloxy-6-chlorobenzimidazolone obtained as the only product from the lead tetraacetate oxidation of 1-benzyloxy-3-p-chlorophenylurea. Similar evidence established that the higher melting isomer from oxidation of 1-benzyloxy-3-m-methylphenylurea has structure **6.** Attempts to hydrogenate the products from 1-benzyloxy-3-m-nitrophenylurea were not successful and assignment of **6** as the higher melting isomer was made on the basis of the position of the NH absorption in the nmr spectra.

The ratio of **5** to **6** was estimated by integrating the two NH peaks in the nmr for each compound, the CH_3 peaks for the methyl compounds, and the CH_2 peaks for the nitro compounds. The results are in Table II.

From the percentage yields the ratios of ortho to para partial rate factors (of/pf) have been calculated.[6] The value for the methyl compound, 0.82, lies between the value 0.60 for the deuteration (D_2SO_4) of toluene[7] and 1.0 for the detritiation (H_2SO_4) of toluene.[8] In contrast, of/pf for the chloro compound is 1.04 and for nitration[6] and detritiation of chlorobenz of/pf are 0.21 and 0.22, respectively. Possibly a lead-containing intermediate **7** in which the lead is coor-



7

dinating with nonbonding electrons on either the chloro or nitro groups could explain the unexpectedly large amount of ortho direction.[10]

Oxidative cyclization of 1-benzyloxy-3-(α-naphthyl)urea led exclusively to attack at the β position of the naphthalene ring rather than the peri position.

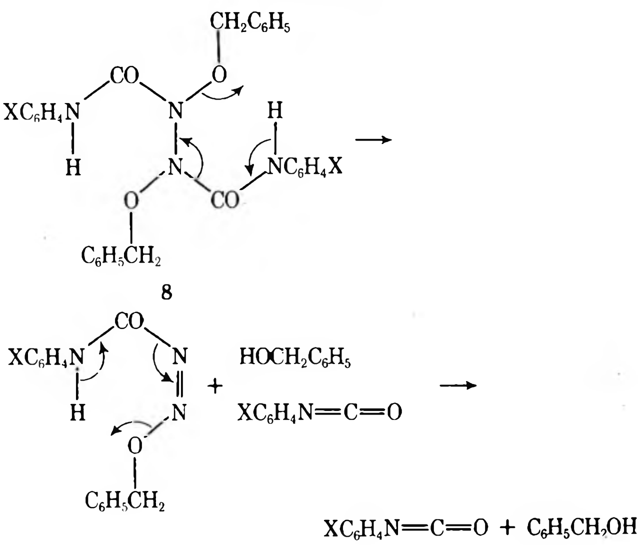
Hydrazines. In those cases where oxidative ring closure failed to occur a nitrogen to nitrogen coupling reaction was observed. In most cases the hydrazines **8** formed by the oxidative coupling of the 1-benzyloxy-3-arylureas were too unstable to isolate and nitrogen gas, which was evolved almost as fast as the reagents were combined, and the carbamates were found as reaction products. Only in the case of 1-benzyloxy-3-o-nitrophenylurea was the hydrazine relatively stable. This hydrazine, which was isolated as a viscous oil, slowly decomposed with the evolution of nitrogen over a period of 32 hr in bromoform or chloroform solutions and benzyl o-nitrophenylcarbamate was isolated as the sole reaction product.

Isocyanates and alcohols were identified as the first reaction products from decompositions of hydrazines. An infrared spectrum of chloroform solution of 1-benzyloxy-3-p-nitrophenylurea, determined 90 sec after addition of lead tetraacetate, showed a strong absorption at 2260 cm^{-1} which was found to be identical, both in position and shape, to the N=C=O absorption of p-nitrophenyl isocyanate. The intensity of this absorption increased for the first 5 min after initiation of the oxidation reaction and then slowly decreased for the next hour. In a subsequent work-up of the reaction solution only benzyl p-nitrophenylcarbamate, the reaction product from p-nitrophenyl isocyanate and benzyl alcohol, was obtained as the major reaction product.

The presence of p-nitrophenyl isocyanate as a reaction intermediate in the lead tetraacetate oxidation of 1-benzyloxy-3-p-nitrophenylurea in chloroform solution was further established by the addition of n-butylamine to the reaction solution. In this case the major reaction products were 1-n-butyl-3-p-nitrophenylurea and benzyl alcohol. Presumably the n-butylamine, which is much more reactive toward isocyanates than benzyl alcohol, reacted with the p-nitrophenyl isocyanate from the decomposition of the hydrazine compound 8 to yield the 1-n-butyl-3-p-nitrophenylurea, along with the unreacted benzyl alcohol. Compounds 1 and 2 do not react with n-butylamine under these conditions. In chloroform solutions containing no n-butylamine the p-nitrophenyl isocyanate slowly reacts with the benzyl alcohol to give the benzyl p-nitrophenylcarbamate as the reaction product.

A mechanism of decompositon of 8 by which it is possible to explain the observations is shown in Scheme II. First,

Scheme II

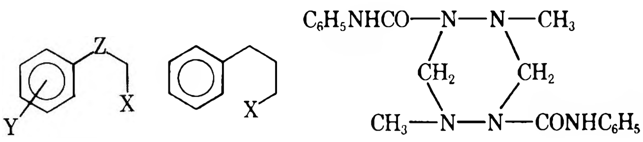


the mechanism provides an explanation of the observed products. Second, intramolecular hydrogen transfer occurs in this system in a similar way as acid catalysis was shown to occur with the 1,2-diacyl-1,2-dialkoxyhydrazines.[3] Such internal protonation would provide an explanation for the much more rapid decomposition of 8 than of 1,2-diacyl-1,2-dialkoxyhydrazines.[3,11] Third, the NH proton in 1,2-dibenzyloxy-1,2-di-o-nitrophenylhydrazine is expected to form a stable hydrogen bond to the nitro group, and thus the hydrogen would not be available for the internal protonation suggested in the mechanism. The o-nitro compound is the most stable that has been encountered in this series. Fourth, as was found earlier[3] 1,2-dialkoxy-1,2-diacylhydrazines decompose in two consecutive steps. Similarly, here it is found that the plot of volume of nitrogen evolved as time was an "S" shaped curve. These four observations support the proposed mechanism.

Oxidation of Related Structures. The supposition that a ring closure might be expected by oxidation of other systems 9,10 containing a readily oxidizable group situated γ with respect to an aromatic ring was tested.

Oxidation of 4-phenyl-1-butanols, 3-phenyl-1-propanols,[13] and 2-phenoxyethanol[13] with lead tetraacetate has been reported to give ring closures analogous to I. Similarly lead tetraacetate oxidation of 5-(p-nitrophenyl)valeric acids and 3-(o-biphenyl)propionic acid resulted in intramolecular cyclization to 6-nitro-1,2,3,4-tetrahydronaphthalene and 9,10-dihydrophenanthrene, respectively.[14] Because of these reports and our finding with 1-benzyloxy-3-phenylurea other compounds with a readily oxidizable group situated γ or δ to an aromatic ring activated by an amido or ether function were studied.

We have reported the fact that ring closure failed in the lead tetraacetate oxidation of malonic anilide, phenoxyacetone oxime, and 1,2,4-triphenylsemicarbazide. Also with 1,1-dimethyl-4-phenylsemicarbazide which is more like I, oxidative dimerization occurred resulting in a very different type of ring closure product, 1,4-dimethyl-2,5-di(phenylcarbamyl)hexahydrotetrazine (11).[15] In a continued



9 10 11

attempt to establish the limitations of the ring closure reaction, oxidations of several structures like 8 with a hydroxylamino group (–NHO–) at X were studied. In all cases the ring was activated by a methoxyl group at Y or an oxygen or nitrogen at Z. N-Acetyl-O-p-methoxybenzylhydroxylamine, N-p-methoxyphenylacetyl-O-benzylhydroxylamine, N-phenoxyacetyl-O-benzylhydroxylamine, N-phenoxyacetyl-O-benzylhydroxylamine, and phenyl benzyloxycarbamate all gave the oxidative nitrogen to nitrogen coupling and not ring closure. In the case of 1,1-diphenyl-3-benzyloxyurea a 99% yield of 1-benzyloxy-3-phenylbenzimidazolone, the ring closed product, was obtained. Thus it is established that the ring closure 1 to 2 has a narrow specific requirement in structure. The hydroxylamino group cannot be replaced by a hydrazine, oximino, or methylene group, and the unoxidized NH group of 1 can only be replaced by N-aryl but not by oxygen or methylene. In general, oxidations of 3-substituted 1-phenylpropanes do not give ring closures under the conditions used for cyclization of 1.

Experimental Section

Melting points were corrected and were determined in capillary tubes using an A. H. Thomas Unimelt apparatus. Infrared spectra were obtained using a Perkin-Elmer grating infrared spectrophotometer, Model 621. The nuclear magnetic resonance spectra (nmr) were taken on a Varian A60 instrument. Mass spectra were run on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Microanaylses were determined at the University of Idaho on a Perkin-Elmer, Model 240, elemental analyzer. Osmotic molecular weight determinations were run on a Hitachi Perkin-Elmer molecular weight apparatus, Model 115.

1-Benzyloxy-3-arylureas. These preparations were carried out by reaction of benzyloxyamine[16] with an equimolar quantity of aryl isocyanate. The details of these preparations are described elsewhere.[17]

Solvent. Chloroform was purified by shaking several times with concentrated sulfuric acid, drying with anhydrous calcium chloride, passing through a column of alumina, and distilling. All lead tetraacetate oxidations run in chloroform were run within 24 hr of the completion of this purification procedure.

Lead Tetraacetate Oxidation of 1-Benzyloxy-3-phenylurea. Method I. To 1.00 g (4.13 mmol) of 1-benzyloxy-3-phenylurea dissolved in 50 ml of dry chloroform was added with stirring a 10-ml solution of chloroform containing 2.01 g (4.53 mmol) of lead tetraacetate analyzed by Arapahoe Chemical Co. as 95% lead tetraacetate and 5% acetic acid. Upon mixing the reaction solutions a precipitate having the same melting point and infrared spectrum as lead diacetate was formed. The solution was filtered, and the precipitate was washed with chloroform until 250 ml of filtrate was obtained. The filtrate was washed twice with 50-ml aliquots of water and dried with anhydrous calcium chloride. On removing the chloroform, 0.96 g (96%) of white solid remained which on recrystallization from ethanol–water gave 0.85 g of pure 1-benzyloxybenzimidazolone: mp 159–160°; ir (Nujol) 1705 (C=O); nmr (DMSO-d_6) δ 5.22 (s, 2), 6.80–7.70 (m, 9), broad 11.10 ppm (s, 1). Major peaks in the mass spectrum at 70 eV include m/e (relative intensities) 240 (26), 134 (100), 108 (60), 105 (95), 91 (52). *Anal.* Calcd for $C_{14}H_{12}N_2O_2$: C, 70.00; H, 5.01; N, 11.67. Found: C, 69.87; H, 5.13; N, 11.93.

Lead Tetraacetate Oxidation of Other 1-Benzyloxy-3-Para-Substituted Arylureas. Physical data and analyses for the oxidation products of other 1-benzyloxy-3-para-substituted arylureas are given in Table III.

Table III
Summary of Physical Data and Analyses for Substituted 1-Benzyloxybenzimidazolone (2) Products Obtained as Sole Reaction Products in High Yields[a] from Oxidation of 1-Benzyloxy-3-Para-Substituted Ureas

Substituent on 2	Registry no.	Mp, °C	Analysis, %		
				Calcd	Found
6-Methoxy	53820-90-9	149–150	C	66.65	66.63
			H	5.22	5.34
			N	10.37	10.32
6-Methyl	53820-91-0	162–163	C	70.85	70.87
			H	5.55	5.56
			N	11.02	10.88
6-Chloro	53820-92-1	153–154	C	61.21	61.22
			H	4.04	4.13
			N	10.20	10.16

[a] All reactions were run in chloroform solutions with an initial concentration of 5.82×10^{-2} *M* 1-benzyloxy-3-arylurea and 6.10×10^{-2} *M* lead tetraacetate. Products from top to bottom of table were obtained in 95, 100, and 94% yield, respectively.

Catalytic Hydrogenation of 1-Benzyloxybenzimidazolone with Palladium on Carbon. In a microhydrogenation apparatus was placed 0.210 g (0.875 mmol) of 1-benzyloxybenzimidazolone in 20 ml of 95% ethanol and 0.1 g of 5% palladium on carbon. The mixture was stirred for 40 min, and 23 ml of hydrogen corrected to STP (1.02 mmol) was absorbed. The catalyst was removed by filtration, and the solution was analyzed for toluene using glc and the internal standard technique. The estimated yield of toluene was 0.070 g, 87%. The solvent was removed and the solid product (0.121 g, 92%, mp 228–232°) was obtained. This product was recrystallized from a mixture of acetone and carbon tetrachloride and was observed to decompose sharply at 230° and produce a green color with a ferric chloride solution: ir (Nujol) broad 3115, 1680 cm^{-1}. *Anal.* Calcd for $C_7H_6N_2O_2$: C, 55.99; H, 4.03; N, 18.66. Found: C, 56.14; H, 4.19; N, 18.82.

Catalytic Hydrogenation of 1-Benzyloxybenzimidazolone with Raney Nickel. Hydrogenation of 0.247 g (1.03 mmol) of 1-benzyloxybenzimidazolone with Raney nickel catalyst occurred in about 8 hr with an observed uptake of 48.5 ml (0.216 mmol) of hydrogen. The solution was filtered and 0.069 g, 73%, of toluene was estimated to be present using glc and the internal standard technique. Upon evaporation 0.130 g, 94%, of white solid (mp 309–313°) was obtained. Purification was achieved by recrystallization from acetone: mp 313–315°; mmp with benzimidazolone[5] 313–315°. *Anal.* Calcd for $C_7H_6N_2O$: C, 62.67; H, 4.51; N, 20.89. Found: C, 62.52; H, 4.64; N, 20.77.

Lead Tetraacetate Oxidation of 1-Benzyloxy-3-*p*-nitrophenylurea. In a closed system connected to a gas buret, a 1.00-g (3.49 mmol) sample of 1-benzyloxy-3-*p*-nitrophenylurea dissolved in 50 ml of chloroform was added with stirring to a 10-ml chloroform solution containing 1.70 g (3.84 mmol) of lead tetraacetate. Upon mixing the reaction solutions 34.0 ml (STP) or 1.518 mmol of a gas was evolved which gave no infrared spectrum and had the same glc retention time as nitrogen. The evolution of gas was complete within 2 min of the initial mixing time. The mixture was filtered, and 0.93 g of solid was obtained when the chloroform was evaporated A 0.75-g sample of this was dissolved in ethyl acetate and placed on 50 g of a neutral alumina column. Upon eluting the column with 50 ml of ethyl acetate, 0.60 g (80%) of a solid product, mp 157–158°, was obtained. This compound had identical ir and nmr spectra with benzyl *p*-nitrophenylcarbamate prepared by the reaction of benzyl alcohol with *p*-nitrophenyl isocyanate: ir (Nujol) 3333 (N–H), 1740 cm^{-1} (C=O); nmr (DMSO-d_6) δ 5.23 (s, 2), 7.31–8.32 (m, 9), 10.46 ppm (broad s, 1). *Anal.* Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.94; H, 4.37; N, 10.32.

Further elution of the column with 75 ml of methanol afforded 0.072 g (9.6%) of a solid product, mp 200–201°, which was identified as 1-benzyloxy-6-nitrobenzimidazolone: ir (Nujol) 1720 (C=O), 1080, 835, 700 cm^{-1}; nmr (DMSO-d_6) δ 5.28 (s, 2), 7.05–8.06 (m, 8), 11.84 ppm (broad s, 1). *Anal.* Calcd for $C_{14}H_{11}N_3O_4$: C, 58.94; H, 3.89; N, 14.73. Found: C, 58.86; H, 3.92; N, 14.68. A comparison of the integration of the N–H protons in the nmr spectrum of the original reaction mixture showed the benzyl *p*-nitrophenylcarbamate and 1-benzyloxy-6-nitrobenzimidazolone to be present in a molar ratio of 88 to 12%, respectively. The volume of nitrogen evolved corresponds to 87% of the urea to hydrazine 8 and on to *p*-nitrophenylcarbamate.

Detection of *p*-Nitrophenyl Isocyanate during Lead Tetraacetate Oxidation of 1-Benzyloxy-3-*p*-nitrophenylurea. To a 1.00-g (3.5 mmol) sample of 1-benzyloxy-3-*p*-nitrophenylurea in 40 ml of chloroform was added 1.40 g (3.15 mmol) of lead tetraacetate, and the mixture was stirred for 30 sec at room temperature. A sample of the reaction mixture was placed in a 464-μ path length liquid infrared cell and the infrared spectrum of the solution was run between 2350 and 2200 cm^{-1}. The first infrared spectrum was run 90 sec after the initial addition of the lead tetraacetate to the reaction solution and showed a strong infrared absorption at 2260 cm^{-1}. The intensity of this band increased for the first 5 min and then slowly decreased for the next hour until it disappeared. A solution of *p*-nitrophenyl isocyanate in chloroform showed a strong infrared absorption at the same wave number (2260 cm^{-1}) and the intensity of this absorption also slowly decreased when benzyl alcohol was added to the solution. Both of these bands had the same characteristic shape being rather broad with the maximum intensity occurring at the lower wavelength side of the band.

Lead Tetraacetate Oxidation of 1-Benzyloxy-3-*m*-nitrophenylurea. When this oxidation was carried out using method I, a 99% yield of solid was obtained. From the nmr it was estimated that this solid was a mixture of 15% of two isomeric 1-benzyloxynitrobenzimidazolones and 85% benzyl *m*-nitrophenylcarbamate. Only this latter compound was isolated from this reaction mixture using column chromatography (alumina and ethyl acetate) and was shown to be identical to the product from *m*-nitrophenyl isocyanate with benzyl alcohol: ir (Nujol) 3306, 1690, 1530, 725 cm^{-1}; nmr (DMSO-d_6) δ 5.27 (s, 2), 7.25–9.67 (m, 9), 10.30 ppm s, 1). *Anal.* Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76, H, 4.44, N, 10.29. Found: C, 61.75, H, 4.42, H, 10.40. From the column chromatograph the 1-benzyloxynitrobenzimidazolones were obtained by elution with methanol. From the nmr spectra of the mixture the yields were estimated to be 87% for the carbamate and 13% for the isomeric benzimidazolones, while the ratio of the latter compounds was estimated to be 60:40.

Lead Tetraacetate Oxidation of 1-Benzyloxy-3-*m*-nitrophenylurea Using High Dilution Conditions. Method II. Isolation of the benzimidazolones was undertaken from a high dilution experiment where 1.00 g (3.49 mmol) of 1-benzyloxy-3-*m*-nitrophenylurea in 500 ml of chloroform was added slowly (100 min) to 1.70 g (3.84 mmol) of lead tetraacetate in 100 ml of chloroform. From this oxidation 0.92 g of solid product which was estimated to be 93% 1-benzyloxynitrobenzimidazolones and 7% benzyl *m*-nitrophenylcarbamate by nmr was obtained. One isomeric benzimidazolone was isolated by fractional crystallization from chloroform: mp 220–221°; ir (Nujol) 1722, 1517, 1337, 693 cm^{-1}; nmr (DMSO-d_6) δ 5.30 (s, 2), 6.93–8.05 (m, 8), 11.68 ppm (s, 1). *Anal.* Calcd for $C_{14}H_{11}N_3O_4$: C, 58.94, H, 3.89, N, 14.73. Found: C, 58.70, H, 3.90, N, 14.72. From chloroform–carbon tetrachloride solution a second isomer precipitated: mp 173–174°; ir (Nujol) 1730, 1532, 1350, 854, 710 cm^{-1}; nmr δ 5.32 (s, 2), 7.02–7.76 (m, 8), 11.86 (s, 1). *Anal.* Calcd for $C_{14}H_{11}N_3O_4$: C, 58.94, H, 3.89, N. 14.73. Found: C, 58.82, H, 3.90, N, 14.93. The ratio of these two isomeric 1-benzyloxynitrobenzimidazolones was estimated to be 40 to 60%, respectively.

Lead Tetraacetate Oxidation of Other 1-Benzyloxy-3-Meta-Substituted Arylureas. Physical data and analyses for the oxidation products of other 1-benzyloxy-3-meta-substituted arylureas are given in Table IV.

Lead Tetraacetate Oxidation of 1-Benzyloxy-3-*o*-nitrophenylurea. From the oxidation of 1.00 g (3.49 mmol) of 1-benzyloxy-3-o-nitrophenylurea with 1 g (2.26 mmol) of lead tetraacetate was isolated 0.950 g of an oily product: ir (neat) 3318, 1725, 735, 693 cm^{-1}; nmr ($CDCl_3$) δ 5.27 (s, 2), 6.90–8.75 (m, 9), 11.11 ppm (s, 1).

A 0.600-g (1.05 mmol) sample of this product was dissolved in 30 ml of bromoform and connected to a gas buret. The temperature of solution was held at 23.0° and Table V shows the observed evolution of nitrogen gas. Upon removal of the bromoform under reduced pressure a solid product was obtained. A pure sample, mp 65–66°, was obtained upon recrystallization of this product from a hexane–carbon tetrachloride mixture. This product was identified as benzyl *o*-nitrophenylcarbamate by comparison of the nmr and infrared spectra with a sample of benzyl *o*-nitrophenylcarbamate prepared by the reaction of benzyl alcohol with o-nitrophenyl iso-

Table IV
Summary of Physical Data and Analyses for Isomeric Aryl-Substituted 1-Benzyloxybenzimidazolones (2) from 1-Benzyloxy-3-Meta-Substituted Arylureas

Substituent on 2	Registry no.	Mp, °C	Ratio of products estimated by nmr, %	Analysis, % Calcd	Found
5-Methyl[b]	53820-93-2	153–154	55	C 70.85	71.13
				H 5.55	5.67
				N 11.02	11.02
7-Methyl	53820-94-3	139–140	45	C 70.85	70.99
				H 5.55	5.66
				N 11.02	11.04
5-Chloro[b]	53820-95-4	204–205	49	C 61.21	61.12
				H 4.04	4.13
				N 10.20	10.31
7-Chloro	53820-96-5	160–161	51	C 61.21	61.00
				H 4.04	3.95
				N 10.20	10.19

[a] Overall yields were 96% for the two methyl compounds and 98% for the two chloro compounds. [b] Structures were identified by conversion of these compounds to 5-methylbenzimidazolone and 5-chlorobenzimidazolone by hydrogenolysis. The same compounds were obtained by hydrogenolysis of 1-benzyloxy-6-methylbenzimidazolone and 1-benzyloxy-6-chlorobenzimidozolone, respectively.

cyanate: ir (Nujol) 3340, 1733, 750, 691, cm^{-1}; nmr ($CDCl_3$) 5.20 (s, 2), 6.85–8.65 (m, 9), 9.86 ppm (s, 1). *Anal.* Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44, N, 10.29. Found: C, 61.88, H, 4.46, N, 10.29.

The decomposition of the oil in $CDCl_3$ was followed by nmr. The nmr absorption due to the oil slowly disappeared while that due to benzyl o-nitrophenylcarbamate slowly increased until the latter absorption was all that was present in the spectrum after 24 hr.

Lead Tetraacetate Oxidation of Other 1-Benzyloxy-3-Ortho-Substituted Arylureas. Physical data and analyses for the oxidation products of other 1-benzyloxy-3-ortho-substituted arylureas are given in Table VI.

Lead Tetraacetate Oxidation of 1-Benzyloxy-3-α-naphthylurea. The oxidation of 1.02 g (3.50×10^{-3} mol) of 1-benzyloxy-3-α-naphthylurea with 1.60 g (3.61×10^{-3} mol) of lead tetraacetate in 60 ml of chloroform, using the same procedure as given above for 1-benzyloxy-3-phenylurea, afforded 0.96 g (97% yield) of a solid product. The nmr spectrum (DMSO-d_6) of this product indicated the presence of a benzyloxynaphthimidazolone compound as the only reaction product. A pure sample with a mp of 156–157° was obtained upon recrystallization of this product from a chloroform–benzene solution: ir (Nujol) 1706, 796, 720, 690 cm^{-1}; nmr (DMSO-d_6) δ 5.32 (s, 2), 7.03–8.32 (m, 11), 12.01 ppm (s, 1). *Anal.* Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96, H, 5.52, N, 9.58. Found: C, 74.02, H, 5.59, N, 9.61.

Table V

Time, min	Ml of N_2 at STP	Time, min	Ml of N_2 at STP
0.0	0.0	945.0	18.0
120.0	0.5	1140.0	20.0
280.0	3.4	1345.0	22.0
370.0	6.0	1535.0	23.2
475.0	9.0	1920.0	23.5
585.0	12.0	∞	23.5 (1.05 mmol)
760.0	15.7		

Table VI
Summary of Physical Data and Analyses for Products of Oxidation of 1-Benzyloxy-3-Ortho-Substitued Arylureas

Aryl substituent on urea reactant	Registry no.	Product	Registry no.	% yield of isolated material	Mp, °C	Analysis, % Calcd	Found
o-Fluoro		Benzyl o-fluorophenylcarbamate	53820-98-7	43	61–62	C 68.56	68.77
						H 4.93	4.96
						N 5.71	5.71
		1-Benzyloxy-4-fluorobenzimidazolone	53820-99-8	34[a]	202–203	C 65.11	65.26
						H 4.29	4.40
						N 10.85	10.87
o-Chloro		Benzyl o-chlorophenylcarbamate	53821-00-4	98[a] 74[b]	53–54	C 64.25	64.40
						H 4.62	4.58
						N 5.35	5.26
		1-Benzyloxy-4-chlorobenzimidazolone	53821-01-5	16[b] 97[c]	211–212	C 61.21	61.01
						H 4.04	4.10
						N 10.20	10.36
2,5-Dichloro	538-20-97-6	Benzyl 2,5-dichlorophenylcarbamate	53821-02-6	97[a,b]	115.5–116.5	C 56.78	56.98
						H 3.74	3.79
						N 4.73	4.86
o-Methoxy		1-Benzyloxy-4-methoxybenzimidazolone	53821-03-7	98	167–168	C 66.65	66.67
						H 5.22	5.27
						N 10.37	10.33
o-Methyl		1-Benzyloxy-4-methylbenzimidazolone	53821-04-8	96[a]	180–181	C 70.85	70.88
						H 5.55	5.58
						N 11.02	10.80

[a] Using method I. [b] Using method II. [c] Using method II with acetic acid instead of chloroform as solvent.

Table VII
***N*-Acyl-*O*-alkylhydroxylamines**

Compd	Registry no.	% yield	Mp/bp, °C	Analysis, %	C	H	N
N-Acetyl-*o*-*p*-methoxybenzylhydroxylamine	23993-49-9	36	140 (0.15 mm)	Calcd	61.33	6.71	7.17
				Found	61.60	6.75	7.10
N-Phenoxyacetyl-*O*-benzylhydroxylamine	53821-05-9	39	89–90	Calcd	70.02	5.88	5.44
				Found	70.03	5.93	5.39
N-*p*-Methoxyphenylacetyl-*O*-benzylhydroxylamine	53821-06-0	59	93–95	Calcd	70.83	6.32	5.16
				Found	70.91	6.31	5.08

Table VIII
***N,N'*-Diacetyl-*N,N'*-dialkoxyhydrazines**

Compd	Registry no.	Mol wt		Nmr[a]
N,N'-Diacetyl-*N,N'*-di-*p*-methoxybenzyloxyhydrazine	53821-07-1	Calcd	388	2.08 (s, 6) 3.78 (s, 6)
		Found	371	5.08 (s, 4) 6.72–7.53 (m, 8)
N,N'-Diphenoxyacetyl-*N,N'*-dibenzyloxyhydrazine	53821-09-3	Calcd	510	4.64 (s, 4) 5.09 (s, 4)
		Found	488	6.62–7.65 (m, 20)
N,N'-Di-*p*-methoxyphenylacetyl-*N,N'*-dibenzyloxyhydrazine	53821-09-3	Calcd	340	3.63 (s, 4) 3.76 (s, 6)
		Found	325	5.0 (s, 4) 6.73–7.48 (m, 18)

[a] Nmr samples were run in $CDCl_3$ solution. Chemical shifts are expressed in ppm relative to TMS.

Hydrogenolysis of a 0.100-g sample of this product, at room temperature and atmospheric pressure using a (W-2) Raney nickel catalyst in 50 ml of absolute ethanol, required 2 mol of hydrogen per mole of sample and yielded a compound with a melting point of 349–350°. This compound was found to have an infrared spectrum identical with that of a sample of 1,2-naphthodimidazolone, mp 347–348°, prepared by the literature method of Bednyagina:[18] ir (Nujol) 1732, 795, 732, cm^{-1}. This reduction of the benzyloxynaphthimidazolone compound to 1,2-imidazolone established that in the lead tetraacetate oxidation of 1-benzyloxy-3-α-nathylurea oxidative ring closure occurred at the β position of the naphthalene ring.

***N*-Acyl-*O*-alkylhydroxylamines.** The method previously described was used for these preparations.[19] Data for these compounds are compiled in Table VII.

Lead Tetraacetate Oxidation of *N*-Acyl-*O*-alkylhydroxylamines. The high dilution procedure described for the oxidation of 1-benzyloxy-3-*m*-nitrophenylurea was used. Data for the hydrazine products are compiled in Table VIII.

1-Benzyloxy-3,3-diphenylurea. A solution of 5.00 g (40.6 mmol) of benzyloxyamine in 50 ml of benzene was added to 4.70 g (20.3 mmol) of diphenylcarbamyl chloride. The reaction mixture was stirred at room temperature for 1 day, and the precipitated benzyloxyamine hydrochloride was removed by filtration. The solvent was removed, and that part (4.6 g) of the residue which was soluble in ether was crystallized from a ether–hexane mixture. Pure product weighing 3.5 g, was obtained: 54%; mp 80–82°; ir (Nujol) 3385, 1696 cm^{-1}. *Anal.* Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.51; H, 5.73; N, 8.76.

Lead Tetraacetate Oxidation of 1-Benzyloxy-3,3-diphenylurea. Using the same procedure as given above for 1-benzyloxy-3-phenylurea 0.50 g (1.57 mmol) of 1-benzyloxy-3,3-diphenylurea was converted to 0.49 g (100%) of product. An analytically pure sample was obtained by recrystallization from hexane, mp 82–84°; ir (Nujol) 1725, 745, 695 cm^{-1}; nmr (DMSO-d_6) 5.32 (s, 4), 7.10 (s, 5), 7.10–7.80 (m, 9); spectrum at 70 eV, *m/e* (relatve intensities) 316 (55), 210 (24), 181 (21), 167 (11), 149 (12), 106 (7), 105 (9), 91 (100), 77 (60). *Anal.* Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.85. Found: C, 75.98; H, 5.15; N, 8.81.

Registry No.—1, 33026-77-6; **2a,** 53821-10-6; **2b,** 53821-11-7; **2c,** 615-16-7; lead tetraacetate, 546-67-8; benzyl *p*-nitrophenylcarbamate, 53821-12-8; 1-benzyloxy-6-nitrobenzimidazolone, 53821-13-9; *p*-nitrophenyl isocyanate, 100-28-7; 5-nitro-1-benzyloxybenzimidazolone, 53821-14-0; 7-nitro-1-benzyloxybenzimidazolone, 53821-15-1; benzyl *m*-nitrophenylcarbamate, 53821-16-2; benzyl *o*-nitrophenylcarbamate, 23091-35-2; 1-benzyloxy-3-α-naphthylurea, 51453-02-7; benzyloxynaphthimidazolone, 53821-17-3; 1-benzyloxy-3,3-diphenylurea, 53821-18-4; benzyloxyamine, 622-33-3; diphenylcarbamyl chloride, 83-01-2; 1-benzyloxy-3-phenylbenzimidazolone, 53821-19-5.

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Reductive Cleavage of Imidazolidines by Borane–Tetrahydrofuran

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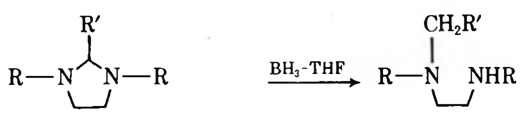
Aldehydes were converted to imidazolidines to test the resistance of these derivatives to reduction by borane–tetrahydrofuran. The compounds were easily cleaved, however, to the corresponding N,N,N′-trisubstituted ethylenediamines. Thus, 1,2,3-triphenylimidazolidine (**1a**) gave *N*-benzyl-*N,N′*-diphenylethylenediamine (**2a**) hydrochloride in 66% yield. 1,3-Dibenzyl-2-phenylimidazolidine (**1b**) and 1,3-diphenyl-2-(1-phenylethyl)imidazolidine (**1c**) gave similar results. 3-Benzyl-2-*p*-tolyloxazolidine (**7**) was cleaved under the same conditions (1–3 hr, room temperature), but Tröger's base and L-thiazolidine-4-carboxylic acid methyl ester were unaffected. The cleavage reaction appears useful for the synthesis of N,N,N′-trisubstituted ethylenediamines.

The conversion of aldehydes to imidazolidines by reaction with ethylenediamines occurs readily in many cases with high yields of crystalline solids that are suitable for isolation and characterization of the aldehydes.[1] We have tested the use of imidazolidines as aldehyde-protecting functions during reductions with borane–tetrahydrofuran (BH_3–THF)[2] and have found that ring cleavage occurs very easily. This is in contrast to the recent report by Birch and Dastur[3] of the successful protection of an aldehyde as a 1,3-dimethylimidazolidine during a lithium–ammonia reduction.

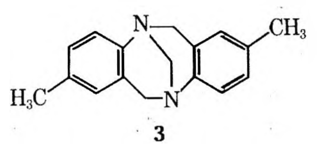
Reduction of the imidazolidine **1a** with an equimolar amount of 1 *M* BH_3–THF for 3 hr at room temperature gave after purification 66% of the ring-opened compound **2a**; likewise, **1b** gave **2b** (57%) and **1c** gave **2c** (83%). In a



1a, R = R′ = C_6H_5 **2a-c**
b, R = $CH_2C_6H_5$; R′ = C_6H_5
c, R = C_6H_5; R′ = $CH(CH_3)C_6H_5$

second run with 1.67 molar equiv of BH_3, the yield of **2b** from **1b** increased to 77%. Shorter reaction times and a lower temperature gave slightly higher yields. These results, summarized in Table I, indicate that an aldehyde cannot be protected from borane reduction by conversion to an imidazolidine. On the other hand, the reaction appears useful for preparing *N,N,N′*-trisubstituted ethylenediamines.

Tröger's base (**3**) failed to react with BH_3–THF even at reflux temperature; **3** is also inert to aqueous HCl,[4] a re-



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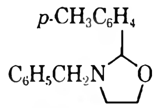
agent that causes rapid decomposition of imidazolidines to the parent aldehyde and diamine.[1,5] The oxazolidine **4** was reduced readily to the dialkylamino alcohol **5**; L-thiazoli-



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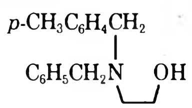

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dine-4-carboxylic acid methyl ester (**6**), however, failed to react at room temperature.

Other agents used to cleave imidazolidines are H_2–Raney nickel at elevated temperature and pressure[6] and H_2–PtO_2.[6] We suggest that the convenience, mild conditions,

Table I
Reduction of Saturated Heterocycles with BH_3–THF

Compd[a]	BH_3: compd, molar ratio	Reaction time, hr[b]	Product[a]	Mp, °C	Yield,[c] %
1a[d]	1:1	3	**2a** HCl	171–172	66
1b[e]	1:1	3	**2b** 2HCl	142–154	57
1b	1.67:1	3	**2b** 2HCl		77
1b	1.67:1	1	**2b** 2HCl		81
1c[f]	1:1	3	**2c** 2HCl	157–175	83
1c	1:1	1[g]	**2c** 2HCl		88
3[h]	1.75:1	5.5[i]	*j*		
4[k]	1:1	3	**5** HCl	147–150	87
4	1:1	1	**5** HCl		92
6[l]	1:1	3	*j*		
6	1:1	2[m]	*n*		

[a] Satisfactory analytical data (±0.4% for C, H, N, Cl) were reported for all new compounds listed in the table. [b] Run at room temperature except as noted. [c] After recrystallization from 2-propanol (**2a** HCl) or ethanol. [d] Reference 1. [e] J. van Alphen, *Recl. Trav. Chim. Pays-Bas*, **54**, 93 (1934). [f] Mp 85–88° (from methanol). [g] At 0–5°. [h] E. Goecke, *Z. Elektrochem.*, **9**, 470 (1903). [i] Includes 1 hr of reflux. [j] Recovered >88% starting material. [k] From *N*-benzylethanolamine and *p*-tolualdehyde in 88% yield; bp 129° (0.1 mm). [l] Prepared from L-thiazolidine-4-carboxylic acid and CH_2N_2 in 56% yield as **6** HCl: mp 166–167° dec [lit. mp 164–165° dec: S. Ratner and H. T. Clarke, *J. Amer. Chem. Soc.*, **59**, 200 (1937)]. [m] At reflux. [n] Recovered mixture of starting material and unidentified products.

and good yields make BH_3–THF a useful alternative reagent, particularly where the presence of nitro or labile benzyl groups may preclude catalytic hydrogenation. Under the conditions used, ester and many amide functions should also be unaffected.[2]

Furthermore, with the recent publication of new methods for the synthesis of unsymmetrical, highly substituted imidazolidines,[7] the BH_3 cleavage reaction might be useful for preparing the corresponding ethylenediamines. However, we have no information on the selectivity of cleavage of unsymmetrical imidazolidines with this reagent.

Experimental Section

Starting materials were obtained commercially and were used as received; tetrahydrofuran was dried over molecular sieves. The 1 *M* borane in tetrahydrofuran was obtained from Ventron Corporation. Imidazolidines were prepared according to Wanzlick and Löchel.[1] Melting points were not corrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Ir and nmr spectra were obtained on all compounds.

Borane Reductions. General Procedure. To a 1 *M* solution of BH_3 in THF, stirred magnetically at 0° under N_2, was added rapidly a solution of the compound to be reduced in dry THF. The cooling bath was then removed and stirring continued for the desired period. The solution was evaporated and the residue treated with an excess of concentrated HCl, followed by dilution with H_2O and basification with 2 *N* NaOH. The product was extracted into $CHCl_3$, dried briefly over $MgSO_4$ and evaporated. The free base thus obtained was converted to its hydrochloride by treatment with ethanolic HCl. In the work-up of the reduction of **6**, methanolic rather than aqueous HCl was used.

Acknowledgments. This work was done under Contract NO1-CM-33728 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare. We thank Dr. Harry B. Wood, Jr., of NCI and Drs. John A. Beisler and Richard D. Costlow for their encouragement.

Registry No.—**1a**, 28341-73-3; **1b**, 4597-81-3; **1c**, 53746-37-5; **2a** HCl, 53746-38-6; **2b** 2 HCl, 53746-39-7; **2c** 2 HCl, 53746-40-0; **4**, 53746-41-1; **5** HCl, 53746-42-2.

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Borohydride Reduction of Pyridinium Salts. V. Thermal Dimerization of 1,6-Dihydro-1-methylpyridine-2-carbonitrile

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The 1,6-dihydropyridine **2**, obtained by $NaBH_4$ reduction of 2-cyano-1-methylpyridinium iodide, smoothly undergoes a thermal dimerization to the head to head [2 + 2] cycloadduct **6**. The cyclobutane derivative **6** rearranges, by heating, to the isomeric ethenonaphtyridine **9**. Label scrambling observed at 110° in the monodeuteriated derivative, **13**, reveals a degenerate thermal [3.3] sigmatropic shift.

Some time ago we started an investigation on the reduction with $NaBH_4$ of substituted pyridinium salts containing electron-attracting groups. In a number of reports already published,[1] we have clarified some aspects of the reduction of 3-cyano- and 4-cyano-1-methylpyridinium iodides; in particular, it was shown that in the reduction of 4-cyano-1-methylpyridinium iodide, dimerization of the intermediate 1,2-dihydropyridine occurs with formation of [2 + 2] and [4 + 2] cycloadducts. The investigation has now been extended to 2-cyano-1-methylpyridinium iodide (**1**), and the results are reported in the present paper.

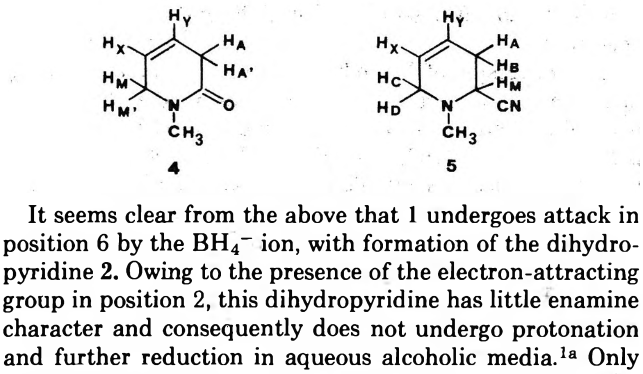
On treatment of **1** with $NaBH_4$ in methanol–water (4:1) at −20°, the initial formation of a dihydropyridine **2** is shown from the changes in the uv spectrum; a maximum appears at 365 nm, and its intensity increases as the reduction proceeds, with simultaneous disappearance of the maximum at 273 nm, which is characteristic of the pyridinium salt.

It is also possible to extract the dihydropyridine with $CHCl_3$ at a low temperature and to record the ir spectrum of the chloroform solution (1660 and 1625 cm^{-1}, C=C; 2210 cm^{-1}, C≡N), but the attempted isolation of the product was unsuccessful, since evaporation of the solvent leads to a new compound **6**, which has spectroscopic characteristics different from those of **2** (see below).

When the reaction was carried out in an nmr tube (CH_3OD–D_2O 9:1) at 30°, it was possible first to detect the formation of the dihydropyridine (δ 6.0–5.3 vinyl protons; 3.8, N–CH_2; 2.7 ppm, N–CH_3) and then to follow its conversion into the compound **6**: the dihydropyridine peaks slowly disappear, while the peaks of **6** gradually become more intense. After 1 hr, 30% of **6** has been formed.

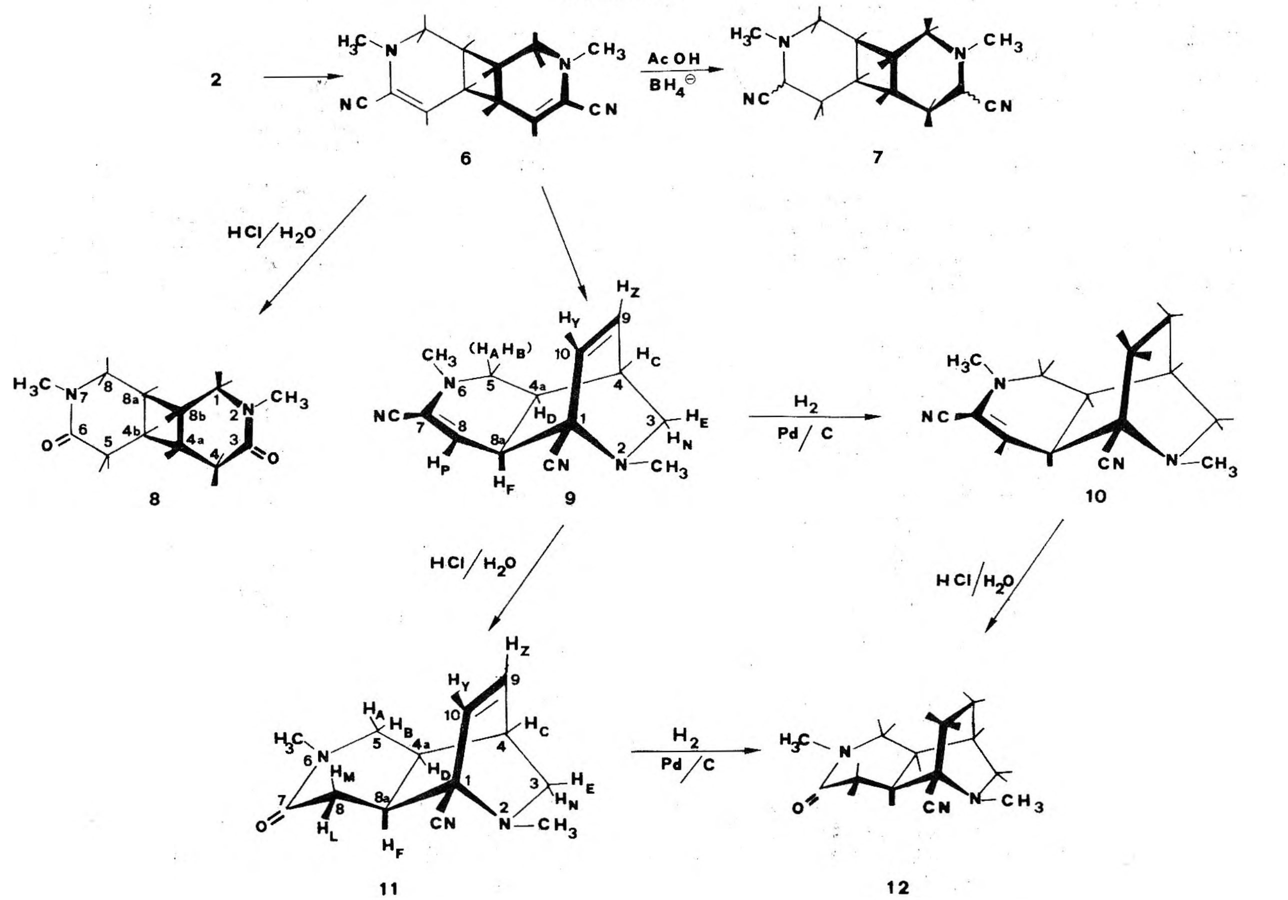
2 has the structure of 1,6-dihydro-1-methylpyridine-2-carbonitrile, as was shown by the formation of 3,6-dihydro-1-methylpyridin-2(1*H*)-one (**4**) and 1,2,3,6-tetrahydro-1-methylpyridine-2-carbonitrile (**5**) on reduction of **1** in methanol–water (4:1) at −20° followed by treatment with 6 *N* hydrochloric acid (Scheme I).

Scheme I



It seems clear from the above that **1** undergoes attack in position 6 by the BH_4^- ion, with formation of the dihydropyridine **2**. Owing to the presence of the electron-attracting group in position 2, this dihydropyridine has little enamine character and consequently does not undergo protonation and further reduction in aqueous alcoholic media.[1a] Only the addition of acid can bring about the protonation in position 3 with formation of the iminium cation **3**, which can competitively undergo attack by the nucleophiles H_2O and BH_4^- to give **4** and **5**, respectively. Thus reactions carried out with a molar excess of sodium borohydride lead to a distinct increase in the quantity of tetrahydropyridine and a corresponding decrease in the quantity of pyridone.

Scheme II



When the reduction of 1 with $NaBH_4$ in methanol–water (2:5) is carried out at 20° the product **6** precipitates out. **6** cannot be crystallized (see below), but can be purified by chromatography. Its ir spectrum shows a nitrile band at 2215 cm^{-1} and a double-bond absorption at 1610 cm^{-1}. The elemental analysis and the molecular weight (240) indicate a molecular formula $C_{14}H_{16}N_4$, which is exactly double than of **2**. Attempts to crystallize **6** from solvents such as ethanol or benzene lead to total conversion into a new compound **9**, which has the same molecular weight and the same elemental analysis, but different spectrographic characteristics. For example, the ir spectrum, among other things, shows an unconjugated nitrile absorption at 2230 cm^{-1}, a conjugated nitrile absorption at 2215 cm^{-1}, and two double-bond absorptions at 1620 and 1615 cm^{-1}, respectively.

The conversion of **6** into **9** can also be observed when **6** is heated as solid; for example, after heating at 85° the ratio **9**–**6** is 0.25, and this ratio tends to increase with rising temperature. At 107–110°, when the solid melts, **9** is practically the only species present. The nmr spectrum ($CDCl_3$) of **6** is not very significant, since the only identifications are two equivalent vinyl protons at δ 5.48 and two equivalent CH_3 groups at δ 2.86, all the other protons falling between δ 3.1 and 2.1. However, the spectroscopic properties and the molecular weight provide reasonable evidence of a symmetrical dimeric structure. The presence of two α-cyano-substituted enamine moieties in **6** is demonstrated by its reduction to **7** (mol wt = 244) on treatment with glacial CH_3COOH and $NaBH_4$ and by conversion into the dilactam **8** (mol wt = 222) on treatment with 6 *N* hydrochloric acid (Scheme II).

The ir spectrum of **7** shows a nitrile band at 2220 cm^{-1}, while the nmr spectrum shows the disappearance of the vinyl protons and confirms the symmetry of the dimeric structure. The ir spectrum of **8** shows a lactam band at 1630 cm^{-1}, while the nmr spectrum once again points to a symmetrical dimeric structure.

These experimental results lead us to postulate that **6** (and hence **7** and **8**) has a symmetrical cyclobutane structure resulting from the thermal dimerization[2] involving the 4–5 double bond of the dihydropyridine **2**. In fact, the only other conceivable symmetric dimeric structures, not containing the cyclobutane ring, are those arising from a [4 + 4] cycloaddition of the dihydropyridine **2**, but these must be excluded because they are largely inconsistent with the experimental results.

Theoretically several cyclobutanic dimers may be formed according to the mode of dimerization (head-to-head or head-to-tail) and the known possibilities for the stereochemistry around the cyclobutane ring. However, the structural symmetries of the compounds **6**, **7**, and **8**, which are clearly demonstrated by the nmr spectra, enable us to rule out the cyclodimers having a single 6–4 trans fusion; cyclodimers with a strained double 6–4 trans fusion, which is itself extremely improbable, can also be ruled out in view of the fact that a dihydropyridine such as **2**, in which the reactive cis olefinic moiety is blocked by the cyclic framework, cannot give cyclodimers with this configuration by thermal dimerization.

There are therefore four cis-fused isomers to be considered; these are the syn head-to-head, the syn head-to-tail, the anti head-to-head, and the anti head-to-tail cyclodimers (Scheme III). However, the easy conversion of **6** into **9**, which has all the features of an intramolecular rearrangement, seems to indicate a head-to-head structure, since only the 1,2-divinylcyclobutanes readily undergo intramolecular rearrangements.[3]

Table I
Nmr Data for 8

Protons	Bz-d_6 δ (ppm)	Bz-d_6 + Eu(DPM)$_3$ δ (ppm)	J,[a] Hz
$H_{8a} + H_{8b}$	1.60	5.68	$\lvert J_{8a,4b} + J_{8a,4a}\rvert = 7.5$
$H_{4a} + H_{4b}$	1.7–2.2	6.71	$J_{8b,1}$ (or $J_{8b,1'}$) = 3.0
H_1 (or $H_{1'}$) + H_8 (or $H_{8'}$)	2.81	6.39	$J_{8b,1'}$ (or $J_{8b,1}$)[b]
$H_{1'}$ (or H_1) + $H_{8'}$ (or H_8)	2.29	5.58	$J_{1,1'} = 13.0$
H_4 (or $H_{4'}$) + H_5 (or $H_{5'}$)	1.7–2.2	8.55	$J_{4,4a}$ (or $J_{4',4a}$)[b]
$H_{4'}$ (or H_4) + $H_{5'}$ (or H_5)	1.7–2.2	7.00	$J_{4',4a}$ (or $J_{4,4a}$) = 4.5
Me-2 + Me-7	2.78	7.72	$J_{4,4'} = 15.5$

[a] Values obtained from solution added of Eu(DPM)$_3$. [b] This coupling cannot be detected because of the broadening by the shift reagent.

Scheme III

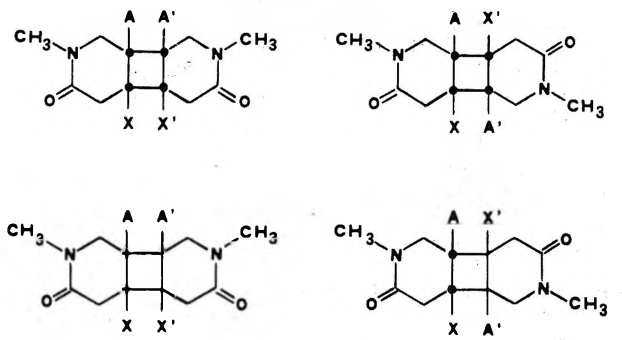


Table II
Nmr Data for 9 and 11

	9		11	
Protons	Bz-d_6, δ (ppm)	J, Hz	$CDCl_3$, δ (ppm)	J, Hz
H_A (or H_B)	2.04	AB = 11.91[a]	3.05 (H_A)	AB = 13.06[a]
H_B (or H_A)	1.79	AD (or BD) = 5.55[a]	3.14 (H_B)	AD = 10.07[a]
H_C	1.60	BD (or AD) = 6.13[a]	2.49	BD = 6.33[a]
H_D	1.68	CD = 1.8[b]	2.40	CD = 2.0[b]
H_E	1.36	CE = 2.5	1.91	CE = 2.6
H_F	2.66	CN = 2.0	2.81	CN = 2.2
H_N	2.65	CY = 1.5	3.22	CY = 1.5
H_M		CZ = 7.0	2.14	CZ = 7.0
H_L		EN = 9.5	2.65	EN = 9.8
H_P	5.60	FD = 8.92[a]		FD = 10.52[a]
H_Y	5.69	FP = 3.7	6.29	FL = 6.15[a]
H_Z	5.76	YZ = 8.2	6.48	FM = 11.50[a]
Me	2.31		2.89	FY = 1.0
Me	2.16		2.38	ML = 14.63[a]
				YZ = 8.0
				ZD = 0.5
				ZN = 0.5

[a] Value obtained by iteration. [b] Value obtained only from spectrum with Eu(DPM)$_3$.

The structures and conformations of the compounds **6, 7,** and **8** were established by the analysis of the nmr spectrum of the dilactam **8**, since the addition of Eu(DPM)$_3$ enables all the protons to be seen separately (Table I).

With regard to the cyclobutane protons H_{8a}, H_{8b}, H_{4a}, H_{4b}, which form an AA′XX′ spin system further coupled with the protons of the adjacent methylene groups, only the sum $\lvert J_{AX} + J_{AX'}\rvert = 7.5$ Hz can be deduced from the spectrum.

According to the values and signs found for the vicinal[4] and diagonal[5] constants of the cyclobutane protons in similar systems, this result points to a vicinal cis J_{AX} and diagonal trans $J_{AX'}$; an anti head-to-head configuration thus seems the most probable for the compound **8**.

Since **7** and **8** are formed directly by an unambiguous path from **6**, it must be assumed that the geometry of all three compounds is the same.

The structure of **6** is compatible with a two-step biradical dimerization mechanism, which, in the light of recent work by Epiotis,[6] may be regarded as the most probable for the thermal dimerization ([2 + 2] AA cycloadditions).

As was mentioned above, **6** is thermally converted into **9,** whose nmr spectrum shows, among other things, three vinyl protons H_P, H_Y, H_Z respectively at δ 5.60, 5.69, and 5.76 (see below) and two methyl signals at δ 2.16 and 2.31. The experimental data clearly indicate that **9** no longer has the symmetrical structure characteristic of **6**. The presence of a single substituted α-cyanoenamine moiety is shown by the halving of the ε value (6,100) of the uv maximum at 278 nm with respect to the corresponding ε value (12,000) for compound **6**, and by conversion into the lactam **11** (mol wt 231; ir 1645 (C=O) and 2235 cm^{-1} (C≡N)) on treatment with 6 *N* hydrochloric acid. Furthermore, the catalytic reduction of **9** affords the dihydro derivative **10.** The nmr spectra show that H_P is the only vinyl proton present in **10,** whereas H_Y and H_Z are the only vinyl protons present in **11.** On catalytic reduction of **11,** 1 mol of hydrogen is absorbed with formation of the compound **12;** there are no vinyl proton signals in the nmr spectrum of **12. 12** is also obtained from **10** on treatment with 6 *N* hydrochloric acid.

The structure of 1,4-etheno-3,4,4aα,5,6,8aα-hexahydro-2,6-dimethyl-2,6-naphtyridine-1,7(2*H*)-dicarbonitrile for the product **9** is proved by these experimental data and by the complete analysis of the nmr spectra of **9** and **11** (Table II).

This analysis was first carried out for the solution with added Eu(DMP)$_3$ to obtain a better first-order approximation. The coupling constants obtained were then used as the input for the second-order LAOCN 3 analysis of the spectra in the absence of the shift reagent.

As was pointed out earlier, the nmr spectrum of **9** shows three olefinic protons H_P, H_Y, and H_Z at δ 5.60, 5.69, and 5.76, respectively; the coupling constant (J_{YZ} = 8.2 Hz) indicates that H_Y and H_Z are situated on the same double bond.

The chemical couplings J_{EN} = 9.5 Hz and J_{AB} = 11.9 Hz in **9** indicate two methylene protons in the α position to an amine nitrogen and to an enamine nitrogen, respectively, whereas J_{LM} = 14.6 Hz in **11** indicates a methylene group α to a C=O group; J_{EN} and J_{AB} in **11** are similar to those in **9.** The sequences

AB　D　C　EN　　　C　Z　Y
N—CH$_2$—CH—CH—CH$_2$—N,　CH—CH—CH

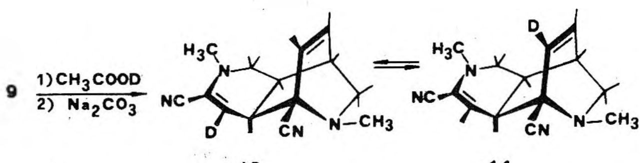
in both **9** and **11,**

P　F　D
=CH—CH—CH

in **9,** and

F　D
CH$_2$—CH—CH

Scheme IV



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in **11** and their connections are clearly suggested by the coupling constants and by the values of the chemical shift. From the absence of coupling between H_D and H_E, the endo configuration can be assigned to **9** and **11** since the sequence H_D-C_{4a}-C_4-C_3-H_E should have perfectly coplanar zig-zag geometry in the exo configuration, and long-range coupling through four bonds should therefore be expected.[7] The low value ($\simeq$2 Hz) of J_{CD} in both **9** and **11** agrees with an angle of about 60° in such a fragment.

The structure and stereochemistry of **9** are consistent with a formation pathway from **6** implying a formal [1.3] sigmatropic shift, which involves the rupture of the C_{4a}–C_{4b} bond and the formation of the C_3–C_{4b} bond.

Treatment of the product **9** with D_1-acetic acid allows selective monodeuteration with formation of **13**, whose nmr spectrum is identical with that of **9** apart from the disappearance of β-enamine proton H_P and the corresponding decoupling of H_F. Heating of **13** to boiling in toluene leads to equilibration with the isomer **14** in which H_Y is replaced by deuterium (Scheme IV); in fact the nmr spectrum of the product, after heating, shows that it consists of an equimolar mixture of **13** and **14** since the areas for H_P and H_Y are halved.

The observed [3.3] sigmatropic shift provides unequivocal confirmation of the structure **9**, which is the only one showing the structural features necessary to undergo a degenerate rearrangement detectable after labeling with deuterium.

Experimental Section

All melting points were taken upon a Tottoli apparatus and are uncorrected; proton nmr spectra were recorded on Varian HA-100 and XL-100-15 spectrometers; chemical shifts are reported as δ units relative to TMS (δ 0) as internal standard. Decoupling experiments were performed in frequency sweep. All *m/e* values were determined on a AEI MS-12, 70 eV, low-resolution mass spectrometer. Ir spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer as Nujol mulls or liquid films and uv spectra on a Perkin-Elmer 402 spectrophotometer. Column chromatography was performed on standardized Al_2O_3 Merck (activity II–III).

Reduction of 1 to 4 and 5. 1 (2.5 g, 0.01 mol) was added in small portions over a period of 30 min, with stirring, to a solution of $NaBH_4$ (0.4 g, 0.01 mol) in H_2O (2 ml) and CH_3OH (8 ml) cooled to −20°. Stirring was continued for 30 min more, and the resulting solution was poured dropwise into 6 *N* HCl (10 ml) previously cooled to −20°. The solution was concentrated under vacuum, H_2O (10 ml) was added, and the solution was extracted with $CHCl_3$. The chloroform extract was dried (Na_2SO_4), concentrated, and distilled, whereupon it gave 4 (0.35 g): bp 70–72° (0.8 mm); mp 30–32°; ir 1635 cm^{-1} (C=O); nmr (C_6D_6) δ 5.39 (1, H_Y), 5.28 (1, H_X, J_{XY} = 10.2 Hz), 3.3 (2, $H_M + H_{M'}$), 2.7 (2, $H_A + H_{A'}$, $\frac{1}{2}|J_{AM} + J_{AM'}| = \frac{1}{2}|J_{A'M} + J_{A'M'}|$ = 4.9 Hz), and 2.7 ppm (3, Me, $J_{A'Me} = J_{A,Me}$ = 0.5 Hz).

Anal. Calcd for C_6H_9NO: N, 12.60; mol wt, 111.14. Found: N, 12.35; *m/e* 111 (parent peak).

The acidic mother liquor was made alkaline with 2 *N* NaOH and extracted with $CHCl_3$. The chloroform extract was dried (Na_2SO_4) and concentrated. Chromatography of the oily residue (eluent, cyclohexane–AcOEt 1:1) gave 5 (0.25 g) and 4 (0.15 g). **5**: bp 65° (0.2 mm); ir 2220 (CN) and 1660 cm^{-1} (C=C); nmr (C_6D_6) δ 5.6–5.2 (2, $H_X + H_Y$), 3.06 (1, H_M), 2.76 (1, H_D) 2.72 (1, H_C, J_{CD} = 17.5 Hz), 2.14 (1, H_B, J_{BC} = 3.5 Hz, J_{BD} = 3.5 Hz, J_{BM} = 5.9 Hz), 2.02 (3, Me), and 1.77 ppm (1, H_A, J_{AB} = 17.2 Hz, J_{AC} = 2.0 Hz, J_{AD} = 2.0 Hz, J_{AM} = 2.0 Hz).

Anal. Calcd for $C_7H_{10}N_2$: C, 68.82; H, 8.25; N, 22.9; mol wt, 122.17. Found: C, 69.15; H, 8.24; N, 23.20; *m/e* 122 (parent peak).

1,2,4aα,4bβ,7,8,8aβ,8bα-Octahydro-2,7-dimethylcyclobuta-[1,2-*c*:4,3-*c'*]dipyridine-3,6-dicarbonitrile (6). 1 (8.5 g, 0.034 mol) was added in small portions over a period of 1 hr, with stirring, to a solution of $NaBH_4$ (1.3 g, 0.034 mol) in H_2O (25 ml) and CH_3OH (10 ml) at 20°. After the addition, stirring was continued for 2 hr. The precipitate was separated by filtration, washed with water, dried under vacuum, and chromatographed (eluent, light petroleum ether–AcOEt 9:1) to give 6 (3.4 g): uv max (95% EtOH) 278 nm (ϵ 12,000).

Anal. Calcd for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.31; mol wt, 240.30. Found: C, 69.70; H, 6.42; N, 23.79; *m/e* 240 (parent peak).

1,2,3,4,4aα,4bβ,5,6,7,8,8aβ,8bα-Dodecahydro-2,7-dimethylcyclobuta[1,2-*c*:4,3-*c'*]dipyridine-3,6-dicarbonitrile (7). $NaBH_4$ (0.3 g) was added in small portions, with stirring, to a solution of 6 (0.3 g) in glacial CH_3COOH (5 ml) cooled to 5°. After the addition, stirring was continued for 30 min more; H_2O (5 ml) was then added, the solution was made alkaline with Na_2CO_3, and extracted with CH_2Cl_2. After drying (Na_2SO_4), evaporation of the extract gave 7 (0.28 g): mp 172–174° (EtOH).

Anal. Calcd for $C_{14}H_{20}N_4$: C, 68.82; H, 8.25; N, 22.93; mol wt, 244.33. Found: C, 68.76; H, 8.16; N, 23.32; *m/e* 244 (parent peak).

1,2,4,4aα,4bβ,5,7,8,8aβ,8bα-Decahydro-2,7-dimethylcyclobuta[1,2-*c*:4,3-*c'*]dipyridine-3,6-dione (8). 6 (2.0 g) was added in small portions, with stirring, to 6 *N* HCl (20 ml) cooled to 0°. After standing for 1 hour the solution was extracted with $CHCl_3$. The dried chloroform extract, on evaporation, yielded a solid residue, which was crystallized from benzene to give 8 (0.7 g): mp 165–166°.

Anal. Calcd for $C_{12}H_{18}O_2N_2$: C, 64.84; H, 8.16; N, 12.60; mol wt; 222.28. Found: C, 64.60; H, 8.13; N, 12.53, *m/e* 222 (parent peak).

Conversion of 6 into 9. 6 (4 g) was heated under reflux in C_2H_5OH (50 ml) for 3 hr. Evaporation of the solvent gave **9**: mp 110–112° (EtOH); uv max (95% EtOH) 278 nm (ϵ 6100).

Anal. Calcd for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.31; mol wt, 240.30. Found: C, 69.72; H, 6.90; N, 23.57; *m/e* 240 (parent peak).

1,4-Ethano-3,4,4aα,5,6,8aα-hexahydro-2,6-dimethyl-2,6-naphtyridine-1,7(2*H*)-dicarbonitrile (10). A solution of 9 (0.240 g, 0.001 mol) in C_2H_5OH (50 ml) was hydrogenated at 20° (3 atm) over 10% Pd/C catalyst (0.1 g) until 0.001 mol of H_2 was absorbed. The reaction mixture was filtered, concentrated, and chromatographed (eluent, light petroleum–AcOEt 95:5) to give **10** (0.15 g): mp 50–51° (light petroleum); uv max (95% C_2H_5OH) 277 nm (ϵ 6200); ir 2235, 2225 (CN), 1615 cm^{-1} (C=C); nmr ($CDCl_3$) δ 5.56 (1, H_P), 2.98 (1, H_F, $J_{P,F}$ = 1 Hz), 2.85 (3, Me), and 2.56 ppm (3, Me).

Anal. Calcd for $C_{14}H_{18}N_4$: C, 69.39; H, 7.49; N, 23.12; mol wt, 242.32. Found: C, 69.67; H, 7.55; N, 23.77; *m/e* 242 (parent peak).

1,4-Ethano-3,4,4aα,5,6,7,8,8aα-octahydro-2,6-dimethyl-7-oxo-2,6-naphtyridine-1(2*H*)-carbonitrile (12). A solution of 11 (1 g, 0.004 mol) in AcOEt (60 ml) was hydrogenated at 20° (1 atm) over 10% Pd/C catalyst (0.2 g) until 0.004 mol of H_2 was absorbed. The reaction mixture was filtered and concentrated to give **12**: mp 117–118° (benzene); ir 2240 (CN), 1645 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01; mol wt, 233.31. Found: C, 67.17; H, 8.40; N, 18.38; *m/e* 233 (parent peak).

12 was also obtained in 75% yield from **10** by treatment with 6 *N* hydrochloric acid (see procedure for compound 11).

1,4-Etheno-3,4,4aα,5,6,7,8,8aα-octahydro-2,6-dimethyl-7-oxo-2,6-naphtyridine-1(2*H*)-carbonitrile (11). 9 (3 g) was added in small portions, with stirring, to 6 *N* HCl solution (15 ml) cooled to 0°. The solution was made alkaline with concentrated NaOH, saturated with Na_2CO_3, and extracted with $CHCl_3$; evaporation of the solvent yielded a solid residue (11) which was crystallized from benzene (1.4 g): mp 87–89°.

Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.50; H, 7.41; N, 18.17; mol wt, 231.29. Found: C, 67.48; H, 7.46: N, 18.44; *m/e* 231 (parent peak).

Labeling of 9. A solution of 9 (0.45 g) in CH_3COOD (5 ml) containing Ac_2O (0.5 ml) was allowed to stand for 30 min at 20°. The solvent was distilled off under reduced pressure, and anhydrous Na_2CO_3 (5 g) and anhydrous benzene (50 ml) were added to the residue. The mixture was stirred for 6 hr and filtered, the solvent was evaporated off, and the residue was chromatographed (eluent, cyclohexane–AcOEt 1:1) to give 13 (0.35 g), which was crystallized from cyclohexane.

Thermal Equilibration of 13 with 14. A solution of 13 (0.25 g) in toluene (30 ml) was refluxed for 2 hr. The solvent was evaporated off and the residue was chromatographed (eluent, cyclohexane–AcOEt 9:1). The product obtained (0.20 g) was examined by nmr spectroscopy and found to be an equimolar mixture of **13** and **14**.

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Registry No.—1, 3785-03-3; 4, 53516-28-2; 5, 53516-29-3; 6, 53516-30-6; 7, 53516-31-7; 8, 53516-32-8; 9, 53516-33-9; 10, 53516-34-0; 11, 53516-35-1; 12, 53516-36-2; sodium borohydride, 16940-66-2.

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An Unequivocal Synthesis of N-Substituted 1,4-Dihydropyridines

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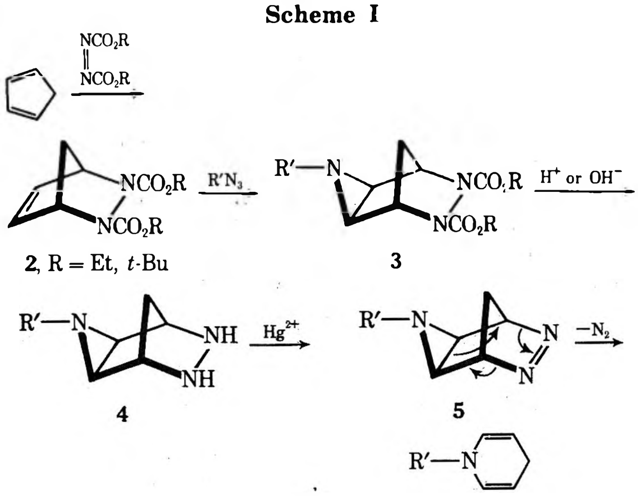
The cycloaddition of alkyl, aryl, and sulfonyl azides to 2,3-diazabicycloheptenes (2) leads to triazolines (10) and aziridino adducts (3). Hydrolysis of 3 followed by oxidation of the hydrazino derivatives (4) products the tricyclic azo compounds which spontaneously fragment with concomitant nitrogen extrusion producing N-substituted 1,4-dihydropyridines in 11–90% yields.

There has been considerable interest in recent years regarding the synthesis and properties of 1,4-dihydropyridines, particularly those possessing little or no substitution.[2] This interest stems from the synthetic utility[3,4] of this system, and in NADH models for biomimetic reductions.[5]

The inherent instability of simple dihydropyridines has deterred complete studies on their potential usefulness as well as synthetic approaches. The route most commonly taken to reach dihydropyridines involves either the Hantzsch synthesis or metal hydride reduction of *N*-substituted pyridinium salts.[2] Addition of cyanide ion to pyridinium salts has been reported to give several stable 4-cyano-1,4-dihydropyridines.[6] Cook and Lyons[7] showed that *N*-trimethylsilyl-1,4-dihydropyridines are among a multitude of products when pyridines are treated with trimethylsilane in the presence of palladium catalysts. Fowler has reported[3,8] the efficient preparation of *N*-carbethoxy-1,4- and -1,2-dihydropyridines by reduction of pyridinium salts.

In 1972, two brief reports appeared which described the synthesis of 1,4-dihydropyridines 1 arising from a retro-

Scheme I

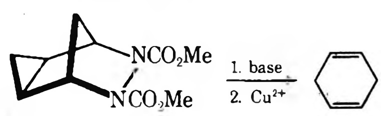


1a, R′ = $PhSO_2$ e, R′ = *p*-CNPh
b, R′ = $MeSO_2$ f, R′ = *p*-MeOPh
c, R′ = Ph g, R′ = $PhCH_2CH_2$
d, R′ = *p*-BrPh h, R′ = Me

Diels–Alder reaction (Scheme I). Deyrup[9] reported the synthesis of *N*-phenyl-1,4-dihydropyridine **1c**, and we described[10] the preparation of the N-benzenesulfonyl derivative **1a**. Our studies were an outgrowth of the previously reported synthesis of divinyl carbamates **6** obtained from a retro-Diels–Alder reaction of the sulfolene derivative **7**.[11]

7 6

The failure of cyclopentadiene to form an adduct with sulfur dioxide led us to the more accessible system 2[12] as a suitable precursor to our goal. This approach (Scheme I) was attractive in view of the symmetry-allowed extrusion of nitrogen from **5** which would lead solely to the 1,4-dihydropyridines. In an analogous sequence, Allred[13] showed that 1,4-cyclohexadiene was cleanly produced from **2** (R = Me) by initial transformation to the cyclopropano derivative **8**.



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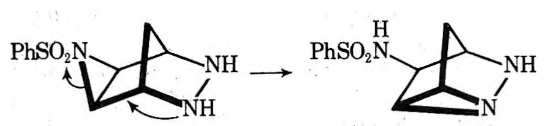
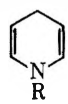
This report enumerates the scope of the synthesis in Scheme I and also describes some of the reactions and properties of the 1,4-dihydropyridines prepared. Heating a benzene solution of **2** (R = Et) with benzenesulfonyl azide produced the *N*-benzenesulfonyl aziridino compound **3a** in 97% yield. Alkaline hydrolysis of the carbamate groups led, not to the hydrazo compound **4a**, but to the tricyclene **9**. It was evident that the 1,3-elimination process (**4a** → **9**) was



4a 9

kinetically a most favorable pathway and all attempts to intercept **4a** by oxidation to **5a** were fruitless. However, repeating the sequence using the *tert*-butyl ester of **2** gave the aziridine derivative **3** (R′ = $PhSO_2$; R = *t*-Bu) in good

Table I
N-Substituted 1,4-Dihydropyridines 1

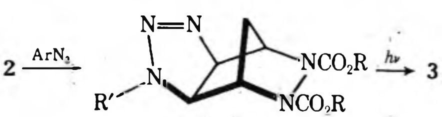


Compd	R	Mp (bp), °C	Yield, %	Mass spectra, M^+	EtOH Uv (ε), nm	Ir, cm^{-1}	Nmr (δ, $CDCl_3$)
1a	$PhSO_2$	86–89 (150°, 0.1 Torr)	63	221[a]	228 (91) 282 (144)	1680, 1630, 1610, 1350, 1185[b]	2.68 (m, 2), 4.92 (m, 2), 6.45 (d of d, J = 8 Hz, 2), 7.4–7.9 (m, 5)
1b	$MeSO_2$	48–51	52	159[f]	212 (114) 260 (48)	1690, 1640, 1337, 1170[c]	2.90 (m, s), 4.90 (m, 2), 6.3 (d of d, 2)[e]
1c	Ph	45–47[d]	80	157[f]	209 (790) 287 (1900)	1675, 1620, 1595, 1575[b]	2.99 (hep, J = 2 Hz, 2), 4.4–4.8 (m, 2), 6.32 (d of d, J = 2, 7.5 Hz, 2), 6.7–7.4 (m, 5)
1d	*p*-BrPh	91–93	30	237[f]	212 (340) 297 (930)	1680, 1670, 1590[b]	2.96 (m, 2), 4.5–4.8 (m, 2), 6.41 (d of d, J = 8 Hz, 2), 7.30 (d, J = 8 Hz, 2)
1e	*p*-CNPh	65–70	11	182[f]	218 (230) 336 (680)	2230, 1690, 1610, 1520[b]	3.00 (m, 2), 4.8–5.0 (m, 2), 6.30 (d of d, J = 2, 8 Hz, 2), 6.95 (d, J = 9 Hz, 2)
1f	*p*-MeOPh	80–82[g]	90 (16)	187[f]	212 (390) 281 (660)	1640, 1500, 1230[b]	3.01 (m, 2), 3.76 (s, 3), 4.6 (m, 2), 6.16 (d of d, J = 2, 7.5 Hz), 6.8–7.0 (m, 4)
1g	$PhCH_2CH_2$	(70°, 0.3 Torr)	50[h]	185[f]	214, 240, 300[h]		2.5–3.3 (m, 6), 4.0–4.4 (m, 2), 5.56 (d of d, J = 2, 7 Hz, 2), 7.17 (s, 5)[e]

[a] *Anal.* Calcd for $C_{11}H_{11}NO_2S$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.40; H, 4.86; N, 6.27. [b] Taken as KBr disks. [c] Taken as film. [d] M. Saunders and E. H. Gold (*J. Org. Chem.*, **27**, 1439 (1962)) report mp 48–50°. [e] Taken in carbon tetrachloride. [f] Satisfactory elemental analyses could not be obtained due to compound instability. [g] P. Karrar, G. Schwarzenbach, and G. Utzinger (*Helv. Chim. Acta*, 20, 72 (1937)) report mp 83°. [h] Impure sample containing 30% di-*tert*-butylhydrazine carboxylate.

yield. When the latter was treated in ethanol with dry hydrogen chloride and mercuric chloride, it passed smoothly through intermediates **4** and **5** and the *N*-benzenesulfonyl-1,4-dihydropyridine **1a** was produced in 60–65% yield. A similar route was employed using methanesulfonyl azide on **2** (R = *t*-Bu) and led to the *N*-methylsulfonyldihydropyridine **1b.** Physical data for all intermediates are given in Table II,[14] while complete spectral data for the dihydropyridines are presented in Table I.

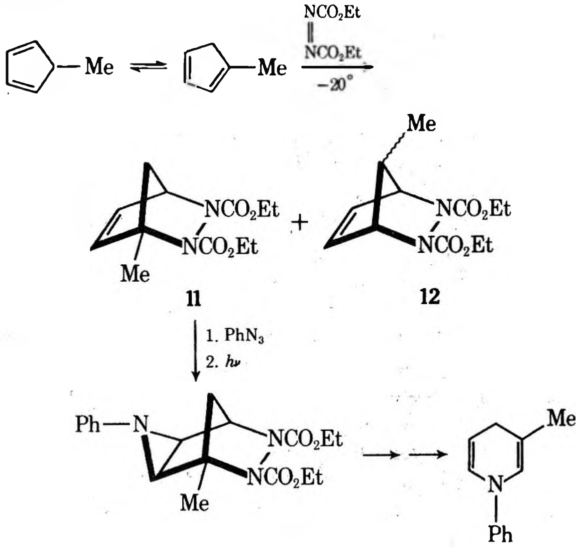
When this technique using the *tert*-butyl esters of **2** was applied to aryl azides, formation of the triazolines **10** (R = aryl) was observed in high yield. Photolysis of the latter gave the corresponding *N*-arylaziridines **3** (R′ = Ph; R = *t*-Bu) likewise in good yield. However, acid treatment to remove the *tert*-butyl groups resulted in extensive decomposition of the *N*-arylaziridino moiety. This is not unexpected in view of the high sensitivity of aziridines to acidic conditions. The sequence was repeated using the ethyl esters of **2,** which could ultimately be removed under basic conditions. A series of aryl azides was condensed with **2** (R = Et) giving the corresponding triazolines **10** which were photolyzed to the *N*-arylaziridines **3,** all in good yield. Hydrolysis was performed in methanolic potassium hydroxide affording the hydrazine derivatives **4** which were usually unstable



10

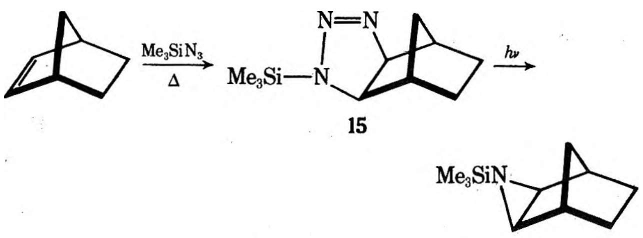
and often difficult to purify. The crude material was simply heated in methanol containing mercuric oxide and led to the *N*-aryldihydropyridines **1c–1f** in yields of 11–90% (Table I). These products were quite air and heat sensitive and underwent considerable deterioration unless stored in an inert atmosphere at −20°. In all cases, purification was accomplished using bulb-to-bulb vacuum distillation which gave pure products (nmr and mass analyses) but, except for **1a,** they could not be analyzed for elemental composition. An effort was made to extend this sequence to *N*-alkyl-1,4-dihydropyridines **1g,** and **1h.** Although methyl and 2-phenethyl azides added smoothly to **2** (R = Et) to give the corresponding triazolines **10** (R = Me, $PhCH_2CH_2$) and photolysis gave the aziridines **3** (Table II), all attempts to produce the dihydropyridines by sequential hydrolysis of **3** and oxidation to **4** gave tarry polymeric products. Since mercuric salts are well known to oxidize tertiary amines,[15] di-*tert*-butyl azodicarboxylate was employed for the conversion of **4** to **5.** A methanol solution of **4** (R = $PhCH_2CH_2$) was treated with the azodicarboxylic ester at 0° and indeed gave a high yield of *N*-(2-phenethyl)-1,4-dihydropyridine **1g** as seen from nmr analysis of distilled (bulb-to-bulb) product. An attempt was also made to prepare *N*-(carboethoxyl)-1,4-dihydropyridine using carboethoxy azide. Although the corresponding triazoline **10** and aziridine **3** were readily formed (Table II), hydrolysis and oxidation to the dihydropyridine did not proceed but gave instead considerable polymeric material.

The process was extended to C-substituted 1,4-dihydropyridines although with moderate success. When 5-methylcyclopentadiene was prepared *in situ* at −78° and treated with diethyl azodicarboxylate at −20°, the adduct **11** was formed in low yield. Apparently, the facile rearrangement[15,16] of methylcyclopentadiene had taken place leading to **11** and no trace of the desired adduct **12** could be recovered. Addition of phenyl azide followed by photolysis of the triazoline gave the aziridine derivative **13.** Alkaline hydrolysis and oxidation with di-*tert*-butyl azocarboxylate gave *N*-phenyl-3-methyl-1,4-dihydropyridine (**14**). Though the efficiency of reaching **14** was poor, the potential was present for acquiring 3-substituted 1,4-dihydropyridines (and pyridines) which are rather inaccessible by direct substitution.[17]



11 12 13 14

Attention was also addressed to the preparation of **3** (R′ = H; R = Et or *t*-Bu) which could serve as a precursor to many *N*-alkyl- or *N*-sulfonyl-1,4-dihydropyridines. By employing trimethylsilyl azide Scheiner[18] was able to prepare the triazoline **15** and the aziridine **16.** When this sequence was repeated with **2,** the triazoline **10** (R′ = Me_3Si)



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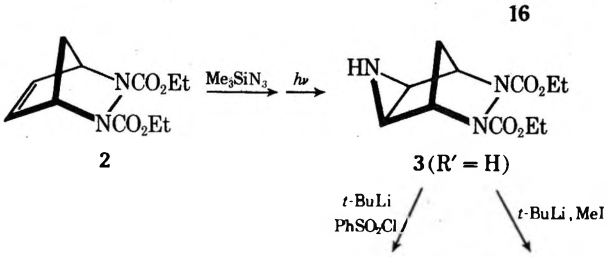


2 3(R′ = H)

3 (R′ = $PhSO_2$) 3 (R′ = Me)

was cleanly formed and photolysis gave the NH aziridine **3** directly and in 73% overall yield from **2.** Thus, it was not necessary to hydrolyze the trimethylsilyl group to reach our goal, **3** (R′ = H). Even though moisture was rigorously excluded, the photolysis gave only the NH aziridine. Treatment of the latter, at −78°, with *tert*-butyllithium followed by introduction of benzenesulfonyl chloride or methyl iodide gave the *N*-benzenesulfonyl and the *N*-methyl derivatives, respectively. These materials were identical with

Table II
Properties of Dihydropyridine Precursors[a]

2: R	Registry no.	% yield	Mp, °C	10: R′	Registry no.	R	% yield	Mp, °C	3: R′	Registry no.	R	% yield	Mp, °C
Et	14011-60-0	87	Oil[b]						$PhSO_2$	53447-29-3	Et	97	123–124
i-Pr	53384-84-2	81	55–56						$PhSO_2$	53384-93-3	*i*-Pr	85	102–103
$PhCH_2$	49675-21-0	83	92–93						$PhSO_2$	53384-94-4	$PhCH_2$	88	Oil[d]
t-Bu	39203-22-0	92	99–100						$PhSO_2$	53447-30-6	*t*-Bu	82	144–145
									$MeSO_2$	53384-95-5	*t*-Bu	85	137–142
				Ph	4953-02-0	Et	89	126–127	Ph	36961-05-4	Et	94	126–127
									Ph	53385-03-8	*i*-Pr	92	117–119
				Ph	53384-85-3	$PhCH_2$	84	141–142	Ph	53385-04-9	$PhCH_2$	94	134–135
				Ph	53384-86-4	*t*-Bu	92	158–159	Ph	53385-05-0	*t*-Bu	88	172–173
				p-BrPh	53384-87-5	Et	92	132–134	*p*-BrPh	53385-06-1	Et	86	145–146
				p-CNPh	53384-88-6	Et	76	169–172	*p*-CNPh	53385-07-2	Et	78	72–74
				p-MeOPh	53384-89-7	Et	97	129–132	*p*-MeOPh	53385-08-3	Et	89	108–110
				$PhCH_2CH_2$	53384-90-0	Et	80	Oil[c]	$PhCH_2CH_2$	53385-09-4	Et	80	Oil[d]
				Me	53384-91-1	Et	92	Oil[d]	Me	53385-10-7	Et	81	Oil[e]
				EtO_2C	53384-92-2	*t*-Bu	90	Oil[c]	EtO_2C	53385-11-8	*t*-Bu	54	175–177

[a] Infrared, nmr, and satisfactory elemental analyses for these compounds are described in the microfilm material (see paragraph at end of paper regarding supplementary material). [b] Bp 117–120° (0.3 Torr). [c] Used as crude product. [d] Purified on silica gel column. [e] Distilled, bp 130° (0.5 Torr).

those prepared using benzenesulfonyl azide and methyl azide in the cycloaddition to **2**. Thus, it was shown that the precursors to a variety of N-substituted (except *N*-aryl) 1,4-dihydropyridines could be obtained utilizing the readily prepared NH aziridine **3** (R′ = H) followed by alkylation of its lithio salt with an appropriate electrophile.

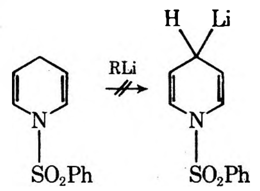
Properties of Dihydropyridines. The spectral data for the seven dihydropyridines prepared are given in Table I. The data are in close agreement with those for other known dihydropyridines. The ultraviolet absorptions indicate that there is little, if any, enamine character in these systems except for the *N*-phenethyl derivative **1g**. Since enamines absorb in the 220–240-nm region with extinction values over 5000, the dihydropyridines fall considerably short of this magnitude.[19] In the nmr spectrum of enamines, the β carbon typically falls in the 3.9–4.5-ppm region[20] whereas the 3-protons in the dihydropyridines appear at 4.5–4.9 ppm, considerably more deshielded than that which would be expected for significant lone-pair overlap. As expected, however, the *N*-phenethyldihydropyridine exhibits the highest field 3-proton at ~4.0–4.4 ppm. This is in agreement with the data of Fowler[3] who reports the 3-proton in *N*-methyl-1,4-dihydropyridine at 4.1–4.4 ppm. A linear correlation between the 2- and 3-proton chemical shift and the Hammett σ–ρ constants for the *p*-methoxy-, bromo-, and cyano-phenyldihydropyridines was obtained indicating direct resonance interaction for these groups.[21]

A cursory investigation into some chemical properties of the dihydropyridines was undertaken and it is of interest to note the results briefly. In view of the relationship between these systems and the coenzyme NADH,[5] the reduction of several aldehydes was examined. When the *N*-benzenesulfonyldihydropyridine **1a** was stirred with benzaldehyde in a degassed solution of ethanol (reflux, 16 hr), a 5% yield of benzyl alcohol was obtained. When this process was repeat-

$$\text{PhCHO} + \mathbf{1a} \longrightarrow \text{PhCH}_2\text{OH}$$

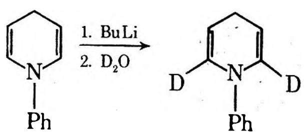
ed with salicylaldehyde, reported by Pandit[5] to be more reactive with Hantzsch esters than simple aldehydes, no reduction could be detected. Examination of the other dihydropyridines **1b**–**1g** gave no reduction of these aldehydes.

Metalation studies on **1a** were attempted in an effort to determine the feasibility of introducing substituents. Treatment of **1a** with a host of organolithium reagents to form the lithio derivative **17** met with failure under a variety of conditions. Thus, **17** is sufficiently antiaromatic (8-π



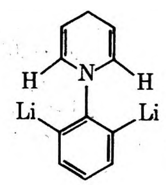
1a **17**

system) that its formation was prohibited. In the case of the *N*-phenyldihydropyridine **1c** metalation (*n*-butyllithium) took place in the two α positions which was confirmed by deuteration to **18**. Whether metalation took place ini-



1c **18**

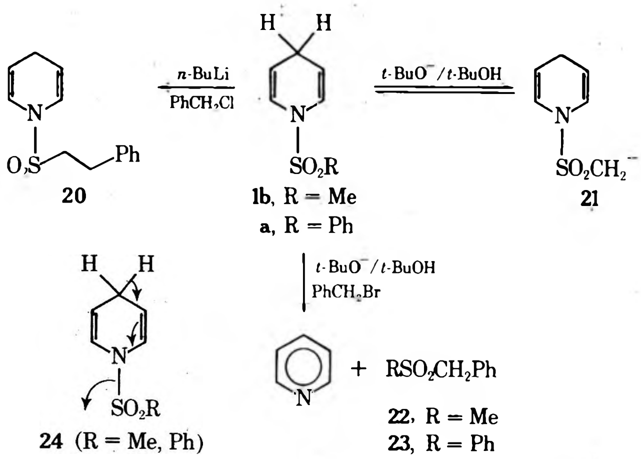
tially at the α positions or whether this is a result of an intramolecular proton transfer from the dihydropyridine ring to the o-lithio derivative **19** is not known at this time. Ani-



19

line derivatives are known to metalate in the ortho position with great facility.[22]

Due to the virtual resistance of the dihydropyridine **1a** toward metalation, the behavior of the *N*-methanesulfonyl derivative **1b** was investigated with respect to its reaction with bases. Treatment of **1b** with *n*-butyllithium (−78°) in THF gave an anion (*i.e.*, **21**) which was stable and could be alkylated with benzyl chloride to give the *N*-phenethylsulfonyl derivative **20**. Fragmentation of **21** to sulfene ($CH_2{=}SO_2$) and the *N*-lithio-1,4-dihydropyridine was considered and searched for[23] but could not be detected. Interestingly, when **1b** was treated with potassium *tert*-butoxide in *tert*-butyl alcohol, followed by addition of benzyl chloride (or bromide), a good yield of benzyl methylsulfone **22** was obtained. This means that the carbanion **21** is formed in a reversible process in a proton-containing media (*t*-BuOH) and, since **21** cannot undergo any subsequent transformations, allows **1b** to eliminate (*via* **24**) to the sulfinate anion. This process is undoubtedly concerted since, as mentioned above, the initial removal of a proton from the 4 position of the ring is energetically unfavorable. This was further confirmed by similarly treating **1a** with *tert*-butoxide ion obtaining benzylphenyl sulfone **23**. This is in sharp contrast to the total inertness of **1a** to much stronger bases which failed to produce **17**. The latter behavior, however, was noted in solvents of lower polarity (THF–hexane) which are incapable of supporting the transition state emanating from **24**.



Experimental Section

All melting points were taken on a Büchi melting point apparatus and are uncorrected. Gas chromatography was carried out with Hewlett-Packard Model 5750 Research Chromatographs equipped with either a flame ionization detector (FID) or a thermal conductivity detector (TC) with integration performed electronically with a Hewlett-Packard 3370B Integrator. Infrared spectra were taken on Perkin-Elmer 267 and 337 spectrophotometers. Nmr spectra were recorded on Varian A-60 and T-60 or JEOL MH-100 spectrometers. Ultraviolet spectra were taken on a Perkin-Elmer 402 ultraviolet–visible spectrophotometer. Mass spectra were carried out on an AEI MS-12 mass spectrometer. Analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind.

Unless otherwise stated, all photolyses were done with a Hanovia medium pressure mercury vapor arc and all tetrahydrofuran was distilled from sodium–benzophenone under a nitrogen atmosphere.

2,3-Dialkoxycarbonyl-2,3-diazabicyclo[2.2.1]hept-5-ene (2). General Procedure. Freshly distilled cyclopentadiene (43.5 mmol) was added dropwise under nitrogen to a solution of 43.5 mmol of dialkyl azodicarboxylate in 50 ml of methylene chloride. The solution was stirred (18 hr) and the solvent evaporated. The residue was crystallized from hexane. Concentration and cooling of the mother liquors afforded additional product (Table II). Spectral and analytical data are given in supplementary tables in the microfilm edition (see paragraph at end of paper regarding supplementary material).

2,3-Dialkoxycarbonyl-2,3,6-triaza-6-phenylsulfonyltricyclo[3.2.1.0^{5,7}]octane (3, R′ = PhSO$_2$; R = Alkyl). General Procedure. A solution of the diazanorbornenes 2 (32 mmol) and benzenesulfonyl azide[24] (32 mmol) in 120 ml of benzene was heated to reflux for 18–20 hr. Evaporation of the solvent left a viscous oily product which was crystallized from hexane (Table II). Complete spectral and elemental analyses are given in supplementary tables in the microfilm edition.

The methanesulfonyl derivative 3 (R′ = MeSO$_2$; R = *t*-Bu) was similarly formed using methanesulfonyl azide[25] prepared as follows. A solution of 23.2 g (0.202 mol) of methanesulfonyl chloride in 50 ml of 95% ethanol was cooled to −5° in an ice–salt bath. A solution of 15.0 g (0.231 mol) of sodium azide in 15 ml of water was added to the cold, well-stirred solution. Stirring was continued for an additional hour. The solvent was decanted from the white solid which crystallized and 100 ml of water was added causing a colorless oil to separate. The oil was extracted with two 125-ml portions of ether, the combined extracts were dried (Na$_2$SO$_4$), and the ether was removed on a rotary evaporator leaving a thick colorless oil. Crystallization from ether in Dry Ice–acetone gave 14.0 g (57.2%) of product: ir (neat) 2150, 1340, 1170 cm^{-1}.

Δ^{7,8}-2,3-Dialkoxycarbonyl-6-aryl-2,3,6,7,8-pentazatricyclo-[5.2.1.0^{5,9}]decene 10 (R′ = Aryl; R = Alkyl). General Procedure. A solution of the appropriate aryl azide (10.0 mmol) and the diazanorbornene 2 (10.0 mmol) in 20 ml of benzene was heated to reflux for 24 hr. The solvent was removed by rotary evaporator and the remaining oil crystallized from hexane–benzene (Table II). Complete spectral and elemental analyses are given in the supplementary tables in the microfilm edition.

Azides. Aryl azides were prepared according to the following: phenyl azide using the method of Lindsay and Allen,[26] *p*-methoxy-, *p*-cyano-, and *p*-bromophenyl azides using the method of Smith and Boyer,[27] phenethyl azide was prepared according to Smith,[28] methyl azide was prepared using the procedure of Leermakers,[29] ethyl azidoformate, according to Forster,[30] and trimethylsilyl azide according to Birkofer.[31]

2,3-Dialkoxycarbonyl-6-aryl-2,3,6-triazatricyclo[3.2.1.0^{5,7}]-octane 3 (R′ = Aryl; R = Alkyl). General Procedure. A solution of 10.0 mmol of *N*-aryltriazoline 10 in 150 ml of benzene was photolyzed in an immersion well equipped with a Pyrex probe. The reaction was followed by collecting the evolved nitrogen and irradiation was stopped when the theoretical amount was collected. The solvent was removed on a rotary evaporator and the residue crystallized from hexane–benzene (Table II). Complete spectral and elemental analyses are given in supplementary tables in the microfilm edition.

***N*-Benzenesulfonyl-1,4-dihydropyridine (1a).** A 7.6-g (28 mmol) sample of mercuric chloride was dissolved in 50 ml of absolute ethanol followed by 1.00 g (2.22 mmol) of aziridine **3a.** Dried (H$_2$SO$_4$) hydrogen chloride was bubbled through the solution for 2 hr after which the solvent was removed on a rotary evaporator leaving a white solid. The solid was treated with 100 ml of a basic (*ca.* 2 g/100 ml of NaOH] 1 *M* solution of sodium borohydride and allowed to react for 2 hr. The aqueous solution was extracted with three 50-ml portions of benzene, the combined benzene extracts were dried (Na$_2$SO$_4$), and the solvent was removed on a rotary evaporator leaving 0.301 g (63.1%) of colorless solid. Purification was effected by bulb-to-bulb distillation (150°, 0.1 mm). Complete physical and spectral data are given in Table I.

***N*-Methanesulfonyl-1,4-dihydropyridine (1b).** A 3.56-g (13.3 mmol) sample of mercuric chloride and 1.02 g (2.63 mmol) of aziridine **3b** were dissolved in 80 ml of absolute ethanol. Dried (H$_2$SO$_4$) hydrogen chloride was bubbled through the solution for 2 hr. The solvent was removed on a rotary evaporator leaving a white solid. The solid was treated with 50 ml of a basic (*ca.* 2 g/100 ml of NaOH) 1 *M* solution of sodium borohydride and allowed to react for 2 hr. The aqueous solution was extracted with three 30-ml portions of benzene, the combined extracts were dried (Na$_2$SO$_4$), and the solvent was removed on a rotary evaporator, leaving 0.221 g (51.7%) of pale yellow oil, which solidified on standing. Further purification was accomplished by bulb-to-bulb distillation. Physical and spectral data are given in Table I.

General Procedure for the Synthesis of *N*-Aryl-1,4-dihydropyridines (1c–1f). A solution of 10.0 mmol of arylaziridine **3c–f** in 30 ml of methanol was mixed with a solution of 7 g of KOH in 13 ml of water. The resulting solution was heated to reflux for 3 hr. The methanol was removed on a rotary evaporator and the remaining aqueous phase was extracted with three 30-ml portions of methylene chloride. The combined extracts were dried (Na$_2$SO$_4$) and the solvent was removed on a rotary evaporator, leaving a solid. The solid was dissolved in 50 ml of methanol, a 6.0-g sample of mercuric oxide (red) was added, and the mixture was heated to reflux for 18 hr. The mixture was filtered and the solvent was removed from the solution on a rotary evaporator, leaving an intense red oil. The product was purified by bulb-to-bulb sublimation [50° (0.1 mm)]. All of the aryldihydropyridines were found to readily decompose when exposed to air; however, they could be stored indefinitely under a nitrogen atmosphere at −20°. Complete spectral and physical data are given in Table I.

***N*-Phenethyl-1,4-dihydropyridine (1g).** A solution of 2.97 g (8.39 mmol) of aziridine 3 (R′ = PhCH$_2$CH$_2$; R = Et) in 25 ml of degassed (N$_2$) methanol was treated with a solution of 7 g of KOH in 15 ml of water. The reaction mixture was heated to reflux under a nitrogen atmosphere for 18 hr and the methanol was removed on a rotary evaporator. The remaining aqueous phase was extracted with three 30-ml portions of methylene chloride. The combined extracts were dried (Na$_2$SO$_4$) and the solvent was evaporated. The residue (4) was placed in a flask with 1.93 g (8.40 mmol) of di-*tert*-butyl azodicarboxylate. While under a nitrogen atmosphere the flask was cooled to 0° and 20 ml of degassed (N$_2$) methanol was added. The solution was stirred at 0° for 24 hr. The solvent was removed with a vacuum pump as the flask was kept cold. When the volume was *ca.* 3 ml, the solution was transferred to a Kugelrohr apparatus where the remaining solvent was removed *in vacuo.* The oil which remained was bulb-to-bulb distilled [70°(0.3 mm)], affording a clear colorless oil in *ca.* 50% yield, which was contaminated with 33% hydrazine di-*tert*-butylcarboxylate. Physical data are given in Table I. The product was extremely unstable; a sample stored under nitrogen at −20° would completely decompose within 6 hr.

A fresh sample of the dihydropyridine gave the following mass spectrum: 70 eV, *m/e* (relative intensities) 185 (45), 184 (59), 105 (55), 94 (100), 80 (18), 79 (30), 77 (25), 67 (25), 57 (75). An ultraviolet spectrum in ethanol had three maxima: 214, 240 (shoulder) and 300 nm (shoulder).

Alkaline Hydrolysis of 3 (R′ = PhSO$_2$; R = Et). Formation of the Diazatricyclene 9. A solution of 3 (1.00 g) in 10 ml of methanol containing 2.8 g of 50% potassium hydroxide solution was heated to reflux (N$_2$) for 2 hr. Filtration of the potassium carbonate precipitate was followed by evaporation of the methanol and the residue was then dissolved in 15 ml of water. The solution was extracted with chloroform and the extracts discarded. The pH of the solution was adjusted to 7 (acetic acid) and again extracted with chloroform; the extracts were dried (MgSO$_4$) and concentrated to give 587 mg (93%) of **9.** Recrystallization from ethanol gave pure material: mp 180–181°; nmr (CDCl$_3$) δ 1.17 (d, *J* = 12 Hz), 1.89 (d, *J* = 12 Hz), 1.93 (m, 1), 2.20 (m, 1), 2.9–2.99 (m, 2), 4.13 (br s, 1, exchangeable with D$_2$O), 7.6–8.0 (m, 5). The NH proton of the sulfonamide group was not discernible as reported in other cases.[32]

Anal. Calcd for $C_{11}H_{13}N_2O_2S$: C, 52.59; H, 5.22; N, 16.72. Found: C, 52.31; H, 5.12; N, 16.54.

Formation of 3 (R′ = H; R = Et). A solution of 9.0 g (78 mmol) of trimethylsilyl azide and 11.6 g (48.5 mmol) of diazanorbornene 2 (R = Et) in benzene was heated to reflux for 4 days. Removal of the solvent on a rotary evaporator afforded 15.0 g of yellow oil. The oil was dissolved in 200 ml of THF and 10 ml of water was added. The solution was photolyzed for 24 hr in an immersion well equipped with a quartz probe. The solvent was removed on a rotary evaporator, leaving a dark oil which was vacuum distilled through a 3-cm Vigreux column, affording a colorless liquid. Crystallization from hexane–benzene gave 8.7 g (70% based on diazanorbornene 2) of colorless crystals: mp 110–111°; ir (KBr) 3300, 1750, 1720 cm^{-1}; nmr (CDCl$_3$) δ 0.0–0.4 (m, 1), 1.0–1.3 (m, 1), 1.33 (t, *J* = 7 Hz, 6), 1.8–2.1 (m, 1), 2.64 (br s, 2), 4.30 (q, *J* = 7 Hz, 4), 4.70 (br s, 2).

Anal. Calcd for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71. Found: C, 51.99; H, 6.81.

Alkylation of Aziridine 3 (R′ = H; R = Et) with Methyl Iodide and Benzenesulfonyl Chloride. A solution of 3 (R′ = H; R = Et) in THF was cooled to −78° under a nitrogen atmosphere and treated with 1 equiv of a 2.3 *M* solution of *tert*-butyllithium (Lithium Corporation). The solution was stirred at −78° for 1 hr and then 1 equiv of an electrophile was added. The solution was allowed to warm to room temperature and stirring was continued for 3 hr, after which it was concentrated. The residual oil was dissolved in water, the aqueous mixture was extracted with benzene, and the combined extracts were dried (Na_2SO_4) and concentrated.

When methyl iodide was added as the electrophile, bulb-to-bulb distillation afforded a 33% yield of aziridine **3** (R′ = Me) having an nmr spectrum and vpc retention time identical with that prepared from methyl azide. When benzenesulfonyl chloride was added as an electrophile, a 62% yield of aziridine **3** (R = $PhSO_2$; R′ = Et) was isolated, having an nmr spectrum and R_f (tlc) value identical with that prepared from benzenesulfonyl azide.

2,3-Diethyloxycarbonyl-6-phenyl-1-methyl-2,3,6-triazatricyclo[3.2.1.0^{5,7}]octane (13). Sodium cyclopentadienide was synthesized using the procedure of King and Stone.[33] The compound was methylated using the procedure of Partridge.[34] The methylcyclopentadiene was kept at −78° while an equivalent of diethyl azodicarboxylate in THF was added dropwise. The solution was stirred for 24 hr at −78° and then allowed to stand for 48 hr at −20°. Filtration and removal of the solvent on a rotary evaporator afforded an oil which, by nmr analysis, was a complex mixture. The oil was taken up in benzene, an equivalent of phenyl azide was added, and the solution was heated to reflux for 24 hr. The solution was then photolyzed in an immersion well with a Pyrex probe for 24 hr. The solvent was removed on a rotary evaporator leaving a dark brown oil. Crystallization of the oil from hexane–benzene afforded a *ca.* 2% yield of **13:** mp 128–128.5°; ir (KBr) 1740, 1718, 1595 cm^{-1}; nmr ($CDCl_3$) δ 1.27 (split t, *J* = 7.5 Hz, 7), 1.95 (s, 3), 1.9–2.2 (m, 1), 2.8–3.0 (m, 2), 4.24 (split quartet, *J* = 7.5 Hz, 4), 4.95 (br s, 1), 6.8–7.4 (m, 5).

Anal. Calcd for $C_{18}H_{23}N_3O_4$: C, 62.59; H, 6.71. Found: C, 62.37; H, 6.80.

1-Phenyl-3-methyl-1,4-dihydropyridine (14). A solution of 0.290 g (0.840 mmol) of aziridine **13** in 20 ml of degassed (N_2) methanol was treated with a solution of 4 g of KOH in 10 ml of water. The solution was heated to reflux under a nitrogen atmosphere for 14 hr. The methanol was removed *in vacuo* and the remaining aqueous phase was extracted with dichloromethane. The combined extract was dried (Na_2SO_4) and concentrated. The residual solid was mixed with 0.194 mg (0.840 mmol) of di-*tert*-butyl azodicarboxylate under a nitrogen atmosphere in a flask. The flask was cooled to 0° and 20 ml of degassed (N_2) methanol was added and the solution stirred for 4 hr at 0°. The solvent was removed on a rotary evaporator while keeping the flask cold. The residue was purified by vacuum bulb-to-bulb sublimation, affording the dihydropyridine, contaminated with *ca.* 50% hydrazine-di-*tert*-butyl dicarboxylate in *ca.* 30% yield: nmr ($CDCl_3$) δ 1.63 (m, 3), 2.8–3.0 (m, 2), 4.5–4.8 (m, 1), 6.1–6.4 (m, 2), 6.8–7.4 (m, 5); uv (EtOH) 211 and 243 nm. The mass spectrum had peaks at *m/e* 171 (M^+) and 170 in the ratio of 35:100, respectively.

Reduction of Benzaldehyde to Benzyl Alcohol with 1a. A solution of 107 mg (0.484 mmol) of **1a** and 50 ml (0.47 mmol) of benzaldehyde in 8 ml of degassed (vacuum transfer) 95% ethanol was heated to reflux. A sample taken after 16 hr was injected into a vpc equipped with an FID, having a 10% UC-W 100 on Chromosorb P column at 110°. Retention times of both starting aldehyde and product were determined using authentic samples. A small disappearance of aldehyde was accompanied by the appearance of benzyl alcohol. Electronic integration determined that *ca.* 5% of the aldehyde had been reduced to alcohol, based on the change in the aldehyde peak area. Subsequent injections showed the alcohol peak area remained constant. When one drop of concentrated hydrochloric acid was added, no increase in alcohol was observed. When the reaction was repeated in the absence of **1a**, no reduction of benzaldehyde was observed.

Metalation of *N*-Phenyl-1,4-dihydropyridine (1c). A solution of **1c** in tetrahydrofuran (1*M*) was treated under a nitrogen atmosphere with 2.0 equiv of *n*-butyllithium (2.2 *M* hexane) at 0°. The solution was stirred at this temperature for 1.5, 4.5, and 18.5 hr and aliquots removed and quenched in deuterium oxide. The aqueous solution was extracted with benzene and the extracts then dried (Na_2SO_4), concentrated, and examined by nmr. The per cent deuterium incorporation was followed by integrating the peak at 6.32 (2 position) relative to the peak at 2.99 (4 position) and 4.0–4.88 (3 position). The results are shown in Table III.

Reaction of *N*-Methanesulfonyl-1,4-dihydropyridine 1b with *n*-Butyllithium. A solution of 500 mg (3.14 mmol) of **1b** in 40 ml of THF was cooled to −78° under a nitrogen atmosphere. A 1.42-ml (3.14 mmol) sample of a 2.2 *M* solution of *n*-butyllithium was added and stirred for 1 hr, and 0.38 ml (2.5 mmol) of benzyl chloride was added. The solution was allowed to slowly rise to room temperature and then poured into 100 ml of water and extracted with three 50-ml portions of benzene. The combined benzene extracts were dried (Na_2SO_4) and the solvent was removed on a rotary evaporator leaving an oil. Bulb-to-bulb distillation gave a 50% yield of unreacted starting material and a *ca.* 25% yield of crude **20:** nmr ($CDCl_3$) δ 2.8 (m, 2), 3.2 (m, 4), 4.9 (m, 2), 6.4 (split doublet, 2), 7.2 (m, 5). An attempt at further purification by bulb-to-bulb distillation resulted in the product's decomposition leaving only a nondistillable tar.

Table III

Time, hr	Rel peak ht[a]	% D in 2 position (18)
1.5	0.71	47
4.5	0.59	82
18.5	0.61	78

[a] Peak at 6.32 ppm *vs.* peaks at 2.99 and 4.4–4.8 ppm.

Treatment of *N*-Methanesulfonyl-1,4-dihydropyridine (1b) with Potassium *tert*-Butoxide in *tert*-Butyl Alcohol. A solution of 75 mg (0.47 mmol) of dihydropyridine and 54 mg (0.48 mmol) of sublimed KO-*t*-Bu in 5 ml of *tert*-butyl alcohol was heated to reflux under a nitrogen atmosphere for 1 hr after which 56 μl (0.47 mmol) of benzyl bromide was added. Heating was continued for 40 hr. Analysis of the reaction solution by vpc revealed that most of the benzyl bromide and dihydropyridine had been consumed and that a new compound with a retention time longer than the dihydropyridine was formed. This new compound was collected using a 0.25-in. 10% UC-W 96 on Chromosorb P column at 150° (retention time, 7.2 min). The nmr of the new compound was identical with that of benzylmethyl sulfone: mp 123–125° (mp[35] 123–125°); ir (KBr) 1310, 1125 cm^{-1}; nmr ($CDCl_3$) δ 2.79 (s, 3), 4.30 (s, 3), 7.47 (s, 5).

Treatment of *N*-Benzenesulfonyl-1,4-dihydropyridine (1a) with Potassium *tert*-Butoxide in *tert*-Butyl Alcohol. A solution of 150 ml (0.678 mmol) of **1a** and 76 mg (0.68 mmol) of sublimed KO-*t*-Bu in 6 ml of *t*-BuOH was heated to reflux for 4 hr. Vpc analysis revealed that nearly all of the starting material was consumed. An 81-μl (0.68 mmol) sample of benzyl bromide was added. A new peak having a longer retention time than the dihydropyridine appeared. A sample was collected using a 0.25-in. 10% SE-30 column at 250°. The product melted at 146–147° (mp[36] 146°); nmr ($CDCl_3$) δ 4.30 (s, 2), 7.2–7.8 (m, 10).

Acknowledgment. The authors wish to thank the National Institutes of Health for financial support.

Registry No.—**1a,** 39203-25-3; **1b,** 53432-93-2; **1c,** 34865-02-6; **1d,** 53384-80-8; **1e,** 53384-81-9; **1f,** 53384-82-0; **1g,** 53384-83-1; **9,** 53447-38-4; **13,** 53385-12-9; **14,** 53385-14-1; **20,** 53385-13-0; **22,** 3112-90-1; **23,** 3112-88-7; cyclopentadiene, 542-92-7; diethyl azodicarboxylate, 1972-28-7; diisopropyl azodicarboxylate, 2446-83-5; dibenzyl azodicarboxylate, 2449-05-0; di-*tert*-butyl azodicarboxylate, 870-50-8; benzenesulfonyl azide, 938-10-3; methanesulfonyl azide, 1516-70-7; phenyl azide, 622-37-7; *p*-methoxyphenyl azide, 2101-87-3; *p*-cyanophenyl azide, 18523-41-6; *p*-bromophenyl azide, 2101-88-4; phenethyl azide, 32366-25-9; methyl azide, 624-90-8; ethyl azidoformate, 817-87-8; trimethylsilyl azide, 4648-54-8; methyl iodide, 74-88-4; benzenesulfonyl chloride, 98-09-9; benzaldehyde, 100-52-7; benzyl alcohol, 100-51-6; *n*-butyllithium, 109-72-8; potassium *tert*-butoxide, 865-47-4.

Supplementary Material Available. Complete spectral elemental analyses and physical constants of this work will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for \$3.00 for photocopy or \$2.00 for microfiche, referring to code number JOC-75-563.

References and Notes

(1) Taken from the thesis of D. M. Stout in partial fulfillment of the requirements for the degree of Doctor of Philosophy.
(2) For a recent review on dihydropyridines see U. Eisner and J. Kuthan, *Chem. Rev.*, **72**, 1 (1972).
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Synthesis of 2-Methyl- and 2-Phenyl-5-thiopyridines

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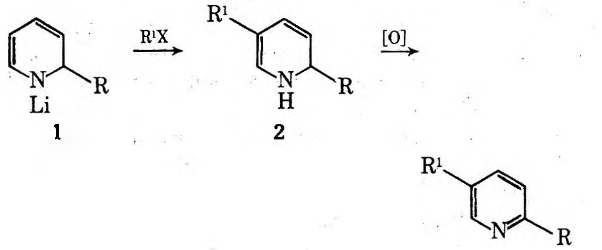
A new procedure is described for the "one pot syntheses" of 2-methyl- or 2-phenyl-5-methylthio-, butylthio-, or phenylthiopyridines, **3** and **4**. This involves formation of the pyridine/methyllithium (**1**, R = CH_3) or pyridine/phenyllithium (**1**, R = Ph) adduct and its reaction with the appropriate disulfide. While yields are low, work-up of the reaction in all cases is simple, and the 2,5-disubstituted product is obtained directly without position isomer problems. Use of the 5-butylthiopyridines **4b** and **4c**, *via* the Pummerer rearrangement of the sulfoxides **5b** and **5c**, as precursor for other 5-thiopyridines is described. An interesting formaldehyde trapping process is observed in one case where 2-phenyl-5-methylthiopyridine **4a** was used as such a precursor. Isolation of 2,5-dihydro-2-methyl-5-bis(phenylthio)pyridine (**9**) from the reaction of the pyridine/methyllithium adduct (**1**, R = CH_3) with phenyl disulfide and the isolation of 2-bis(*tert*-butylthio)methylpyridine from the reaction with *tert*-butyl disulfide suggested a mechanism for this "one pot synthesis" of 2-substituted-5-thiopyridines.

Reaction of the appropriate mercaptide anion with a 2- or 4-halopyridine provides ready access to the 2- and 4-thiopyridines.[1] Preparation of 3-thiopyridines by this procedure requires high temperatures, copper catalysis, and in most cases gives poor yields,[2] unless activating groups are appropriately positioned relative to the halogen, *e.g.*, as in 5-bromo-2-nitropyridine.[3]

A variety of alternative methods have been developed. Reduction of 3-pyridylsulfonyl chloride by stannous chloride[4] or red phosphorus and iodine[5] provides moderate yields of 3-pyridylthiol from which the ethers can be obtained by alkylation. Diazotization of 3-aminopyridine and reaction of the diazonium salt with a sulfur nucleophile gives the desired product, but in poor yield.[6,7]

More recently, use of thiocyanate as the nucleophile has been reported to give a 72% yield of 2-chloro-5-pyridylthiocyanate from 5-amino-2-chloropyridine *via* diazotization.[8] This procedure is the best reported to date. Reaction of pyridine *N*-oxide with benzenesulfonyl chloride and a thiophenol yields a mixture of 2- and 3-thiopyridines and appears to be of limited preparative value.[9]

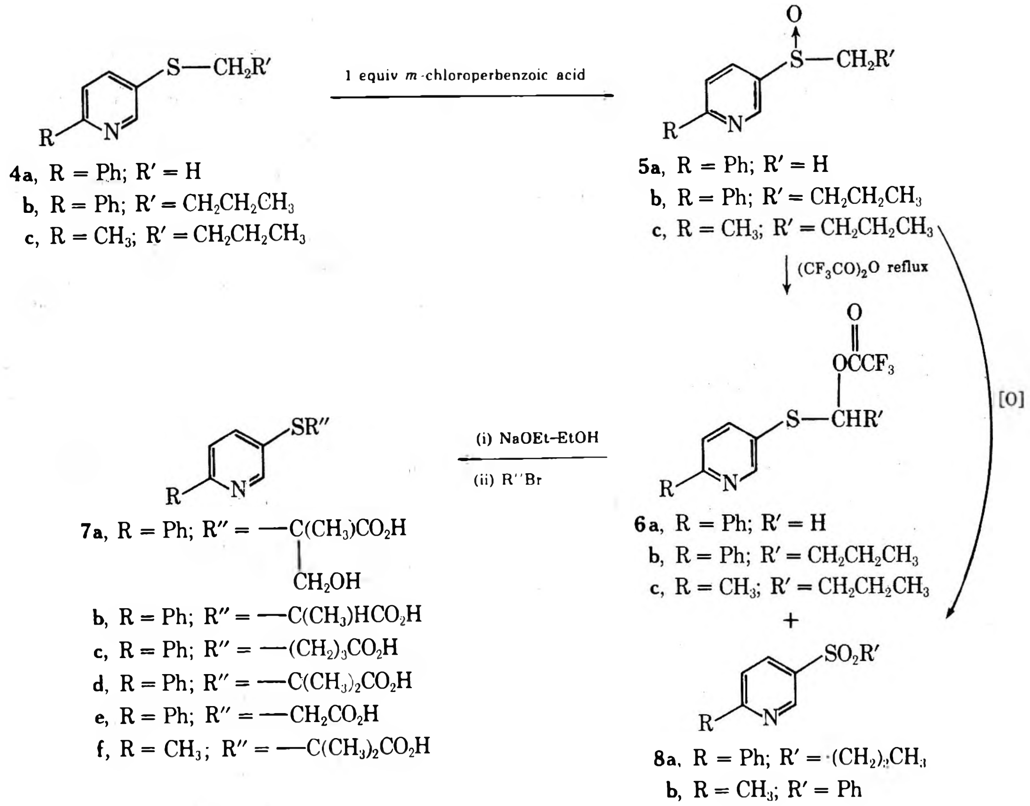
A need for 2-substituted 5-thiopyridines prompted us to develop a new synthetic procedure. We were attracted by recent reports of specific syntheses of 2,5-disubstituted pyridines **3**[10,11] by alkylation of the adduct **1** formed from



3a, R = Ph; R¹ = ·SPh
b, R = CH_3; R¹ = ·SPh
c, R = CH_3; R¹ = ·S(→O)Ph

pyridine and an organolithium reagent. Such adducts **1** have been well characterized[12,13] and exclusively involve

Scheme I



addition to the 2 position. The striking feature of the chemistry of such adducts 1 is their reaction with most electrophiles exclusively at position 5 rather than at positions 1 and/or 3, although acylation does give substantial amounts of *N*-acylation.[14] The product obtained initially, *i.e.*, compound **2**, is a dihydropyridine. A mechanism by which intermediate **2** is oxidized to the final 2,5-disubstituted pyridine **3** has been suggested to be loss of lithium hydride.[15] Such a mechanism has been proposed for the aromatization of other dihydro heterocyclic aromatic systems.[16] Therefore, achievement of our goal should be possible by addition of a sulfur electrophile to the intermediate complex 1 formed from an appropriate organolithium reagent. Reaction of pyridine with phenyllithium to give 1 (R = Ph) and addition of benzenesulfenyl chloride gave a small yield of the desired 2-phenyl-5-phenylthiopyridine (**3a**). Since the use of a sulfenyl chloride perhaps favored reaction on nitrogen, as in the case of an acyl chloride,[14] we explored the use of diphenyl disulfide as the sulfur electrophile. The yield (29%) was still low, but acceptable in view of the simple isolation procedure which involved distillation of the crude reaction product. 2-Phenyl-5-phenylthiopyridine (**3a**) was the only isomer in the distillate and by-products were either much more volatile or were undistillable tars. That this product **3a** was a 2,5-isomer was immediately evident from the nmr spectrum. This spectrum showed only one low-field α-pyridyl proton (δ 8.78), which was a broadened singlet, *i.e.*, no ortho coupling. This was also true for the nmr spectrum of compound **4a;** however, in the nmr spectra other primary products **3b**, **4b**, and **4c** meta splitting of the one low-field α-pyridyl proton could be seen, which provided additional support. As previous workers[12,13] have established that the addition of the organolithium reagent to the pyridine takes place at the 2 position, these spectral results indicate that reaction with electrophilic sulfur has also taken place at position 5.

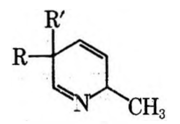
To improve the utility of this synthesis, it was necessary that we provide a route to 2-substituted-5-pyridinethiols. Thus, substituents could be obtained at the 5 position, which would either not be accessible by the "one pot process" due to side reactions with the pyridine–lithium complex or because of the unavailability of the appropriate disulfide. It was envisioned that the thiol anion could be prepared *in situ* by collapsing a Pummerer rearrangement product **6** with sodium ethoxide (Scheme I) and then addition of the appropriate alkylating agent would give the desired product **7**. The initial choice of precursor for this process was 2-phenyl-5-methylthiopyridine (**4a**). Reaction of the pyridine adduct 1 (R = Ph) with methyl disulfide gave a low yield (17%) of the desired product (**4a**), but in this case it could be directly crystallized from the crude reaction mixture. Oxidation to the sulfoxide (**5a**) proceeded in 79% yield, without any concomitant oxidation of the pyridine nitrogen being evident. Reaction of the sulfoxide **5a** with refluxing trifluoroacetic anhydride gave a quantitative yield of the Pummerer product **6a,** which was used without further purification. Reaction of the Pummerer product **6a** with ethanolic sodium ethoxide at room temperature, followed by addition of ethyl 2-bromopropionate and heating, gave a crude ester which was hydrolyzed by aqueous base to a crystalline acid. This acid was not the expected product **7b**, but a product **7a** derived by trapping of the formaldehyde liberated on collapse of the Pummerer product **6a.** The desired product **7b** could be obtained by the simple expedient of removing the ethanol and then replacing it with fresh ethanol prior to addition of the alkylating agent. With the same process and use of ethyl 4-bromobutyrate, an excellent overall yield (87%) of the 4-(6-phenyl-3-pyridinylthio)butanoic acid (**7c**) could be obtained from the sulfoxide **5a.**

The additional step of removing the ethanol and formaldehyde after decomposition of the Pummerer product **5a** was troublesome for large scale use of the process, and other sulfoxides which would yield less reactive aldehyde by-products were examined. Reaction of dibutyl disulfide with 1 (R = Ph) gave a 35% yield of 3-butylthio-6-phenylpyridine **4b**, which was readily isolated and then oxidized to the sulfoxide **5b** in 72% yield (Scheme I). Further oxidation of **5b** gave the sulfone **8a**; no oxidation at nitrogen was observed. As the sulfoxide **5b** and this sulfone **8a** had very different tlc behavior, this provided a simple analytical check on the quality of the sulfoxide **5b**. Reflux of the sulfoxide **5b** in trifluoroacetic anhydride yielded the Pummerer product **6b** which was treated with ethanolic sodium ethoxide at room temperature, followed by addition of the alkylating agent and warming. As expected, the butyraldehyde formed from **6b** does not interfere with the subsequent alkylation process, which therefore can be carried out from the sulfoxide **6b**, as we had originally intended from the sulfoxide **6a**, as a "one-pot" process. The overall yield of 2-methyl-2-(6-phenyl-3-pyridinylthio)propanoic acid (**7d**) from the sulfoxide **6b** using this process was 78%. Thus, we had achieved our goal of being able to vary widely the substituent on sulfur at position 5.

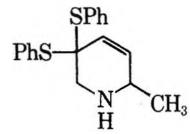
There remained a need for potential variation at position 2. Since 2-picolines can be transformed into a variety of functionalized pyridine derivatives,[17] reaction of the methyllithium-pyridine adduct 1 (R = CH_3) with phenyl and butyl disulfide was investigated. Reaction of butyl disulfide with the adduct 1 (R = CH_3) gave a comparable yield (27%) of 3-butylthio-6-methylpyridine (**4c**) to that obtained of **4b** from the phenyllithium adduct 1 (R = Ph). Oxidation with 1 equiv of *m*-chloroperbenzoic acid analogously yielded the sulfoxide **5c**, without competing reactions from the pyridyl nitrogen. However, unlike the sulfoxide of 3-butylthio-6-phenylpyridine (**5b**), this sulfoxide **5c** was thermally unstable; deterioration was observed on attempted chromatography and **5c** was therefore used directly from the reaction mixture. Reflux in trifluoroacetic anhydride converted it to **6c**, which was treated with ethanolic sodium ethoxide briefly at room temperature. Then the alkylating agent was added and the mixture warmed. Using ethyl 2-bromoisobutyrate as the alkylating agent and hydrolyzing the product gave 2-methyl-2-(6-methyl-3-pyridinylthio)propionic acid (**7f**) in 50% overall yield from the crude sulfoxide **5c**.

Reaction of the methyllithium-pyridine adduct 1 (R = CH_3) with phenyl disulfide gave only a small yield (8%) of the desired 2-methyl-5-phenylthiopyridine (**3b**), which could be also oxidized preferentially at sulfur by metachloroperbenzoic acid to give both the sulfoxide **3c** and the sulfone **8b** according to the amount of peracid added. A by-product was also isolated in 1% yield from the reaction of phenyl disulfide with the adduct 1 (R = CH_3). This proved to be 2,5-dihydro-2-methyl-5,5-bis(phenylthio)pyridine (**9**), *i.e.*, the thioacetal of the ketone tautomer of 6-methyl-3-pyridinol! This was transformed by acid into the major product 2-methyl-5-phenylthiopyridine (**3b**). If the acid wash in the work-up of the reaction was omitted, **9** became the major product (11.5% yield) and could be isolated from the crude reaction mixture by direct crystallization. The nmr spectrum of this compound **9** showed the methyl group to be unusually shielded by a phenylthio group. Reduction of **9** by sodium cyanoborohydride yielded the tetrahydropyridine **11**, which is more conformationally mobile and showed the methyl resonance in the nmr at a normal position.

Isolation of such a compound as **9** sheds some light on the mechanism of this reaction and such dihydropyridines may be on the reaction pathway from **1** to **3** in the other examples we have described. Such dihydropyridines have not been isolated in previous studies of the reaction of **1** with other electrophiles.[10,11,14] The reason for this difference may be similar to that provided to explain that while enamines give exclusively monosubstituted products on alkylation or acylation, with sulfur electrophiles they give disubstituted products.[18] Further support for the view that such dihydropyridine compounds such as **9** are intermediates on the pathway to the final 2,5-disubstituted pyridines **3**, was obtained by the behavior of the methyl lithium-pyridine adduct 1 (R = CH_3) with *tert*-butyl disulfide. No 3-*tert*-butylthio-6-methylpyridine could be isolated; instead 2-bis(*tert*-butylthio)methylpyridine was the only isolable product. The identity of this material was confirmed by synthesis from 2-picoline. A plausible explanation for the appearance of this new reaction pathway is that the intermediate 2 (R' = $SC(CH_3)_2CH_3$; R = CH_3) is too hindered at position 5 to react again with *tert*-butyl disulfide to give the crowded intermediate **10**. Instead, **2** is diverted onto polymeric materials or eliminates *tert*-butylthiol to give picoline *via* **12**.



9, R = R' = SPh
10, R = R' = S-C(CH$_3$)$_3$
12, R = H; R' = SC(CH$_3$)$_3$



11

Experimental Section[19]

2-Phenyl-5-phenylthiopyridine (3a) *via* Phenylsulfenyl Chloride. Pyridine (3.95 g, 0.05 mol) was dissolved in ether (30 ml) and added dropwise with stirring to an ethereal solution of phenyllithium (25 ml of 1.3 *M* solution; 0.0325 mol) at room temperature. The mixture was stirred for 1 hr following addition and then cooled to −70°. A solution of phenylsulfenyl chloride (7.2 g, 0.05 mol) in an ether-benzene mixture was added dropwise . The mixture stirred at −70° for 2 hr and was allowed to come to room temperature overnight. The reaction mixture was diluted with ether and shaken with 2 *N* NaOH. The ether phase was extracted three times with 4 *N* HCl. The acid extract was made basic and reextracted with ether. Removal of the ether gave an oil (1.58 g). This was distilled in a Kugelrohr apparatus (130–170° (0.1 mm)). The bulk of the oil distilled to give a pale yellow oil which crystallized. This was recrystallized from ethanol to give 2-phenyl-5-phenylthiopyridine (**3a**): mp 58–60°; ir (Nujol) 1580 (m), 1552 (w), 735 (s), 690 (s) cm^{-1}; uv λ max (MeOH) 264 mμ (ϵ 15,440), 281 (15,030), 312 (10,600); nmr (CDCl$_3$) δ 8.78 (s, 1), 8.10–7.10 (m, 12).

Anal. Calcd for $C_{17}H_{13}NS$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.59; H, 5.17; N, 5.13.

2-Phenyl-5-phenylthiopyridine (3a) *via* Phenyl Disulfide. Pyridine (8.7 g, 0.11 mol) in benzene (50 ml) was added to phenyllithium (80 ml of 1.4 *M*, 0.11 mol) during 10 min. The mixture was then warmed at 50° for 1.5 hr. Phenyl disulfide (23.9 g, 0.11 mol) in benzene (100 ml) was added rapidly with stirring. The internal temperature rose to 64°. Heating was continued for 4 hr. Then the reaction was cooled to room temperature. Oxygen was bubbled through the reaction for 1.5 hr. The reaction was washed with water and brine and dried (MgSO$_4$). The benzene was removed *in vacuo*. The residue distilled in a Kugelrohr (130–170° (0.1 mm)). The main fraction (8.3 g, 0.0315 mol, 29%) crystallized and was recrystallized from ethanol to give 2-phenyl-5-phenylthiopyridine (**3a**) (5.5 g), mp 59–60°.

3-Methylthio-6-phenylpyridine (4a). Pyridine (158.2 g, 2.0 mol) was dissolved in benzene (500 ml) and added slowly with stirring to a solution of commercial phenyllithium (2.0 mol in 70:30 benzene-ether; Alfa) under nitrogen. After addition, the mixture was stirred at room temperature for 2 hr. Dimethyl disulfide (188 g, 2.0 mol) dissolved in benzene (250 ml) was added slowly with stirring and the mixture stood overnight at room temperature. The reaction mixture was washed with water and brine and dried (MgSO$_4$). The solvents were removed *in vacuo*. The residue, a red oil, was dissolved in ethanol, seeded, and cooled in the ice box. 3-

Methylthio-6-phenylpyridine (**4a**) (68 g, 0.34 mol, 17%): mp 92–94°; ir (Nujol) 1544 (m), 1108 (m), 1014 (m), 828 (m), 772 (m), 730 (s), 688 (m) cm^{-1}; uv λ max (MeOH) 244 mμ (ε 8,230), 280 (16,400); nmr ($CDCl_3$) δ 8.54 (s, 1), 8.1–6.9 (m, 7), 2.34 (s, 3).

Anal. Calcd for $C_{12}H_{11}NS$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.65; H, 5.60; N, 6.79.

3-Methylsulfinyl-6-phenylpyridine (5a). 3-Methylthio-6-phenylpyridine (**4a**) (18.5 g, 0.092 mol) was dissolved in methylene chloride (200 ml). With ice cooling and stirring, a solution of *m*-chloroperbenzoic acid (18.8 g, 0.097 *M*) in methylene chloride was added slowly. The mixture was stirred for 2 hr at room temperature following addition. No peracid was evident at this time based on starch iodide paper. The mixture was washed (2 × 10% aqueous $KHCO_3$ and water) and dried ($MgSO_4$) and the solvent was removed *in vacuo*. The solid remaining was recrystallized from 2-propanol–methylene chloride to give the sulfoxide **5a** (15.7 g, 79%): mp 128–130°; ir (Nujol) 1575 (m), 1556 (m), 1292 (m), 1048 (s), 1038 (s), 732 (m), 686 (m) cm^{-1}; uv λ max (MeOH) 258 mμ (ε 15,270), 286 (16,490); nmr ($CDCl_3$), δ 8.80 (d, 1 *J* = 2 Hz), 8.20–7.70 (m, 4), 7.43 (t, 3), 2.77 (s, 3).

Anal. Calcd for $C_{12}H_{11}NOS$: C, 66.35, H, 5.10; N, 6.45. Found: C, 66.10; H, 5.39; N, 6.55.

Attempted *in Situ* Alkylation of 2-Phenyl-5-pyridylthiol *via* the Sulfoxide 5a. 3-Methylsulfinyl-6-phenylpyridine (**5a**) (6 g, 0.028 mol) was refluxed with trifluoroacetic anhydride (40 ml) for 2 hr. The material slowly dissolved during that time. The anhydride was removed *in vacuo*. The residue was dissolved in ether. The ether solution was washed (2 × 10% aqueous $KHCO_3$, brine) and dried ($MgSO_4$) and the ether was removed *in vacuo*. The trifluoroacetate **6a** (8 g) was checked by nmr (($CDCl_3$, δ 8.72 (m, 1), 8.10–7.60 (m, 4), 7.40 (t, 3), 5.50 (s, 2)) and dissolved in ethanol. Ethanolic sodium ethoxide was added (from dissolving 772 mg of sodium metal) and the mixture was stirred at room temperature for 3 hr. Ethyl 2-bromopropionate (5.4 g, 0.030 mol) was added and the mixture was warmed at 70° overnight. The ethanol was removed *in vacuo*. The residue was washed with ether. The ethereal washings were dried ($MgSO_4$) and the ether was removed *in vacuo* to give the crude ester as an oil (6.4 g, 70%). This was hydrolyzed by reflux in methanolic sodium hydroxide. The reaction was acidified and the precipitate collected and recrystallized from 2-propanol to give 3-hydroxy-2-methyl-2-(6-phenyl-3-pyridinylthio)propanoic acid (**7a**): mp 165–167°; mass spectrum *m/e* M^+ 289; ir (Nujol) 1688 (s), 1590 (m), 1580 (m), 1542 (w), 1030 (s), 856 (m), 778 (m), 736 (s), 690 (s) cm^{-1}; nmr (DMSO) δ 8.74 (br s, 1), 8.30–7.90 (m, 4), 7.50 (t, 3), 3.70 (q, 2, *J* = 2 Hz), 1.44 (s, 3).

Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.70; H, 5.30; N, 4.81.

2-(6-Phenyl-3-pyridinylthio)propanoic Acid (7b) *via* the Sulfoxide 5a. The crude trifluoroacetate **6a** (7 g, 0.023 mol) obtained as above was added to a solution of sodium metal (0.66 g, 0.023 mol) in ethanol (50 ml). The mixture was stirred for 2 hr at room temperature under nitrogen and then concentrated *in vacuo*. The residue was redissolved in ethanol and ethyl 2-bromopropionate (4.2 g, 0.023 mol) added. The mixture was heated overnight at 75°. The ethanol was removed *in vacuo*. The residue was shaken between ether and water. The ether was separated, dried ($MgSO_4$), and removed. The residue was refluxed for 5 hr in methanolic NaOH (40 ml of 1 *N* NaOH–40 ml of MeOH). The methanol was removed *in vacuo*. The aqueous residue was washed with ether, acidified (2 *N* HCl), and reextracted with ether. Removal of the ether *in vacuo* gave a solid which was recrystallized from 2-propanol to give 2-(6-phenyl-3-pyridinylthio)propanoic acid (**7b**) (3.4 g, 0.013 mol, 57%): mp 139–141°; ir (Nujol) 1712 (s), 1590 (m), 1582 (m), 1550 (m), 1326 (s), 1236 (s), 1180 (s), 1032 (m), 848 (m), 782 (m), 738 (m), 694 (m), 664 (m), 650 (m) cm^{-1}; nmr (DMSO) δ 8.70 (s, 1), 8.25–7.90 (m, 4), 7.48 (t, 3), 3.95 (q, 1, *J* = 7 Hz), 1.42 (d, 3, *J* = 7 Hz).

Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.70; H, 5.11; N, 5.13.

4-(6-Phenyl-3-pyridinylthio)butanoic acid (7c) was prepared in an analogous manner using ethyl 4-bromobutyrate as the alkylating agent. After acidification of the hydrolysis reaction mixture with 2 *N* HCl, 4-(6-phenyl-3-pyridinylthio)butanoic acid (**7c**) was obtained: mp 89–91° (87%); ir (Nujol) 1714 (s), 1544 (w), 1318 (m), 1198 (m), 772 (m), 728 (m), 680 (m) cm^{-1}; uv λ max (MeOH), 280 mμ (ε 15,950); nmr ($CDCl_3$) δ 8.68 (s, 1), 8.0–7.2 (m, 7), 2.97 (t, 2), 2.50 (t, 2), 2.00 (q, 2).

Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.90; H, 5.65; N, 5.53.

3-Butylthio-6-phenylpyridine (4b). Pyridine (15.8 g, 0.2 mol) was added slowly with stirring to commercial phenyllithium (125 ml of a 1.6 *M* solution, 0.2 mol) under nitrogen. A yellow solid separated. The mixture was stirred overnight at room temperature. Butyl disulfide (35.6 g, 0.2 *M*) was added slowly (exothermic). The mixture was stirred at room temperature for a further 6 hr, then washed with water and brine, and dried ($MgSO_4$). The solvents were removed *in vacuo*, and the residue was distilled. A forerun of butyl disulfide was obtained. The main fraction, bp 145–155° (0.1 mm) (16.8 g, 0.069 mol, 35%), crystallized on standing. This was recrystallized from 2-propanol to give 3-butylthio-6-phenylpyridine (**4b**) (10.6 g): mp 33–34°; ir (Nujol) 1574 (m), 1545 (m), 728 (s), 686 (s) cm^{-1}; uv λ max (MeOH) 247 mμ (ε 10,660), 281 (16,250); nmr ($CDCl_3$) δ 8.60 (d, 1, *J* = 2 Hz), 8.12–7.80 (m, 2), 7.68–7.24 (m, 5), 2.90 (t, 2), 1.90–1.10 (m, 4), 0.88 (t, 3).

Anal. Calcd for $C_{15}H_{17}NS$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.04; H, 6.89; N, 5.84.

3-Butylsulfinyl-6-phenylpyridine (5b). 3-Butylthio-6-phenylpyridine (**4b**) (20.2 g, 0.083 mol) was dissolved in methylene chloride (200 ml) and cooled in an ice bath. With stirring, a solution of *m*-chloroperbenzoic acid (16.2 g, 0.083 mol based on 88.5% peracid) in methylene chloride was added dropwise during 20 min. The mixture stirred for a further 30 min and then washed with 10% aqueous $KHCO_3$ and brine and dried ($MgSO_4$). Removal of the methylene chloride *in vacuo* gave a yellow oil, which slowly crystallized. This was recrystallized from ether to give the sulfoxide **5b** (15.4 g, 0.0595 *M*, 72%): mp 68–70°; ir (Nujol) 1580 (m), 1560 (m), 1296 (m), 1034 (s), 836 (m), 776 (m), 732 (s), 686 (m) cm^{-1}; uv λ max (MeOH) 260 mμ (ε 15,740), 287 (17,290); nmr ($CDCl_3$) δ 8.80 (s, 1), 8.26–7.74 (m, 4), 7.45 (t, 3), 2.92 (t, 2), 2.00–1.10 (m, 4), 0.92 (t, 3).

Anal. Calcd for $C_{15}H_{17}NOS$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.50; H, 6.74; N, 5.31.

3-Butylsulfonyl-6-phenylpyridine (8a). The sulfoxide **5b** (11.9 g 0.046 mol) was dissolved in methylene chloride (100 ml) and cooled in an ice bath. *m*-Chloroperbenzoic acid (8.95 g, 0.046 *M* of a 88.5% peracid mixture) was dissolved in methylene chloride (200 ml) and added slowly with stirring. The mixture was allowed to stir overnight at room temperature, and then washed (aqueous 10% $KHCO_3$, brine), dried ($MgSO_4$), and concentrated *in vacuo*. The residue (11.94 g) was recrystallized from ether to give the sulfone **8a** (10.1 g, 0.037 mol, 80%): mp 83–85°; homogeneous by tlc (silica gel GF eluted by $CHCl_3$–ethyl acetate 4:1) sulfoxide R_f 3.0, sulfone 8.0; ir (Nujol) 1594 (m), 1560 (w), 1314 (m), 1154 (s), 1100 (m), 838 (m), 732 (s), 680 (m) cm^{-1}; uv λ max (MeOH) 260 mμ (ε 15,890), 286 (20,260); nmr ($CDCl_3$) δ 9.12 (d, 1 *J* = 3 Hz), 8.24–7.80 (m, 4), 7.52 (t, 3), 3.18 (t, 2), 2.00–1.10 (m, 4), 0.90 (t, 3).

Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.11; H, 6.32; N, 4.92.

2-Methyl-2-(6-phenyl-3-pyridinylthio)propanoic Acid 7d *via* the Sulfoxide 5b. 3-Butylsulfinyl-6-phenylpyridine (**5b**) (6 g, 0.023 mol) was refluxed in trifluoroacetic anhydride (40 ml) for 3 hr. The anhydride was removed *in vacuo* and the residue was dissolved in ether. The ethereal solution was washed (10% aqueous $KHCO_3$, 2 *N* NaOH, brine) and dried ($MgSO_4$). The ether was removed *in vacuo* and the residue dissolved in ethanol and added to a solution of sodium metal (0.55 g, 0.024 mol) in ethanol. The solution was stirred for 2 hr at room temperature. Ethyl α-bromoisobutyrate (4.98 g, 0.025 mol) was added in ethanol and the mixture was refluxed overnight. The ethanol was removed *in vacuo*. The residue was dissolved in ether, washed with water and brine, and dried ($MgSO_4$). The ether was removed *in vacuo*. The residue was dissolved in ethanol (60 ml), and 2 *N* NaOH (30 ml) was added. The mixture was refluxed for 2 hr. The ethanol was removed *in vacuo*. The aqueous residue was slowly made acid with 2 *N* HCl. 2-Methyl-2-(6-phenyl-3-pyridinylthio)propanoic acid (**7d**) (4.90 g, 0.018 mol, 78%) separated as a crystalline solid: mp 178–180°; ir (Nujol) 2400–1900 (br m), 1690 (s), 1590 (m), 1582 (m), 1268 (s), 1168 (s), 858 (m), 804 (m), 778 (m), 738 (s) cm^{-1}; uv λ max (MeOH) 256 mμ (ε 17,170), 285 (15,260); nmr (DMSO) δ 8.70 (t, 1), 8.30–7.94 (m, 4), 7.50 (t, 3), 1.45 (s, 6).

Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.10; H, 5.71; N, 4.97.

(6-phenyl-3-pyridinylthio)acetic acid (7e) was prepared in an analogous manner using ethyl bromoacetate. On acidification of the hydrolysis reaction mixture with 2 *N* HCl, the hydrochloride salt of (6-phenyl-3-pyridinylthio)acetic acid (**7e**) separated: mp 214–216°; ir (Nujol) 1710 (s), 1594 (m), 1584 (m), 1532 (m), 1380 (s), 1276 (s), 1192 (s), 896 (m), 846 (m), 772 (m), 712 (m), 678 (m)

cm^{-1}; nmr (DMSO) δ 8.78 (d, 1 J = 2 Hz), 8.5–8.0 (m, 4), 7.60 (t, 3), 4.20 (s, 2).

Anal. Calcd for $C_{13}H_{11}NO_2S{\cdot}HCl$ (½H_2O): C, 53.64; H, 4.47; N, 4.81. Found: C, 53.19; H, 4.40; N, 4.63.

3-Butylthio-6-methylpyridine (4c). Pyridine (15.8 g, 0.2 mol) was added dropwise to an ethereal solution of methyllithium (131 ml of a 1.6 M solution, 0.2 mol) under nitrogen. The mixture stirred overnight at room temperature. Butyl disulfide (35.6 g, 0.2 mol) in tetrahydrofuran was slowly added with stirring. The mixture was stirred at room temperature for 6 hr, then washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was redissolved in ether and washed three times with 4 N H_2SO_4. The acid washings were made basic and reextracted with ether. Removal of the ether gave a red oil which was distilled. 3-Butylthio-6-methylpyridine (**4c**) was the major fraction (10.0 g, 0.055 mol, 27%): bp 84–8° (0.1 mm) ir (film) 2925 (s), 1584 (m), 1552 (w), 1478 (s), 1364 (m), 1020 (m), 822 (m) cm^{-1}; nmr ($CDCl_3$) δ 8.50 (d, 1, J = 3 Hz), 7.62 (d, 1, J = 3 Hz), 7.50 (d, 1, J = 3 Hz), 7.03 (d, 1, J = 7 Hz), 2.84 (t, 2), 2.50 (s, 3), 1.90–1.10 (m, 4), 0.88 (t, 3).

Anal. Calcd for $C_{10}H_{15}NS$: C, 66.27; H, 8.34. Found: C, 65.84; H, 8.66.

2-Methyl-2-(6-methyl-3-pyridinylthio)propanoic Acid (7f). 3-Butylthio-6-methylpyridine (**4c**) (56 g, 0.309 mol) was dissolved in methylene chloride (700 ml) and cooled in an ice bath. *m*-Chloroperbenzoic acid (66.3 g, 0.325 mol based on 88.5% peracid) was dissolved in methylene chloride (700 ml) and added during 1 hr with stirring. After stirring overnight, a negative starch–iodide reaction was observed. The reaction mixture was washed (10% aqueous $KHCO_3$, brine), dried ($MgSO_4$), and concentrated *in vacuo*. The residue, an orange red oil, was checked by tlc (Silica gel GF eluted by $CHCl_3$–ethyl acetate 4:1), no starting material was evident. A portion of this crude sulfoxide **5c** (4.0 g, 0.020 M) in ether (50 ml) was refluxed with trifluoroacetic anhydride (30 ml) for 1.5 hr, then concentrated to dryness *in vacuo*. The residue was dissolved in ether. The ethereal solution was washed (water and brine), dried ($MgSO_4$), and removed *in vacuo*. The residue (5 g) was the Pummerer product **6c** based on: nmr ($CDCl_3$) δ 8.42 (d, 1 J = 2 Hz), 7.56 (pr of d, 1, J = 2 and 7 Hz), 6.98 (d, 1, J = 7 Hz), 5.96 (t, 1), 2.48 (s, 3), 2.06–1.10 (m, 4), 0.90 (t, 3). This residue was dissolved in ethanol (20 ml) and added to a solution of sodium metal (500 mg, 0.022 mol) in ethanol and stirred at room temperature for 1.5 hr. Ethyl 2-bromoisobutyrate (4.29 g, 0.022 mol) was added. The mixture was heated at 75° overnight. The ethanol was removed *in vacuo*. The residue was dissolved in ether. The ethereal solution was washed (water), dried ($MgSO_4$), and concentrated *in vacuo*. The residue (4.5 g) was dissolved in methanol (60 ml) and 20% aqueous KOH (20 ml) and refluxed for 6 hr. The methanol was removed *in vacuo;* the aqueous residue was washed with ether. The pH was adjusted to 6.5; a solid separated. The mixture was extracted ($CHCl_3$). The chloroform extracts were washed (water), dried ($MgSO_4$), and concentrated *in vacuo*. The crystalline residue (4.0 g) was recrystallized from 2-propanol to give 2-methyl-2-(6-methyl-3-pyridinylthio)propanoic acid (**7f**) (2.4 g, 0.011 mol, 50%): mp 195–197°; ir (Nujol) 1702 (s), 1592 (s), 1288 (s), 1172 (s), 1124 (s), 1038 (m), 838 (m), 812 (m), 724 (m) cm^{-1}; uv λ max (MeOH) 219 mμ (11,650), 266 (3,640); nmr ($CDCl_3$) δ 8.42 (d, 1, J = 2 Hz), 7.70 (pr of d, 1, J = 2 and 7 Hz), 7.22 (d, 1, J = 7 Hz), 2.48 (s, 3), 1.40 (s, 6).

Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.86; H, 6.20; N, 6.63. Found: C, 57.00; H, 6.22; N, 6.44.

2-Methyl-5-phenylthiopyridine (3b). Pyridine (7.9 g, 0.1 M) was dissolved in benzene (70 ml) and added dropwise to methyllithium (55 ml of a 2 M solution, 0.11 mol) under nitrogen. The mixture was stirred at room temperature for 1 hr. Phenyl disulfide (21.8 g, 0.1 mol) dissolved in benzene (80 ml) was added slowly with stirring. The mixture stirred overnight at room temperature. Oxygen was passed through the mixture for 1 hr and then it was washed (water, brine), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was redissolved in ether and extracted with 4 N H_2SO_4. The acid washings were made basic and reextracted with ether. The ethereal extracts were washed (water), dried ($MgSO_4$), and concentrated *in vacuo*. The residue (4.2 g) was chromatographed on neutral III alumina, made up in hexane. The major fraction (1.62 g, 0.0081 M, 8%) eluted by benzene–hexane 1:1 was 2-methyl-5-phenylthiopyridine (**3b**) which was characterized as the crystalline hydrochloride: mp 137–139°; ir (Nujol) 2300–2000 (br m), 1604 (m), 1530 (m), 1342 (m), 1140 (m), 1020 (m), 840 (m), 756 (s), 692 (s) cm^{-1}; uv λ max (MeOH) 250 mμ (ε 22,570), 322 (4,950); nmr ($CDCl_3$) δ 8.5 (d, 1, J = 3 Hz), 7.54 (pr of d, 1, J = 3 and 7 Hz), 7.26 (s, 5), 7.06 (d, 1, J = 7 Hz), 2.50 (s, 3).

Anal. Calcd for $C_{12}H_{11}NS{\cdot}HCl$: C, 60.58; H, 5.05; N, 5.89. Found: C, 60.80; H, 5.04; N, 5.76.

A minor fraction collected subsequently by benzene–hexane 1:1 elution (310 mg, 1.0 mmol, 1%) crystallized. Recrystallization from ethanol gave 2,5-dihydro-2-methyl-5,5-bis(phenylthio)pyridine (**9**): mp 93–95°; ir (Nujol) 1634 (m), 794 (m), 744 (s), 688 (m) cm^{-1}; uv λ max (MeOH) 244 mμ (ε 25,660); nmr ($CDCl_3$) δ 7.76 (br s, 2), 7.68–7.10 (m, 9), 5.66 (br s, 3), 3.24 (q, 1), 0.54 (d, 3, J = 7 Hz).

Anal. Calcd for $C_{18}H_{17}NS_2$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.68; H, 5.73; N, 4.47.

2,5-Dihydro-2-methyl-5,5-bis(phenylthio)pyridine (9). Pyridine (82 g, 1.04 mol) was dissolved in benzene (400 ml) and added slowly to methyllithium (1 mol) with stirring under nitrogen. The mixture was stirred for two further hours after addition. Phenyl disulfide (218 g, 1 mol) in benzene (1 l.) was added slowly and the mixture was stirred overnight at room temperature. The mixture was washed (water, 2 N NaOH, water, brine), dried ($MgSO_4$) and concentrated *in vacuo*. The residue, a red-yellow oil (171 g) was dissolved in 2-propanol, cooled, and seeded. 2,5-Dihydro-2-methyl-5,5-bis(phenylthio)pyridine (**9**) (35.8 g, 11.5%), mp 91–94°, crystallized on standing.

1,2,5,6-Tetrahydro-2-methyl-5,5-bis(phenylthio)pyridine (11). 2,5-Dihydro-2-methyl-5,5-bis(phenylthio)pyridine (**9**) (10 g, 0.032 mol) was dissolved in methanol (160 ml) and sodium cyanoborohydride (2.02 g, 0.032 mol) dissolved in water (440 ml) at pH 6–7 added slowly with stirring. The pH of the reaction mixture was maintained between 6 and 7 by addition of acetic acid. After addition, the mixture was stirred overnight at room temperature. The mixture was concentrated *in vacuo*. The aqueous residue was made basic with ammonia and ether extracted. The ether extracts were washed with 2 N HCl. The acid washings were made basic with 20% aqueous KOH and reextracted with ether. The ether extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue (9.09) was a pale yellow oil which crystallized on standing. This was recrystallized from ether to give 1,2,5,6-tetrahydro-2-methyl-5,5-bis(phenylthio)pyridine (**11**) (6.2 g, 0.0198 mol, 62%): mp 69–71°; ir (Nujol) 1582 (w), 1572 (w), 1306 (m), 1294 (m), 1174 (m), 1000 (m), 934 (m), 854 (m), 832 (m), 750 (m), 734 (s), 700 (m), 688 (s) cm^{-1}; uv λ max (MeOH) 225 mμ (ε 24,370), 264 (4310); nmr (C_6D_6) δ 7.82–7.42 (m, 4), 7.24–6.82 (m, 6), 5.78 (pr of m, 1, J = 8 Hz) 5.36 (pr of d, 1, J = 8 Hz), 3.80 (q, 2, J = 14 Hz), 3.20–2.70 (m, 1), 0.80 (d, 3, J = 7 Hz).

Anal. Calcd for $C_{18}H_{19}NS_2$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.95; H, 6.37; N, 4.52.

2-Methyl-5-phenylsulfinylpyridine (3c). 2-Methyl-5-phenylthiopyridine (**3b**) (17.3 g, 0.086 mol) was dissolved in methylene chloride (300 ml) and *m*-chloroperbenzoic acid (16.8 g, 0.086 mol based on 88.5% peracid) added portion-wise with stirring during 2 hr. The mixture was stirred for a further 2 hr, then washed (10% $KHCO_3$, 2 N NH_4OH, brine), dried ($MgSO_4$), and concentrated *in vacuo*. The residue, a red oil, was dissolved in 2-propanol, seeded, and cooled. The sulfoxide **3c** (8.0 g, 0.037 M, 43%) crystallized out: mp 63–64°; ir (Nujol) 1578 (m), 1554 (w), 1300 (m), 1048 (s), 1010 (m), 834 (m), 746 (m), 722 (m), 682 (m) cm^{-1}; uv λ max (MeOH) 231 mμ (ε 14,260), 267 (5500); nmr ($CDCl_3$) δ 8.70 (d, 1, J = 2 Hz), 8.00–7.00 (m, 7), 2.55 (t, 3).

Anal. Calcd for $C_{12}H_{11}NOS$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.29; H, 5.21; N, 6.29.

2-Methyl-5-phenylsulfonylpyridine (8b). 2-Methyl-5-phenylthiopyridine (**3b**) (2.37 g, 0.0118 mol) was dissolved in methylene chloride (200 ml). *m*-Chloroperbenzoic acid (4.60 g, 0.0236 mol based on 88.5% peracid) was added portion-wise with stirring during 2.5 hr. The mixture was stirred overnight at room temperature. It was then washed (10% aqueous $KHCO_3$, NH_4OH, brine), dried ($MgSO_4$), and concentrated *in vacuo*. The residue (2.38 g, 87%) was recrystallized from 2-propanol to give the sulfone **8b**: mp 114–116°; ir (Nujol) 1590 (m), 1300 (s), 1162 (s), 1118 (m), 732 (m), 722 (m) cm^{-1}; uv λ max (MeOH) 234 mμ (ε 16,500), 266 (6,260); nmr ($CDCl_3$) δ 9.00 (d, 1, J = 2 Hz), 8.17–7.17 (m, 8), 2.59 (s, 3).

Anal. Calcd for $C_{12}H_{11}NSO_2$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.87; H, 4.95; N, 5.96.

2-Bis(*tert*-butylthio)methylpyridine. 2-Picoline (9.3 g, 0.1 mol) in benzene (20 ml) was added dropwise during 5 min to a solution of methyllithium (61 ml of a 1.66 M solution, 0.1 mol) with stirring under nitrogen. After a further 5 min *tert*-butyl disulfide (17.8 g, 0.1 M) in benzene (20 ml) was added dropwise. The mixture stirred overnight at room temperature. It was washed (water, 2 *N* NaOH, brine), dried ($MgSO_4$), and concentrated *in vacuo*. The residue, a red oil (7.4 g), was chromatographed on neutral III alumina made up in pentane. Elution by pentane gave 2.11 g which was discarded. Elution by ether gave 2-bis(*tert*-butylthio)methylpyridine (3.05 g, 0.0113 mol, 11%) which was distilled in a short path apparatus: bp 80° (0.1 mm); ir (film) 1588 (s), 1568 (m), 1470 (s), 1432 (s), 1364 (s), 1154 (s), 990 (m), 742 (m), 718 (m) cm^{-1}; uv λ max (MeOH) 271 mμ (ϵ 4480); nmr ($CDCl_3$) δ 8.42 (broad d, 1, J = 6 Hz), 7.64 (m, 2), 7.10 (q, 1), 5.16 (s, 1), 1.28 (s, 18).

Anal. Calcd for $C_{14}H_{23}NS_2$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.40; H, 8.95; N, 5.22.

Pyridine (7.9 g, 0.1 *M*) was treated with methyllithium (78 ml of a 1.60 *M* solution, 0.12 mol) and *tert*-butyl disulfide (17.8 g, 0.1 mol) in an analogous manner. The bulk of the products were water soluble, presumably 2-picoline. The material eluted from neutral III alumina by ether (0.91 g, 0.0034 *M*, 3%) was identical (ir, nmr, mass spectrum) with 2-bis(*tert*-butylthio)methylpyridine prepared above. Comparison was also made by tlc (silica gel GF eluted by $CHCl_3$–ethyl acetate 4:1).

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Registry No.—**3a**, 53730-69-1; **3b** HCl, 53730-70-4; **3c**, 53730-71-5; **4a**, 53730-72-6; **4b**, 53730-73-7; **4c**, 53730-74-8; **5a**, 53730-75-9; **5b**, 53730-76-0; **5c**, 53778-52-2; **6a**, 53730-77-1; **6c**, 53730-78-2; **7a**, 53730-79-3; **7b**, 53730-80-6; **7c**, 53730-81-7; **7d**, 53730-82-8; **7e** HCl, 53730-83-9; **7f**, 53730-84-0; **8a**, 53730-85-1; **8b**, 53730-86-2; **9**, 53730-87-3; **11**, 53730-88-4; pyridine, 110-86-1; phenylsulfenyl chloride, 931-59-9; phenyl disulfide, 882-33-7; dimethyl disulfide, 624-92-0; *m*-chloroperbenzoic acid, 937-14-4; trifluoroacetic anhydride, 407-25-0; ethyl 2-bromopropionate, 535-11-5; ethyl 4-bromobutyrate, 2969-81-5; butyl disulfide, 629-45-8; ethyl α-bromoisobutyrate, 600-00-0; ethyl bromoacetate, 105-36-2; 2-bis(*tert*-butylthio)methylpyridine, 53730-89-5; 2-picoline, 109-06-8.

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New Fluorinating Reagents. Dialkylaminosulfur Fluorides[1]

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Dialkylaminosulfur trifluorides (**2**) and bis(dialkylamino)sulfur difluorides (**5**) are easy to handle fluorinating reagents useful for replacing hydroxyl and carbonyl oxygen with fluorine under very mild conditions. The trifluorides (**2**) were prepared by the reaction of dialkylaminotrimethylsilanes (**1**) with SF_4, and the difluorides (**5**) were prepared by the reaction of **2** with **1**. These fluorides are particularly useful in fluorinating sensitive alcohols and aldehydes. For example, reaction of diethylaminosulfur trifluoride (DAST) with isobutyl alcohol gave isobutyl fluoride as the principal product, reaction of DAST with pivaldehyde at 25° gave $(CH_3)_3CCHF_2$ in 78% yield, and reaction of $Me_2NSF_2NEt_2$ with crotyl alcohol at 25° gave crotyl fluoride in 78% yield.

Sulfur tetrafluoride is a useful fluorinating agent for replacing oxygen with fluorine in organic compounds.[2] The substitution of one or two of the fluorine atoms in sulfur tetrafluoride with dialkylamino groups would result in aminosulfur fluorides that also may be expected to be fluorinating agents. We have examined the preparation and chemical properties of dialkylaminosulfur trifluorides and bis(dialkylamino)sulfur difluorides with the hope of developing new selective fluorinating reagents.

Preparation. The dialkylaminosulfur trifluorides (**2**) were prepared by an adaptation of a literature procedure,[3] which consists of treating sulfur tetrafluoride with a dialkylaminotrimethylsilane (**1**). Diethylaminosulfur trifluoride[4] (DAST), dimethylaminosulfur trifluoride,[3] and the new pyrrolidinosulfur trifluoride were prepared by this method. When this reaction is conducted in trichlorofluoromethane (bp 25°) at −70°, high yields of a product of very high purity are obtained, since the only appreciable by-product is fluorotrimethylsilane (**3**), an easily separated low-boiling (bp 17°) material. These three trifluorides are stable products that can be distilled and stored in plastic bottles at room temperature.

$$\underset{\mathbf{1}}{R_2NSi(CH_3)_3} + SF_4 \longrightarrow \underset{\mathbf{2}}{R_2NSF_3} + \underset{\mathbf{3}}{FSi(CH_3)_3}$$

Diisopropylaminosulfur trifluoride (**2**, R_2N = diisopropylamino) was also prepared, but it was unstable to distillation and decomposed to isopropyliminosulfur difluoride (**4**) when heated above 60°.

$$\underset{\mathbf{4}}{(CH_3)_2CHN{=}SF_2} \qquad \underset{\mathbf{5}}{R_2N{-}SF_2{-}NR'_2}$$

Bis(dialkylamino)sulfur difluorides (**5**) have not been prepared previously. We prepared them by the reaction of a dialkylaminotrimethylsilane (**1**) with a dialkylaminosulfur trifluoride (**2**) at 25°. The sulfur difluorides were not stable to distillation, but they could be easily purified by removing the volatile solvent (CCl_3F) and by-product (**3**) by evaporation at reduced pressure. The ^{19}F nmr spectra of

Table I
Reactions[a] of Alcohols with Et_2NSF_3

Alcohol	Registry No.	Reaction solvent	Products	Registry No.	Yield, %[b]	Bp, °C (mm)	^{19}F nmr, δ, ppm
1-Octanol	111-87-5	CH_2Cl_2	1-Fluorooctane[c]	463-11-6	90	42–43 (20)	−218.8
2-Methyl-2-butanol	75-85-4	$CH_3O(CH_2CH_2O)_2CH_3$	2-Fluoro-2-methylbutane[d]	661-53-0	88	45–46	−139.2
Isobutyl alcohol	78-83-1	$CH_3O(CH_2CH_2O)_2CH_3$	Isobutyl fluoride[e]	359-00-2	49	20–22	−221.4
			tert-Butyl fluoride[f]	353-61-7	21	10–12	−132.1
Menthol	1490-04-6	CCl_3F	1-Fluoro-2-isopropyl-5-methylcyclohexane[h]	53731-15-0	50	40 (5)	−175.9
Benzyl alcohol	100-51-6	CCl_3F	Benzyl fluoride	462-06-6	75	139	−207.5
Benzyl alcohol[i]		CH_2Cl_2	Benzyl fluoride		100[g]		−207.5
Cyclooctanol	696-71-9	CCl_3F	Cyclooctyl fluoride	53731-16-1	70[g]		−160.5
			Cyclooctene	931-88-4	30[g]		
2-Methyl-3-butyn-2-ol	115-19-5	$CH_3O(CH_2CH_2O)_2CH_3$	2-Fluoro-2-methyl-3-butyne[j]	53731-17-2	75	43–44	−129.3
Ethylene glycol	107-21-1	$CH_3O(CH_2CH_2O)_2CH_3$	1,2-Difluorothane[k]	624-72-6	70	25–27	−225.9
exo-Borneol	124-76-5	CCl_3F	3-Fluoro-2,2-dimethylbicyclo[2.2.1]heptane[l]	53731-18-3	74	Mp 93–94	−134.4
			Camphene		18		
endo-Borneol	507-70-0	CCl_3F	3-Fluoro-2,2-dimethylbicyclo[2.2.1]heptane		72	Mp 93–94	−134.4
			Camphene		17		
3-Buten-2-ol	598-32-3	$CH_3O(CH_2CH_2O)_2CH_3$	3-Fluoro-1-butene[m]	53731-19-4	78[g]	22–24	−171.6
			1-Fluoro-2-butene[n]	53731-20-7	22[g]		−210.0
3-Buten-2-ol		Isooctane	3-Fluoro-1-butene		91[g]		
			1-Fluoro-2-butene		9[g]		
2-Buten-1-ol	6117-91-5	$CH_3O(CH_2CH_2O)_2CH_3$	3-Fluoro-1-butene		72[g]		
			1-Fluoro-2-butene		28[g]		
2-Buten-1-ol		Isooctane	3-Fluoro-1-butene		64[g]		
			1-Fluoro-2-butene		36[g]		
2-Bromoethanol[i]	540-51-2	$CH_3O(CH_2CH_2O)_2CH_3$	1-Bromo-2-fluoroethane	762-49-2	70	72	−213.4
2-Chloroethanol	107-07-3	$CH_3O(CH_2CH_2O)_2CH_3$	1-Chloro-2-fluoroethane[o]	762-50-5	69	50–53	−219.8
Ethyl lactate	97-64-3	CH_2Cl_2	Ethyl 2-fluoropropionate	349-43-9	78	50–51 (50)	−184.6
Ethyl 1-naphthyleneglycolate	53731-14-9	CCl_3F	Ethyl α-fluoronaphthaleneacetate[p]	24021-14-5	60	*q*	−178.4
2-Phenylethanol	60-12-8	CH_2Cl_2[r]	2-Fluoroethylbenzene[s]	458-87-7	60	68–69 (25)	−215.2

[a] All reactions were carried out between −50 and −78° unless otherwise noted. [b] Yield cf isolated products unless otherwise noted. [c] Y. Kobayashi, C. Akashi, and K. Morinaga, *Chem. Pharm. Bull.*, 1784 (1968). [d] K. Wiechart, C. Gruenert, and H. J. Preibisch, *Z. Chem.*, 8, 64 (1968). [e] M. Moissan, *J. Chem. Soc.*, 931 (1888). [f] K. A. Cooper and E. D. Hughes, *J. Chem. Soc.*, 1183 (1937). [g] Product was not isolated in pure state. Yield is based on glc analysis. [h] *Anal.* Calcd for $C_{10}H_{18}F$: F, 12.01. Found: F, 12.12. [i] Me_2NSF_3 used in place of Et_2NSF_3. [j] *Anal.* Calcd for C_5H_7F: C, 73.4; H, 7.2; F, 19.4. Found: C, 73.7; H, 7.3; F, 19.2 [k] A. L. Henne and M. W. Renoll, *J. Amer. Chem. Soc.*, 58, 887 (1936). [l] M. Hanack, *Chem. Ber.*, 94, 1082 (1961). [m] *Anal.* of sample separated by glc. Calcd for C_4H_7F: C, 64.8; H, 9.5; F, 25.6. Found: C, 65.0; H, 9.5; F, 25.5. [n] *Anal.* of sample separated by glc. Calcd for C_4H_7F: C, 64.8; H, 9.5; F, 25.6. Found: C, 65.0; H, 9.5; F, 25.5. [o] W. F. Edgell and L. Parts, *J. Amer. Chem. Soc.*, 77, 4899 (1955). [p] *Anal.* Calcd for $C_{14}H_{13}FO_2$: C, 72.4; H, 5.6; F, 8.2. Found: C, 72.5; H, 5.7; F, 7.9. [q] Viscous oil, $n^{25}D$ 1.5788, purified by chromatography over silica ($CHCl_3$). [r] Reaction temp was 40°. [s] C. H. DePuy and C. A. Bishop, *J. Amer. Chem. Soc.*, 82, 2535 (1960).

the difluorides at −80° and at 30° show a single sharp resonance at 5 to 10 ppm downfield from CCl_3F. This relatively high field absorption and lack of spin–spin coupling indicate that both fluorine atoms are equivalent and are probably in the axial position. These spectra are in contrast to the spectra of the trifluorides (2), which show both equatorial and axial fluorines coupled to each other.[5]

Fluorinations with Aminosulfur Fluorides

Markovskij, Pashinnik, and Kirsanov[6] recently reported that the dialkylaminosulfur trifluorides are useful in replacing carbonyl oxygen of aldehydes and ketones with fluorine. The work that we have done independently fully supports these observations. In addition, we have found that the dialkylaminosulfur trifluorides are perhaps even more useful in replacing the hydroxyl groups of sensitive alcohols with fluorine, and the bis(dialkylamino)sulfur difluorides are also useful reagents for preparing organofluorine compounds.

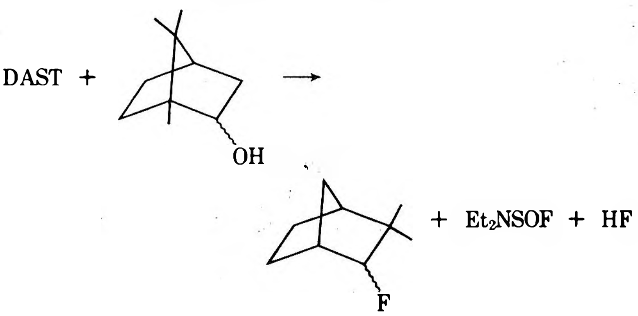
Fluorination of Alcohols

The reaction of DAST and the other dialkylaminosulfur trifluorides with alcohols to replace the hydroxyl group with fluorine appears to be a broadly general reaction with distinct advantages over other reagents used for this purpose, including SF_4,[7] $SeF_4 \cdot$pyridine,[8] α-fluorinated amines,[7] and HF and HF–amine reagents.[9] Primary, secondary, and tertiary alcohols all react, with high yields of the unrearranged fluoride usually resulting.

These reactions can be conducted under very mild conditions so that other groups, including ester groups and other halogens, can also be present. Typically, the alcohol can be added slowly to a solution of DAST in an inert solvent cooled to −50 to −78°. For many alcohols, the reaction occurs rapidly even at this low temperature. Diglyme is a convenient solvent for the preparation of low-boiling fluorides because the product can be distilled out of the reaction mixture and the HF that is formed in the reaction remains behind complexed with the diglyme. For the preparation of higher boiling fluorides, lower boiling solvents such as pentane, methylene chloride, or trichlorofluoromethane are useful. Table I contains a list of the alcohols that have been converted to fluorides.

Two problems can occur when replacing the OH groups of an alcohol with fluorine: carbonium ion type rearrangements and dehydration. The carbonium ion type rearrangements are less likely to occur when DAST is used than when other known fluorinating agents are used. For example, fluorination of isobutyl alcohol with DAST gave more than a 2:1 ratio of isobutyl fluoride (6) to *tert*-butyl fluoride, whereas fluorination with $SeF_4 \cdot$pyridine is reported[8] to give only the rearranged *tert*-butyl fluoride. However, the more easily rearranged *exo*- and *endo*-borneol gave the rearranged fluoride 7.

$$\text{DAST} + (CH_3)_2CHCH_2OH \longrightarrow \underset{49\%}{(CH_3)_2CHCH_2F} + \underset{21\%}{(CH_3)_3CF} + Et_2NSOF + HF$$



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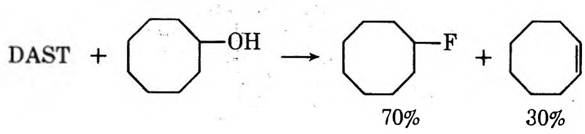
Dehydration (elimination) also appears to be less of a problem with DAST than with other fluorinating reagents. For example, cyclooctanol reacts with DAST to give a 70:30 ratio of cyclooctyl fluoride (8) to cyclooctene, whereas Et_2NCF_2CHClF reacts to give only cyclooctene.



70% 30%
8

$$\underset{\mathbf{9}}{CH_3CH{=}CHCH_2OH} \text{ or } \underset{\mathbf{12}}{CH_3CHOHCH{=}CH_2} + \text{DAST} \longrightarrow \underset{\mathbf{10}}{CH_3CH{=}CHCH_2F} + \underset{\mathbf{11}}{CH_3CHFCH{=}CH_2}$$

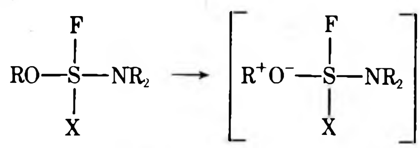
Crotyl alcohol (9) is sensitive to both double-bond rearrangement and dehydration. For example, it reacts with SF_4 to give a 90% yield of butadiene, a 9% yield of 3-fluoro-1-butene (11), and only a trace of crotyl fluoride (10). Reactions of DAST with crotyl alcohol under the same conditions (diglyme solvent) gave virtually no butadiene and a high yield of monofluorides consisting of a 72:28 ratio of 11–10.

Reaction of DAST with crotyl alcohol in a less polar solvent (isooctane) gave larger amounts of 10 (36%), but still gave the rearranged 11 as the major product (64%). Fluorination of the isomeric alcohol, 3-buten-2-ol (12), gave the same two products, but in different ratios (see Table I). Since both 9 and 12 should form the same carbonium ion, it appears that a free carbonium ion is not involved in the reaction, but from the rearranged products observed in these reactions and in the reactions with borneol, it is clear that these fluorination reactions do have considerable carbonium ion character.

The bis(dialkylamino)sulfur difluorides (5) are also useful reagents for replacing hydroxyl groups with fluorine in sensitive alcohols. Although they are less reactive, the difluorides have certain advantages over the trifluorides in that they cause less rearrangement and elimination. For example, diethylaminodimethylaminosulfur difluoride (5, R = CH_3; R′ = C_2H_5) reacts with crotyl alcohol (9) to give the unrearranged 10 as the principal product, with only smaller amounts of the rearranged 11 formed (ratio 72:21). The difluorides 5 also cause less dehydrations of easily dehydrated alcohols, such as cyclohexanol, as compared to the reaction of the same alcohols with the trifluorides (2).

The smaller amounts of rearrangement and dehydration products that are formed in the fluorination of alcohols with the difluorides 5, as opposed to the trifluorides 2, can be rationalized by assuming that both reactions go through an unisolated intermediate in which one of the fluorines on sulfur has been replaced by an alkoxide group (13). This intermediate could then dissociate to give an ion pair consisting of a carbonium ion and a sulfur oxide anion (14). The sulfur oxide ion containing two amino groups (14, X = NR_2) would be expected to lose fluoride more readily than the anion containing only one amino group (14, X = F), and therefore have a shorter lifetime. Since the ion pair formed in the reaction of the difluoride 5 with an alcohol would have a shorter lifetime than the ion pair formed from 2 and an alcohol, less carbonium ion type reactions would occur.

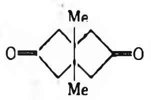
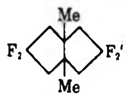
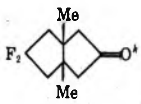
An alternate explanation would be based on leaving group ability instead of fluoride ion transfer. Since the leaving ability of $R_2NSF_2O^-$ should be greater than $(R_2N)_2SFO^-$, the decomposition of intermediate 13 (X = F) to give products should involve more carbonium ion character than decomposition of 13 (X = NR_2), and therefore would be subject to more extensive rearrangement and elimination.



13, X = F, NR_2 14, X = F, NR_2

Fluorination of Aldehydes and Ketones. DAST is a convenient reagent for replacing the carbonyl oxygen of aldehydes and ketones with two fluorine atoms (See Table II). This reagent is particularly useful for fluorinating aldehydes and ketones that are sensitive to acidic conditions or contain other functional groups that are unstable in the presence of acid, since no acid other than adventitious HF is formed in the reactions and no additional acidic catalyst is needed. Even aqueous work-ups do not result in the formation of acidic solutions, since the only by-product, diethylaminosulfinyl fluoride (15), is hydrolyzed to give sulfur dioxide and diethylamine hydrofluoride.

Table II
Reactions of Carbonyl Compounds with DAST

Carbonyl compd	Registry No.	Reaction solvent	Temp, °C	Time	Product	Registry No.	Isolated yield, %	Bp (mp), °C	^{19}F nmr, δ, ppm
Isovaleraldehyde	590-86-3	CCl_3F	25	30 min	1,1-Difluoro-3-methylbutane	53731-22-9	80	59–60	−115.5
Propionaldehyde	123-38-6	CCl_3F	25	30 min	1,1-Difluoropropane	430-61-5	95[a]		−118.2
Pivaldehyde	630-19-3	CCl_3F	25	1 hr	$(CH_3)_3CCHF_2$[b]	53731-23-0	78	47–48	−128.6
Pivaldehyde		Diglyme	25	1 hr	$(CH_3)_3CCHF_2$		24	47–48	−128.6
					$CH_2{=}C(CH_3)CHFCH_3$[c]	53731-24-1	26	51–52	−174.4
					$FC(CH_3)_2CHFCH_3$[d]	53731-25-2	31	65–66	−152.0, −185.5
Benzaldehyde	100-52-7	CH_2Cl_2	25	2 hr	Benzal fluoride[e]	455-31-2	75	57 (35 mm)	−110.9
1-Naphthaldehyde	66-77-3	CH_2Cl_2	25	18 hr	1-(Difluoromethyl)-naphthylene[f]	53731-26-3	72	78–79 (0.4 mm)	−111.1
4-Heptanone	123-19-3	CCl_3F	25	7 day	4,4-Difluoroheptane[g]	53731-27-4	68	110–111	−98.6
Acetophenone	98-86-2	Glyme	85	20 hr	1,1-Difluoroethylbenzene[h]	10541-59-0	66	64–65 (40 mm)	−87.7
	53731-21-8	Benzene	78	24 hr		53731-28-5	60[j]	(106–109)	−86.2, −86.6
						53731-29-6	15[j]	(145–150)	−80.9, −81.0

[a] Glc yield. [b] *Anal.* Calcd for $C_6H_{10}F_2$: C, 55.5; H, 9.3; F, 35.1. Found: C, 55.7; H, 9.4; F, 35.0. [c] *Anal.* Calcd for C_6H_9F: C, 68.2; H, 10.3; F, 21.6. Found: C, 68.3; H, 10.5; F, 21.8. [d] *Anal.* Found: C, 55.3; H, 9.5; F, 35.4. [e] W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Amer. Chem. Soc.*, 82, 543 (1960). [f] *Anal.* Calcd for $C_{11}H_8F$: C, 74.1; H, 4.5; F, 21.3. Found: C, 74.2; H, 4.2; F, 21.2. [g] *Anal.* Calcd for $C_7H_{14}F_2$: C, 61.7; H, 10.4; F, 27.9. Found: C, 62.1; H, 10.2; F, 28.1. [h] K. Matsuda, J. A. Sedlak, J. S. Noland, and G. C. Cleckler, *J. Org. Chem.*, 27, 4015 (1962). [i] *Anal.* Calcd for $C_{10}H_{14}F_4$: C, 57.1; H, 6.7; F, 36.1. Found: C, 57.1; H, 6.8; F, 36.1. [j] Purified by chromatography on Al_2O_3 (pentane–ether). [k] *Anal.* Calcd for $C_{10}H_{14}F_2O$: C, 63.8; H, 7.5; F, 20.2. Found: C, 63.1; Hn 7.3; F, 20.9.

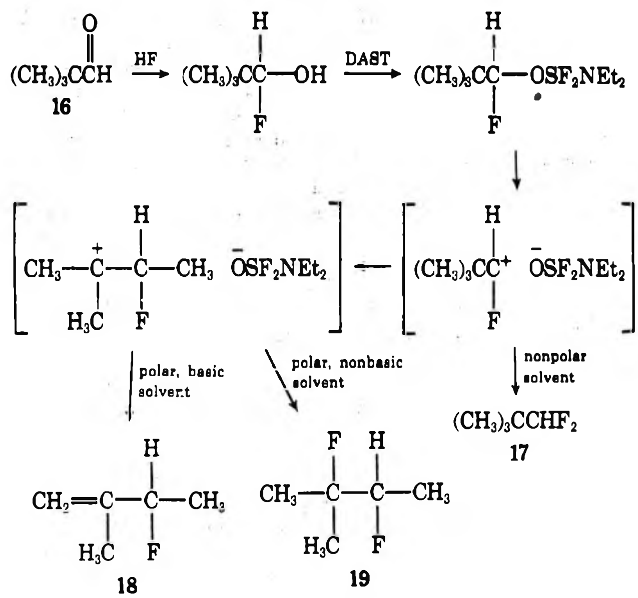
Table III
Effect of Solvent on Product Distribution in the Fluorination of Pivaldehyde with DAST

Solvent	% of products (glc yields) $(CH_3)_3CCHF_2$	$CH_2{=}C(CH_3)$-$CHFCH_3$	$FC(CH_3)_2$-$CHFCH_3$
CCl_3F	88	2	10
Pentane	87	3	10
CCl_3H	72	3	25
CH_2Cl_2	72	2	26
Xylene	64	8	28
Tetrahydrofuran	65	20	15
Pivaldehyde	60	10	30
Diglyme	30	32	38

$$R_2C{=}O + DAST \longrightarrow R_2CF_2 + Et_2N{-}\overset{O}{\overset{\|}{S}}F$$
15

Pivaldehyde (16) is an example of an acid-sensitive aldehyde. Previous attempts to prepare the corresponding *gem*-difluoride have resulted in rearrangements or trimerization. However, pivaldehyde can be successfully fluorinated to 17 by the use of DAST in a nonpolar solvent such as pentane or CCl_3F. Carbonium ion type rearrangements will occur, however, if more polar solvents are used (See Table III). Thus, if diglyme (a basic, polar solvent) is used, the rearranged products 18 and 19 are formed, and if chloroform is used (a nonbasic, polar solvent), considerable rearrangement product 19 is formed, but only a small amount of the elimination product 18 is formed. The solvent dependancy of this reaction is consistent with the reaction shown in Scheme I.

Scheme I



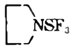
Experimental Section[10]

Dialkylaminosulfur Trifluorides (Table IV). The four trifluorides listed in Table IV were prepared by the reaction of an aminotrimethylsilane with sulfur tetrafluoride in CCl_3F, as illustrated by the preparation of diethylaminosulfur trifluoride (DAST).

A solution of 96 g (0.66 mol) of diethylaminotrimethylsilane in 100 ml of CCl_3F was added dropwise to a solution of 40 ml (measured at −78°, 0.72 mol) of sulfur tetrafluoride in 200 ml of CCl_3F at −65 to −60°. The reaction mixture was warmed to room temperature and then distilled to give 88.9 g (84%) of DAST as a pale yellow liquid.

Bis(dialkylamino)sulfur Difluorides (Table IV). The four

Table IV
Aminosulfur Fluorides

Compd	Registry No.	Bp, °C (mm)	^{19}F nmr, δ, ppm	% yield	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Fluorine, % Calcd	Fluorine, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Sulfur, % Calcd	Sulfur, % Found
$(CH_3)_2NSF_3$	3880-03-3	49–49.5 (33)	19.7, 59.2		18.0	18.3	4.6	4.7	42.8	42.6	10.5	10.7	24.1	23.8
$(C_2H_5)_2NSF_3$	38078-09-0	46–47 (10)	31.2, 55.5	84	29.8	30.0	6.3	6.4	35.4	35.1	8.7	8.5	19.9	19.7
	53731-09-2	54–55 (15)		83	30.2	29.9	5.1	5.3	35.8	35.5	8.8	8.8	20.1	20.0
$[(CH_3)_2CH]_2NSF_3$	50713-80-9	*a*		99[b]					30.1	29.9				
$(CH_3)_2NSF_2N(CH_3)_2$	53731-10-5	Mp 64–65.5	6.9	60	30.4	30.5	7.7	7.9	24.0	24.1	17.7	17.6	20.3	19.7
$(CH_3)_2NSF_2N(C_2H_5)_2$	53731-11-6	*a*	10.9	92[b]					20.4	20.4				
$(C_2H_5)_2NSF_2N$-$(C_2H_5)_2$	53731-12-7	*a*	9.7	92[b]					17.7	17.9				
	53731-13-8	Mp 25–26	5.9	99	44.7	44.5	3.2	3.1	20.2	20.0				

[a]Not distilled. [b]Crude yield.

difluorides listed in Table IV were prepared by the reaction of dimethylaminosulfur trifluoride or DAST with an aminotrimethylsilane, as illustrated by the preparation of bis(dimethylamino)sulfur difluoride.

A 29.25-g (0.25 mol) sample of dimethylaminotrimethylsilane was added dropwise to a solution of 33.2 g (0.25 mol) of dimethylaminosulfur trifluoride in 100 ml of CCl_3F cooled to −78°. The reaction mixture was warmed to 25° and then filtered under nitrogen to remove a small amount of suspended solid. The filtrate was evaporated to dryness under reduced pressure to give 23.5 g (60%) of bis(dimethylamino)sulfur difluoride as a white crystalline solid.

***N*-Isopropyliminosulfur Difluoride (4).** Attempted distillation of crude diisopropylaminosulfur trifluoride caused this product to decompose at about 60° (2 mm). The volatile decomposition products were collected in a cooled trap and redistilled to give an 80% yield of 4 as a light yellow liquid: bp 63°; ^{19}F nmr (CCl_3F) δ 72.9 ppm; ^{1}H nmr (CCl_3F) δ 1.28 ppm (d, J = 6.5 Hz, 6 H) and 4.17 ppm (septet, J = 6.5 Hz, 1H).

Anal. Calcd for $C_3H_7F_2NS$: C, 28.3; H, 5.6; F, 29.9; N, 14.0; S, 25.2. Found: C, 28.4; H, 5.6; F, 29.5; N, 14.0; S, 25.4.

Fluorination of Alcohols (Table I). The alcohols listed in Table I were added to a solution of DAST or dimethylaminosulfur trifluoride in an inert solvent cooled to −50 to −78°. The reaction mixture was then warmed to room temperature or higher. An initial exothermic reaction usually occurred at low temperature. In some cases, a second exothermic reaction was evident during the warm-up period. The lower-boiling product fluorides were distilled out of the reaction mixture at reduced pressure. Reaction mixtures containing higher-boiling fluorides were mixed with water, and the organic layer was separated and dried, and the solvent was distilled off. The product fluorides were purified by distillation, recrystallization, or column chromatography. The following are representative examples.

Ethyl 2-Fluoropropionate. A solution of 1.18 g (0.01 mol) of ethyl lactate in 2 ml of methylene chloride was slowly added to a solution of 1.25 g (0.01 mol) of DAST in 5 ml of methylene chloride cooled to −78°. The reaction mixture was warmed to room temperature and mixed with cold water. The lower layer was separated, washed with water, dried ($MgSO_4$), and distilled to give 0.93 g of ethyl 2-fluoropropionate[10] as a colorless liquid.

1-Bromo-2-fluoroethane. Ethylene bromohydrin, 31.25 g (0.25 mol), was added dropwise to a solution of 33 g (0.25 mol) of dimethylaminosulfur trifluoride in 150 ml of diglyme cooled to −50°. The reaction mixture was warmed to room temperature, and 50 ml of the most volatile portion was distilled out at reduced pressure. The distillate was mixed with water, washed with 5% sodium bicarbonate solution, dried ($MgSO_4$), and redistilled to give 22.2 g of 1-bromo-2-fluoroethane[11] as a colorless liquid.

Fluorination of Crotyl Alcohol with (Diethylamino)(dimethylamino)sulfur Difluoride. A solution of 1.44 g (0.02 mol) of crotyl alcohol (2-buten-1-ol) in 2 ml of diethylene glycol dimethyl ether was slowly added to a stirred solution of 3.7 g (0.02 mol) of (diethylamino)(dimethylamino)sulfur difluoride in 10 ml diethylene glycol dimethyl ether cooled to −78°. The reaction mixture was warmed to 25° and the volatile products were distilled out under reduced pressure to give 1.3 ml of colorless liquid. Redistillation gave 1.06 g (72%) of a mixture containing 79% 1-fluoro-2-butene (crotyl fluoride) and 21% 2-fluoro-3-butene, bp 24–27°.

When the reaction was repeated, using isooctane in the place of diethylene glycol dimethyl ether as the reaction solvent, a 65% yield of fluorobutene was obtained consisting of 87% 1-fluoro-2-butene and 13% 2-fluoro-3-butene.

Fluorination of Alcohols with $(Me_2N)_2SF_2$. A solution of 1.08 g (0.01 mol) of benzyl alcohol in 2 ml of methylene chloride was added slowly to a solution of 0.0066 mol of bis(dimethylamino)sulfur difluoride in 6 ml of methylene chloride cooled to −78°. The reaction mixture was warmed to room temperature and mixed with water. The organic layer was separated, washed with water, and then 5% sodium bicarbonate, and dried ($MgSO_4$). Analysis by glc and ^{19}F nmr showed that benzyl fluoride had been formed in 91% yield. Cyclohexanol was fluorinated in a similar manner to give fluorocyclohexane, ^{19}F nmr (CCl_3F) δ −161.2 ppm (m).

Fluorination of Aldehydes and Ketones with DAST (Table II). The ketones and aldehydes in Table II were fluorinated by stirring them in an inert solvent with DAST at temperatures and for times indicated. The fluorinated products were isolated by pouring the reaction mixture into water, and then separating, drying, and distilling the organic layer. The following example illustrates this procedure.

Fluorination of Isovaleraldehyde. A 1.72-g (0.02 mol) sample of isovaleraldehyde was slowly added to a solution of 2.5 ml (0.02 mol) of DAST in 10 ml of CCl_3F at 25°. The reaction mixture was stirred for 30 min, and then mixed with 25 ml of water. The lower organic layer was separated, washed with water, dried ($MgSO_4$), and distilled to give 1.73 g (80%) of 1,1-difluoro-3-methylbutane as a colorless liquid.

Anal. Calcd for $C_5H_{10}F_2$: C, 55.5; H, 9.3; F, 35.1. Found: C, 55.8; H, 9.6; F, 35.1.

Registry No.—1 (R = Me), 2083-91-2; 1 (R = Et), 996-50-9; 1 [R_2 = $-(CH_2)_4-$], 15097-49-1; 1 (R = Pri), 17425-88-6; **4**, 53731-08-1; sulfur tetrafluoride, 7783-60-0.

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2,4-Dinitrobenzenesulfonylhydrazine, a Useful Reagent for the Eschenmoser α,β Cleavage of α,β-Epoxy Ketones. Conformational Control of Halolactonization

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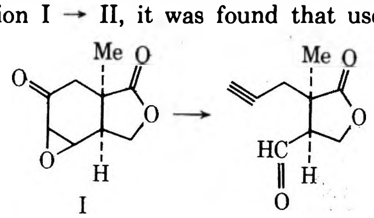
2,4-Dinitrobenzenesulfonylhydrazine has been found to be a useful reagent in the Eschenmoser α,β cleavage of α,β-epoxy ketones especially in instances where the product is an acetylenic aldehyde. Several representative examples are given. In connection with the synthesis of one of the substrates studied in the cleavage reaction, an interesting and useful observation has been made of selective bromolactonization of a Diels–Alder adduct which depends on conformational control.

In connection with the attempted application of the Eschenmoser α,β epoxy ketone cleavage reaction[1-8] for the transformation I → II, it was found that use of *p*-tolu-



I II

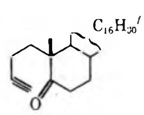
enesulfonylhydrazine[1] as reagent was completely ineffective. Although the epoxy ketone was completely consumed, only a very complex mixture could be obtained under a variety of conditions, and little or no aldehyde was detected by infrared and nmr analysis. This result underscores previous indications[2] that this reagent is unsatisfactory for the synthesis of acetylenic aldehydes. Further, it was found that use of *N*-aminoaziridine reagents[2] led to low and irreproducible yields of the desired product and also that no aldehyde could be obtained on a scale larger than a few millimoles. These facts prompted us to study 2,4-dinitrobenzenesulfonylhydrazine as a reagent which might induce fragmentation at relatively low temperatures and under conditions allowing survival of the acetylenic aldehyde II. This expectation was realized in four different cases which are presented herein. In addition, the path of synthesis of the substrate I, which involves a novel selective reaction, is detailed.

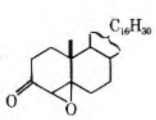
In general, the cleavage reactions were conducted in methylene chloride or tetrahydrofuran at temperatures between 0 and 25° simply by allowing the epoxy ketone and the hydrazine reagent to combine. Pyridine, sodium bicarbonate, or sodium carbonate are effective catalysts. In some instances somewhat higher yields could be obtained by including in the reaction ethyl isocyanate (added to scavenge the sulfinic acid produced in the fragmentation). The overall results are summarized in Table I.

The substrate I (originally of interest as a precursor of 8-methyl prostanoids) was prepared starting with the Diels–Alder adduct from butadiene and citraconic anhydride[9] using the sequence III → IV → V → VI → VII → I. An especially noteworthy step is the bromolactonization in which only one of the two carboxyl groups participates. This selectivity can be rationalized in terms of a more favorable lactonization pathway *via* IX relative to X. This example illustrates what appears to be a new approach to positional control in addition reactions to Diels–Alder adducts of butadiene.

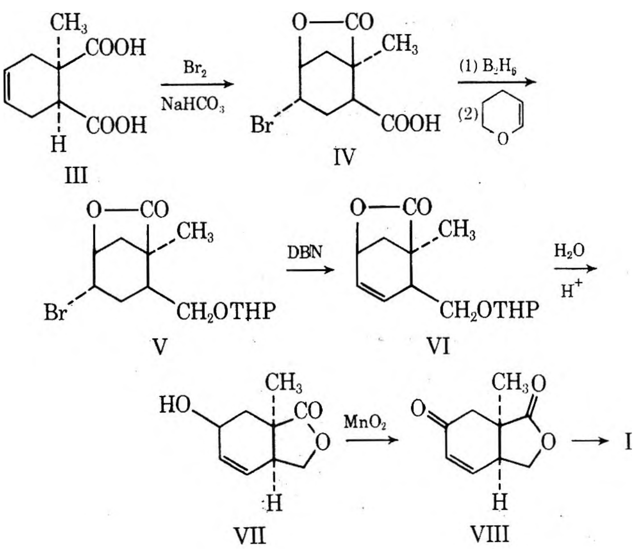
The structure IV was confirmed by partial esterification of III to give *cis*-1-methyl-2-carbomethoxy-4-cyclohexene-1-carboxylic acid (XI),[10] mp 120–121°, followed by bromolactonization to the lactone ester XII, mp 90–91°, which was identical with a sample of the methyl ester obtained by

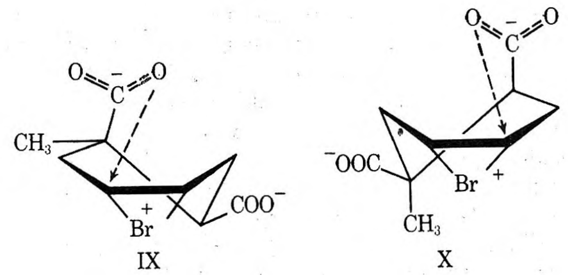
Table I
Reaction of α,β-Epoxy Ketones with 2,4-Dinitrobenzenesulfonylhydrazine

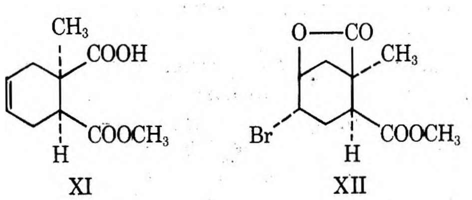
Substrate	Registry No.	Product	Registry No.	Yield, %
(1) 2,3-Epoxycyclohexan-1-one	6705-49-3	5-Hexynal[a,b]	1871-33-6	62
(2) 2-Methyl-2,3-epoxycyclohexan-1-one	21889-75-8	6-Methyl-5-hexynal[c]	32813-63-1	62
(3) I		II		62
(4) 3-Methyl-5,5-dimethyl-2,3-epoxycyclohexan-1-one	10276-21-8	4,4-Dimethylheptyn-6-one	17520-15-9	91
(5) 4,5-Epoxycholestan-3-one[d,e]	1975-34-4		21489-86-1	95



[a] Isolated as the 2,4-dinitrophenylhydrazone. [b] A yield of 72% was obtained when 1 equiv of ethyl isocyanate was used in the reaction. [c] Isolated as the 2,4-dinitrophenylhydrazone, mp 100–101°. *Anal.* Calcd for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.8; N, 19.30. Found: C, 53.53; H, 4.86; N, 19.04. [d] Reaction was carried out at 25° for 30 min, then with Na_2CO_3 at 25° for 2 hr and at 50° for 2 hr. [e] Pl. A. Plattner, H. Heusser, and A. B. Kulkarni, *Helv. Chim. Acta*, 31, 1822 (1948). [f] Ir max ($CHCl_3$) 3.02 (C≡CH), 4.72 (C≡C), and 5.89 μ (C=O); molecular ion at 384.3387 (calcd for $C_{27}H_{44}O_2$: 384.3392).







esterification of IV with diazomethane by infrared, pmr, mp, and mmp comparison.

Experimental Section

2,4-Dinitrobenzenesulfonylhydrazine. To a well-stirred solution of 95% hydrazine (6.8 g, 200 mmol) in tetrahydrofuran (400 ml) cooled in a Dry Ice–acetone bath was added 2,4-dinitrobenzenesulfonyl chloride (26.6 g, 100 mmol) dissolved in tetrahydrofuran (50 ml). After 30 min the mixture was allowed to warm to ambient temperature. After 15 min the solvent was removed by rotary evaporation and the yellow-colored residue was leached with two 50-ml portions of ice-cold water. The solid was washed with ethanol (50 ml) and then with ether (30 ml). The light yellow solid thus obtained was dissolved in cold, dry tetrahydrofuran (170 ml) without heating, and the solution was filtered, reduced in volume to 30–40 ml by rotary evaporation at ambient temperature, diluted with ethanol (50 ml), and chilled at −10° for 2 hr. The crystalline product, 18.2 g (70%), had mp 120° (lit.[11] mp 110°).

Fragmentation of 2,3-Epoxycyclohexan-1-one. To a solution of 2,4-dinitrophenylsulfonylhydrazine (0.576 g, 2.2 mmol) in tetrahydrofuran (20 ml) cooled to −25° was added the epoxy ketone (0.224 g, 2 mmol). The reaction mixture was kept at −25 to −30° for 30 min and then at −10° for 30 min. The mixture was allowed to warm to 0° and dried at this temperature over anhydrous magnesium sulfate for 20 min and filtered below 0°. After stirring for 1 min a drop of pyridine was added and the stirring was continued. The mixture was taken out of the ice bath, and after 2 min another drop of pyridine was added. This caused an extensive effervescence, and the mixture turned deep orange in color. After 2 min, more pyridine (a total of 0.16 g, 2 mmol) was added, and the stirring was continued for 5 min. The mixture was filtered through Celite 545, and the filtrate was stirred with powdered $CuSO_4 \cdot 5H_2O$ (1 g) for 25 min. It was filtered and the volatile substances from the filtrate were transferred under vacuum (0.03 mm) at ambient temperature into a receiver containing 2,4-dinitrophenylhydrazine (0.792 g, 4 mmol) in tetrahydrofuran (75 ml). The mixture was stored at 25–30° for 48 hr. The solvent was removed by rotary evaporation, and the residue was purified by preparative tlc on silica gel (methylene chloride, R_f 0.8) to give the orange crystalline 2,4-dinitrophenylhydrazone of 5-hexynal (342 mg, 62%): mp 90–91°, nmr ($CDCl_3$) δ 1.7–2.7 (m, 7 H), 7.91 (t, J = 5 Hz, 1 H), 8.2 (d, J = 10 Hz, 1 H), 8.34 (pair of doublets, J_A = 10 Hz, J_B = 2.7 Hz, 1 H), 9.37 (d, J = 2.7 Hz, 1 H), 11.29 (broad s, 1 H); *m/e* (P) 276.0861.

Anal. Calcd for $C_{12}H_{12}N_4O_4$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.95; H, 4.28; N, 19.76.

Fragmentation of 3-Methyl-5,5-dimethyl-2,3-epoxycyclohexan-1-one. To a solution of 2,4-dinitrobenzenesulfonylhydrazine (0.577 g, 2.1 mmol) in dry tetrahydrofuran (20 ml) at −25° was added the epoxy ketone (0.308 g, 2 mmol). The mixture was kept at −25° for 30 min and then at 4° for 12 hr, after which it was allowed to warm to 25°. It was treated with pyridine (0.16 g, 2 mmol) which caused an instantaneous effervescence, and the mixture turned deep orange in color. After 20 min the mixture was stirred with powdered $CuSO_4 \cdot 5H_2O$ (0.5 g) for 30 min and filtered through Celite 545. The filter cake was washed with tetrahydrofuran (5 ml). The volatile substances were distilled from the filtrate at ambient temperature at 0.03 mm. Tetrahydrofuran was removed from the distillate by careful distillation, and the residue was transferred under reduced pressure (0.02 mm) into a receiver cooled in liquid nitrogen to give pure 4,4-dimethylheptyn-6-one (250 mg, 91%) as colorless oil. Its ir and nmr spectra were identical with those reported in the literature.[1]

Fragmentation of the Keto Epoxide I. To a solution of 2,4-dinitrobenzenesulfonylhydrazine (0.275 g, 1.05 mmol) in tetrahydrofuran (20 ml) at 0° was added the epoxide I (0.182 g, 1 mmol). The mixture was stored at 0° for 2 hr and then at 20° for 10 min. The solvent was evaporated and the residue was dissolved in methylene chloride (15 ml). It was filtered to remove traces of undissolved material. The filtrate upon chilling at −25° deposited an off-white solid which was collected under suction to give the intermediate 2,4-dinitrobenzenesulfonylhydrazone (0.404 g, 95%): mp 103°. The ir spectrum in chloroform showed only absorption for lactone C═O at 5.6 μ in the carbonyl region. This material was unstable at ambient temperature.

To a solution of the hydrazone (0.404 g) in tetrahydrofuran (20 ml) was added sodium bicarbonate (0.25 g), and the mixtue was stirred for 30 hr at 25–28°, which caused it to turn light orange in color. It was filtered through Celite 545. The clear filtrate was evaporated to give a pale colored gum which according to nmr analysis contained 61–62% of the desired aldehyde II. A sample was chromatographed by preparative tlc on silica gel (ethyl acetate–benzene 2:3, R_f 0.35). The ir spectrum had λ_{max} ($CHCl_3$) 3.0 (C≡CH), 4.71 (C≡CH), 5.6 (C═O, lactone), and 5.78 μ (C═O, aldehyde); nmr ($CDCl_3$) δ 1.56 (s, 3 H), 2.21 (t, J = 2.5 Hz, 1 H), 2.56 (d, J = 2.5 Hz, 2 H), 3.4 (m, 1 H), 4.45 (m, 2 H), 10.0 (d, J = 1 Hz, 1 H); *m/e* (P) 166.0628, calcd for $C_9H_{10}O_3$ 166.0630.

Bromo Lactone IV. To a well-stirred solution of the diacid III (9.2 g, 50 mmol) in water (100 ml) containing sodium bicarbonate (10.5 g, 125 mmol) was added bromine (8.4 g, 52.5 mmol) over a period of 30 min. After stirring for another 30 min, the reaction mixture was acidified to pH 4–5 which caused a white solid to precipitate. The solid was collected under suction after washing with water to give 10.9 g (80%) of white crystals: mp 206–207°. This material (at least 95% pure by nmr and ir analysis) was used for the next step without further purification. An analytical sample was prepared by recrystallization from ethyl acetate: mp 210°; λ_{max} (Nujol) 5.6 (C═O, lactone), 5.85 (C═O, acid), 7.5, 7.82, 8.15, 8.31, 8.58, 8.92, 9.3 μ.

Anal. Calcd for $C_9H_{11}BrO_4$: C, 41.06; H, 4.14; Br, 30.41. Found: C, 40.95; H, 4.11; Br, 30.25.

Tetrahydropyranyl Ether V. To a well-stirred suspension of bromolactone IV (26.3 g, 0.1 mol) in tetrahydrofuran (350 ml) cooled in ice was added dropwise (30 min) 1.3 *M* borane in tetrahydrofuran (84 ml, 0.1092 mol). The mixture was a clear solution at this stage. It was maintained at 0° for another 3 hr after which excess borane was destroyed by adding water (70 ml). This was then basified with sodium bicarbonate (10 g). The organic solvent was removed *in vacuo.* The aqueous residual solution was treated with solid sodium chloride and extracted with five 50-ml portions of ethyl acetate. The combined extracts were washed with brine (15 ml) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure at 10–15° furnished 21.5 g (86%) of a low-melting white solid which deteriorated on keeping at ambient temperature. It was used for the next step without further purification. An analytical sample was prepared by recrystallization from ethyl acetate–pentane mixture: mp 98–99°; λ_{max} ($CHCl_3$) 2.8 (OH), 5.62 (C=O), 8.62, and 9.18 μ; nmr ($CDCl_3$) δ 1.27 (s, 3H), 1.08–2.9 (m, 6 H), 3.7 (d, J = 4.5 Hz, 2 H), 4.45 (m, 1 H), 4.82 (t, J = 5 Hz, 1 H).

Anal. Calcd for $C_9H_{13}BrO_3$: C, 43.37; H, 5.2; Br, 32.12. Found: C, 43.29; H, 5.18; Br, 32.26.

A stirred ice-cooled solution of the alcohol obtained above (12.45 g, 50 mmol) in tetrahydrofuran (100 ml) containing dihydropyran (6.3 g, 75 mmol) was treated with *p*-toluenesulfonic acid (100 mg) at 0°. After 12 hr the mixture was treated with 10% aqueous sodium bicarbonate (5 ml). The excess dihydropyran and the organic solvent were removed by rotary evaporation. The residue was taken up in methylene chloride (150 ml) and washed with two 10-ml portions of water. After drying ($MgSO_4$), the solvent was evaporated to give 16.6 g (100%) of a colorless thick syrup. This material was used for the following step without any further purification. An analytical sample was prepared by preparative layer chromatography on silica gel (benzene–ethyl acetate, 2:1, R_f 0.8): λ_{max} ($CHCl_3$) 5.62 (C=O), 6.9, 7.22, 8.86, 9.28, 9.78, and 10.18 μ; nmr ($CDCl_3$) δ 1.27 (s, 3 H), 1.64 (broad s, 6 H), 1.9–4.2 (m, 9 H), 4.3–5.2 (m, 3 H).

Anal. Calcd for $C_{14}H_{21}BrO_4$: C, 50.45; H, 6.3; Br, 24.02. Found: C, 50.28; H, 6.15; Br, 23.95.

Lactone VI. A solution of V (9.99 g, 15 mmol) in dry dioxane (250 ml) protected from atmospheric moisture was refluxed for 10 hr after adding diazabicyclo[4.3.0]non-5-ene (DBN) (4.092 g, 16.5 mmol). Shining crystals of DBN hydrobromide were formed. The reaction mixture was allowed to cool to ambient temperature and filtered through Celite 545. The filter cake was washed with dioxane (50 ml). The filtrate upon evaporation *in vacuo* gave a light brown oil. It was taken up in ether (150 ml) and washed with two 10-ml portions of 0.1 *N* hydrochloric acid, then with 10% sodium bicarbonate solution (10 ml), and finally with water (15 ml). The ether solution was dried ($MgSO_4$) and evaporated to give a pale colored oil (6.8 g) which was used as such for the next step. An analytical sample was prepared by preparative layer chromatography on silica gel (benzene–ethyl acetate, 5:1, R_f 0.5) to give a colorless oil. The yield of the purified material was 75%: λ_{max} ($CHCl_3$) 5.62 (C=O), 6.88, 8.8, 8.9, 9.26, and 9.19 μ; nmr ($CDCl_3$) δ 1.44 (s, 3 H), 1.68 (broad s, 6 H), 2.28 (narrow m, 2 H), 2.68–4.21 (m, 6 H), 4.69 (m, 2 H), 6.2 (m, 2 H).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.48; H, 7.86.

Hydroxy Lactone VII. A suspension of the γ lactone VI (2.52 g, 10 mmol) in a mixture of acetic acid (4 ml), tetrahydrofuran (4 ml), and water (24 ml) was heated at 60° for 12 hr during which time the mixture became a clear solution. It was treated with excess sodium bicarbonate, and the organic solvent was evaporated under reduced pressure. The aqueous solution was treated with excess solid sodium chloride, and the slurry was extracted with five 25-ml portions of ethyl acetate. The combined extracts after drying ($MgSO_4$) were evaporated to give a colorless syrup which on keeping in ether solution at 0° overnight deposited colorless crystals (0.83 g, 50%): mp 49–50°; λ_{max} ($CHCl_3$) 2.76, 2.88 (OH), 5.63 (C=O), 8.2, 8.68, 9.0, 9.6, and 9.9 μ; nmr ($CDCl_3$) δ 1.25 (s, 3 H), 1.48 (d, J = 6 Hz, 2 H), 2.76 (m, 2 H), 3.8–4.3 (m, 3 H), 5.85 (m, 2 H).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.16; H, 7.24.

Keto Lactone VIII. To a well-stirred solution of the lactone VII (336 mg, 2 mmol) in methylene chloride (50 ml) was added manganese dioxide (3.5 g), and the mixture was kept at 4–5° for 16 hr. It was treated with methanol (20 ml) and filtered through Celite 545. The filter cake was washed with methanol (10 ml). The filtrate was evaporated under reduced pressure to give a white solid (320 mg, 97%): mp 82–83°. It was used as such for the next step. An analytical sample was prepared by crystallization from ethyl acetate–pentane mixture: mp 84–85°; λ_{max} ($CHCl_3$) 5.61 (C=O, lactone), 5.91 (C=O, conjugated), 6.75, 6.9, 7.2, 7.35, 7.48, 7.7, 8.0, 8.85, 9.11, 9.23, 9.65, 9.86, and 10.15 μ; nmr ($CDCl_3$) δ 1.4 (s, 3 H), 2.43 and 2.92 (pair of doublets, J = 17 Hz, 2 H), 3.17 (m, 1 H), 4.19 (doublet of doublets, J_1 = 10 Hz, J_2 = 4 Hz, 1 H), 4.63 (doublet of doublets, J_1 = 10 Hz, J_2 = 6.5 Hz, 1 H), 6.14 (doublet of doublets, J_1 = 9.5 Hz, J_2 = 2.5 Hz, 1 H), 6.8 (doublet of doublets, J_1 = 9.5 Hz, J_2 = 3.5 Hz, 1 H).

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.96; H, 6.1.

Epoxy Ketone I. To a well-stirred suspension of the conjugated ketone VIII (249 mg, 1.5 mmol) in methanol (8 ml) cooled to −25° was added 33% hydrogen peroxide (0.5 ml). Aqueous 40% sodium hydroxide (50 μl) was then added, and the mixture was kept at −25 to −30° for 16 hr, during which time a clear solution developed. It was diluted with cold 1% ammonium chloride solution (10 ml), and the methanol was removed under reduced pressure. The aqueous solution was extracted with eight 20-ml portions of methylene chloride. The combined organic extracts were washed with two 6-ml portions of brine, dried ($MgSO_4$), and evaporated to give a colorless crystalline solid. It was recrystallized from methylene chloride–ether–pentane mixture to give colorless crystals (165 mg, 61%): mp 108°; λ_{max} ($CHCl_3$) 5.61 (C=O, lactone), 5.77 (C=O, epoxy ketone), 6.73, 6.88, 7.08, 7.23, 7.18, 8.38, 8.69, 9.06, 9.5, and 10.1 μ; nmr ($CDCl_3$) δ 1.37 (s, 3 H), 2.46 (d, J = 14.5 Hz, 1 H), 2.88 (d, J = 14.5 Hz, 1 H), 3.03 (m, 1 H), 3.29 (d, J = 3.5 Hz, 1 H), 3.59 (d, J = 3.5 Hz, 1 H), 4.3 (doublet of doublets, J_1 = 2.5 Hz, J_2 = 10.5 Hz), 4.6 (doublet of doublets, J_1 = 10.5 Hz, J_2 = 7 Hz).

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.12; H, 5.51.

***cis*-1-Methyl-2-carbomethoxy-4-cyclohexene-1-carboxylic Acid XI.** This substance was obtained by partial esterification of the diacid III according to the procedure of Nazarov and Kucherov:[10] mp120–121°.

Bromolactonization of XI. To a well-stirred solution of XI (192 mg, 1 mmol) in water (10 ml) containing sodium bicarbonate (252 mg, 3 mmol) was added dropwise bromine (168 mg, 1.05 mmol) in water (5 ml). After 30 min the reaction mixture was acidified with 1 *N* hydrochloric acid to pH 4–5, and the mixture was extracted with four 20-ml portions of methylene chloride. After drying ($MgSO_4$), the combined extracts upon evaporation of the solvent furnished an oil which immediately crystallized. It was recrystallized from ether–pentane to give 180 mg (66%) of white needle-like crystals: mp 91–92°. The ir and nmr spectra of this material were superimposable with those of the methyl ester XII prepared below; also the mixture mp of the two was undepressed.

Methyl Ester XII. To an ice-cooled solution of the bromolactone IV (132 mg, 0.5 mmol) in 50 ml of ether was added dropwise with shaking 0.2 *N* diazomethane in ether till a faint yellow color persisted. The solvent and excess diazomethane were removed under reduced pressure to give 145 mg of a white solid: mp 90–91° (100%). It was recrystallized from ether–pentane to furnish white crystals: mp 91–92°; λ_{max} ($CHCl_3$) 5.58 (C=O, lactone), 5.75 (C=O, ester), 6.93, 7.45, 7.87, 8.12, 9.2, 9.35, 9.7, 9.96, 10.18, and 10.42 μ; nmr ($CDCl_3$) δ 1.26 (s, 3 H), 3.75 (s, 3 H), 4.52 (m, 1 H), 4.8 (t, J = 5 Hz, 1 H).

Anal. Calcd for $C_{10}H_{13}BrO_4$: C, 43.32; H, 4.33; Br, 28.52. Found: C, 43.11; H, 4.15; Br, 28.35.

Acknowledgment. This work was supported by the National Institutes of Health.

Registry No.—I, 53777-66-5; I 2,4-dinitrobenzenesulfonylhydrazone, 53777-69-8; II, 53777-67-6; III, 35216-43-4; IV, 53777-68-7; V free alcohol, 53777-70-1; V, 53777-71-2; VI, 53777-72-3; VII, 53777-73-4; VIII, 53777-74-5; XI, 14679-29-9; XII, 53798-25-7; 2,4-dinitrobenzenesulfonylhydrazine, 53777-75-6; 2,4-dinitrobenzenesulfonyl chloride, 1656-44-6; hydrazine, 302-01-2; dihydropyran, 25512-65-6.

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(9) (a) I. N. Nazarov and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 282 (1952); *Chem Abstr.*, **47**, 5363 (1953); (b) J. J. Bloomfield and S. L. Lee, *J. Org. Chem.*, **22**, 3919 (1967).
(10) I. N. Nazarov and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 63 (1954); *Chem. Abstr.*, **49**, 2454 (1955).
(11) W. Davies, F. R. Storrie, and S. H. Tucker, *J. Chem. Soc.*, 624 (1931).

Addition of *N*-Chlorosulfonyl Isocyanate to 1,1-Dimethyl-2,5-diphenyl-1-silacyclopenta-2,4-diene

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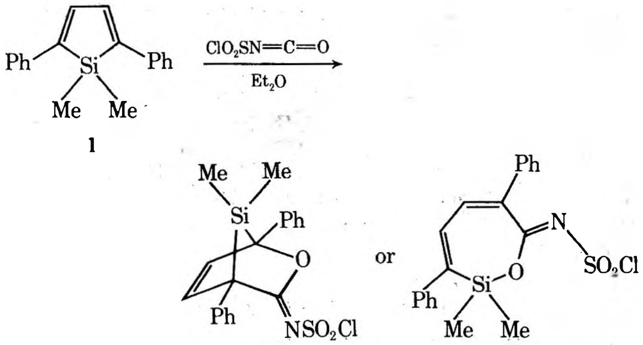
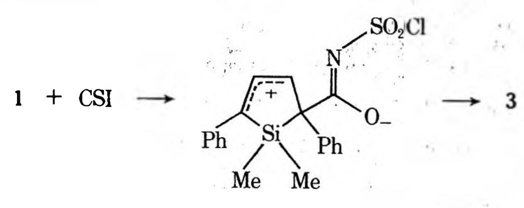
The reaction of *N*-chlorosulfonyl isocyanate (CSI) and 1,1-dimethyl-2,5-diphenyl-1-silacyclopenta-2,4-diene (**1**) in ether at room temperature affords the ring enlarged iminosiloxypinone (**3**). The mechanistic origin of **3** presumably involves Si to O migration in the zwitterionic intermediate **4**. Evidence for the generality of this migration was obtained from the observation that *trans*-β-trimethylsilylstyrene smoothly reacted with CSI to give *trans*-cinnamamide **7** after hydrolysis. When performed in $DCCl_3$ at 0° and immediately quenched *via* thiophenol–pyridine reduction, the reaction of **1** and CSI afforded β-lactam **11**. The corresponding *N*-chlorosulfonyl β-lactam **10** rearranged to **3** when allowed to stand at room temperature.

As part of a general study of the addition of *N*-chlorosulfonyl isocyanate (CSI) to heterocyclopentadienes we have examined the reaction of CSI with 1,1-dimethyl-2,5-diphenyl-1-silacyclopenta-2,4-diene (**1**). Recently there has been considerable interest in the reactions of vinyl silanes and electrophiles.[1] We wished not only to examine such a reaction with a uniparticulate electrophile[2] but also to utilize the expected β-lactam product for further synthetic studies.

At room temperature a stirred ether solution of CSI and **1** soon precipitated a bright yellow, one-to-one adduct (43%) which rapidly decomposed in the presence of moisture or hydroxylic solvents. The absence of a carbonyl band in the infrared eliminated the expected lactam or amide products and left structures **2** and **3** for consideration. Although the nmr spectrum [δ 7.50–7.01 (m, 12 H), 0.65 (s, 6 H)] might be consistent with either structure, **2** was excluded on the basis that the olefinic protons absorbed at lower field than would be expected from the spectra of model compounds (Table I). The intense color of the product and the position of the C=N band in the ir (1506 cm^{-1}) are clearly more consistent (Table II) with the extensive conjugation of **3**.



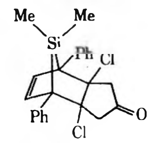
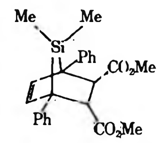
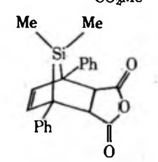
Mechanistically, the formation of **3** can be envisioned as arising from electrophilic attack of CSI on **1** to generate zwitterion **4** which can be rearranged to **3** through silicon migration to oxygen.



4

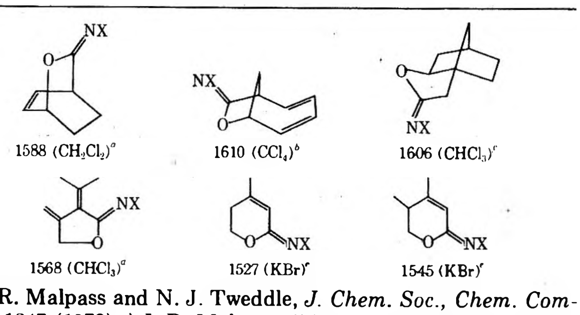
While there is considerable precedent for both carbonium ion rearrangements in CSI–olefin reactions[3] and migrations of silicon from carbon to oxygen,[4] we needed to unambiguously establish CSI initiated silicon migrations. To this end the reaction of CSI and *trans*-β-trimethylsilylstyrene (**5**) was investigated. The reaction of **5** with acid yields styrene[5] and the mechanism has been established as involving a silicon-bridged cation.[1b] CSI reacted rapidly with **5** to yield an unstable adduct (92%) which was assigned the structure of **6** on nmr [δ_{CCl_4} 7.93 (d, 1 H, J = 16 Hz), 7.77–7.36 (m, 6 H), 0.50 (s, 9 H)] and ir [1540 cm^{-1} (C=N stretch)] evidence and its facile hydrolysis to *trans*-cinnamamide **7** (63%). Treatment of *in situ* generated **6** with β-phenethyl alcohol quantitatively precipitated **8** and distillation of the filtrate afforded β-phenethoxytrimeth-

Table I
Nmr Chemical Shifts (δ, ppm) of Model Bridged Silanes[a]

Silane	Olefinic H	Silicon methyls
	6.42	1.01, 0.49
	6.59	0.50, 0.50
	6.60	0.16, 0.10

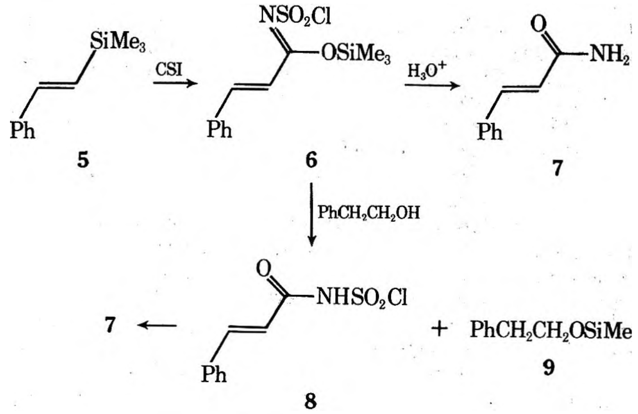
[a] A. J. Nelson, Ph.D. Thesis, Iowa State University, 1972.

Table II
Infrared Absorption Bands (C=N, cm^{-1}) of Model Compounds (X = SO_2Cl)

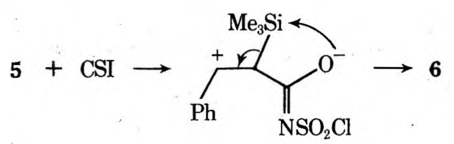


[a] J. R. Malpass and N. J. Tweddle, *J. Chem. Soc., Chem. Commun.*, 1247 (1972). [b] J. R. Malpass, *ibid.*, 1246 (1972). [c] Reference 3b. [d] Reference 3f. [e] E. J. Moriconi and W. C. Meyer, *J. Org. Chem.*, 36, 2841 (1971).

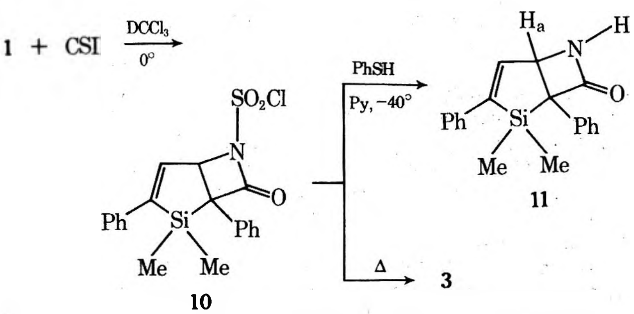
ylsilane (9) in 39% yield. This yield represents only a center cut and the reaction was observed to be quantitative by nmr. Reagents such as 6 could prove useful as silating agents for sensitive alcohols as the conditions are essentially neutral.



The conversion of 5 to 6 by CSI is easily interpreted as arising from zwitterion formation followed by silicon migration to oxygen. This then lends further support to the assignment of structure 3 to the adduct of CSI and silole 1.

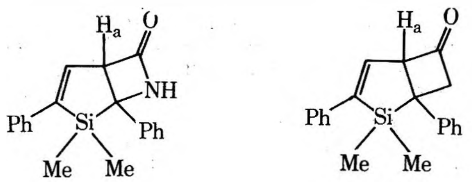


While this work was in progress, examples of initial β-lactam formation from CSI and olefins followed by thermal conversion to rearranged products through dipolar intermediates were discovered in our laboratory.[6] Hence, the reaction of 1 and CSI was reinvestigated. In $DCCl_3$ at room temperature admixture of 1 and CSI initially gave rise to an nmr spectrum assignable to NCS β-lactam 10 and a minor amount of 3. The relative amount of 3 steadily increased until 3 precipitated from solution. Reaction in $DCCl_3$ at 0° followed by reduction with thiophenol–pyridine at −40° provided β-lactam 11 (43%).



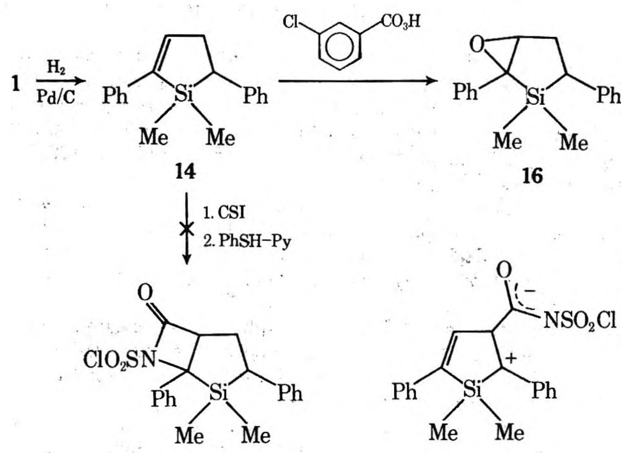
10

Structure 11 is favored over the isomeric β-lactam 12, derived from opposite addition of CSI, from nmr comparison with ketone 13.[7] The chemical shift of H_a in 13 is 4.49 ppm. From chemical shift correlation tables[8] H_a of 11 is predicted to absorb at δ 4.69 (4.49 + 0.20) while 12 is predicted to



12 13

absorb at δ 4.29 (4.49–0.20). As the resonance absorption of the β-lactam is found at δ 4.69, structure 11 is favored. In order to further substantiate this structural assignment, an unambiguous synthesis of β-lactam 12 was attempted. Reaction of CSI with silacyclopentene 14 should occur to give only β-lactam 15 after reduction. Dehydrogenation of 15 with DDQ would then provide 12. Hydrogenation of 1 gave a mixture of reduced material composed of 92% 14 by nmr. Silacyclopentene (14) was not further purified but was characterized by its high-resolution mass spectrum and conversion to pure epoxide 16. Unfortunately, no reaction occurred between 14 and CSI even when heated to 75° for 24 hr. The failure of 14 to react with CSI lends support to the assignment of structure 11. If initial attack of CSI had occurred at C-3 of 1 and formed zwitterion 17, then 14 should have reacted with CSI at least as rapidly as 1 since the additional double bond is essentially insulated from affecting the energy of the transition state.



15 17

The question of the mechanism of CSI addition to olefins is not answered by this work. However, once again it has been found that a reaction of CSI which gives products obviously resulting from an intermediate dipolar species can be made to afford the β-lactam under appropriate conditions.

Experimental Section

General. Nmr spectra were recorded on Varian A-60, Hitachi R 20-B, and Varian HA-100 spectrometers. Mass spectra were obtained on MS-9 and CH-4 spectrometers. Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, West Germany. Chloroform was passed through basic alumina to remove ethanol.

Reaction of 1,1-Dimethyl-2,5-diphenylsilole (1) and CSI in Ether. CSI (0.85 g, 6.0 mmol) was added to a stirred solution of silole 1[9] and ether (20 ml). The reaction mixture was stirred at room temperature for 12 hr during which time 3 had precipitated as a bright yellow solid. The reaction mixture was filtered and the collected solid recrystallized from methylene chloride–ether to give 3 (1.03 g, 43%) as yellow needles: mp 140–142° dec; nmr ($CDCl_3$) δ 7.50–7.01 (m, 12 H), 0.65 ppm (s, 6 H); ir (KBr) 1582 (m, w), 1541 (m), 1506 (s), 1441 (m, w), 1399 (m), 1359 (s), 1312 (m), 1256 (m), 1167 (s), 1153 (m), 1006 (m), 931 (m, w), 866 (m), 750 (s), 696 cm^{-1} (s).

Anal. Calcd for $C_{19}H_{18}ClNO_3SiS$: C, 56.50; H, 4.49; N, 3.47. Found: C, 56.59; H, 4.20; N,3.70.

Reaction of *trans*-β-Trimethylsilylstyrene (5) with CSI and Acid Work-up. CSI (1.66 g, 11.7 mmol) was added to a solution of 5[10] (2.00 g, 11.3 mmol) in carbon tetrachloride (10 ml) cooled to 0°. After 0.5 hr, the ice bath was removed and the solution stirred for an additional hour at room temperature. Carbon tetrachloride was removed under vacuum, the residual oil dissolved in acetone, and 0.1 *N* hydrochloric acid (1.6 ml) added. The reaction mixture spontaneously refluxed for 5 min. Water (10 ml) was added, the resulting mixture extracted with ether (150 ml), the ether layer separated and dried (sodium sulfate), and ether removed under vacuum which gave an oily white solid. Recrystallization from chloroform–cyclohexane gave *trans*-cinnamamide 7 (1.05 g, 63%): mp 146–148° (lit.[11] mp 148–148.5°); nmr ($CDCl_3$) δ 7.67 (d, J = 16 Hz), and 7.80–7.28 (m) (combined 6 H), 6.46 (d, 1 H, J = 16 Hz), 5.90 ppm (br, 2 H); mass spectrum (70 eV) m/e 147 (P^+). The ir spectrum corresponded exactly with an authentic spectrum of **14**.[12] Solvent was removed under vacuum from the mother liquor which gave *trans*-cinnamonitrile (0.17 g,): nmr ($CDCl_3$) δ 7.40 (s) and 7.36 (d, J = 17 Hz) (combined 6 H), 5.82 ppm (d, 1 H, J = 17 Hz); mass spectrum (70 eV) m/e 129 (P^+). The ir spectrum corresponded exactly with an authentic spectrum.[12]

Reaction of *trans*-β-Trimethylsilylstyrene (5) with CSI. A solution of 5 (2.00 g, 11.3 mmol) and carbon tetrachloride (10 ml) was cooled to 0° and CSI (1.66 g, 11.7 mmol) added. After 1.0 hr, the reaction mixture was warmed to room temperature at which time the ir spectrum showed the absence of CSI and 2960 [m, $Si(CH_3)_3$], 1628 (s, C=C), 1540 (s, C=N), 1450 (m, s, SiC), 1380 (s, SO_2 asym), 1185 cm^{-1} (s, SO_2 sym), assigned to **6**. Removal of carbon tetrachloride under vacuum gave a semisolid material (3.32 g, 9) which when washed with hexane gave white crystalline **6**: mp 72–74°; nmr (CCl_4) δ 7.93 (d, 1 H, J = 16 Hz), 7.77–7.36 (m, 6 H), 0.50 ppm (s, 9 H). Exposure of **6** to moisture led to formation of *N*-chlorosulfonylamide **8**.

Reaction of 6 with β-Phenethyl Alcohol. A solution of adduct **6** (11.3 mmol) and carbon tetrachloride was prepared in the usual way. To this a solution of β-phenethyl alcohol (1.07 g, 8.8 mmol) and carbon tetrachloride was added which led to immediate precipitation of *N*-chlorosulfonylamide 8 (2.18 g, 100%): mp 120–124°. Rapid recrystallization from acetone–hexane gave pure **8** as white microcrystals: mp 124–125° dec; nmr (acetone-d_6) δ 7.82 (d, J = 16 Hz) and 7.65–7.20 (m) (combined 6 H), 6.68 ppm (d, 1 H, J = 16 Hz); ir (KBr) 3185 (br, NH), 1704 (s, C=O), 1629 (s, C=C), 1456 (s, SO_2 asym), 1389 (m), 1202 (m), 1117 (s, SO_2 sym), 776 (m), 892 cm^{-1} (m).

The filtrate was distilled at atmospheric pressure until most of the carbon tetrachloride had been removed. Vacuum distillation of the residue and collection of a middle cut gave trimethylphenethoxysilane **9**, 0.68 g, 39%): bp 94° (12 mm) [lit.[13] bp 102° (18 mm)]. Further purification by gas chromatography (4 ft × ⅜ in., 3 SE-30 on Chromosorb W, column temperature 165°, flow rate 51 cc/min, retention time 14.8 min) resulted in collection of pure **9** as a colorless liquid: nmr (CCl_4) δ 7.14 (s, 5 H), 3.72 (t, 2 H, J = 7 Hz), 2.75 (t, 2 H, J = 7 Hz), 0.00 ppm (s, 9 H); mass spectrum (70 eV) m/e (rel intensity) 194 (trace, P^+), 179 (45, $P^+ - CH_3$), 103 [74, $CH_2OSi(CH_3)_3$], 73 [100, $Si(CH_3)_3$].

Hydrolysis of *N*-Chlorosulfonylamide 8. *N*-Chlorosulfonylamide 8 (0.48 g, 1.95 mmol) was dissolved in acetone (10 ml) and water (12 ml) added. This solution was gently refluxed for 5 min, followed by addition of 2 *N* sodium hydroxide until the solution was just basic to pH paper. Cooling the solution led to precipitation of *trans*-cinnamamide **7** (0.20 g, 70%). Recrystallization from chloroform–cyclohexane gave *trans*-cinnamamide **7** which was identical in every respect with the previously identified material.

Nmr Observation of the CSI-1,1-Dimethyl-2,5-diphenylsilole (1) Reaction in Deuteriochloroform. A solution of silole **1** (100 mg, 3.81 mmol) in deuteriochloroform (0.3 ml) contained in an nmr tube was cooled at 0°. To this a solution of deuteriochloroform (0.1 ml) and CSI (54 mg, 3.81 mmol) was added slowly with periodic shaking. Immediately upon addition, the solution exhibited a bright green color which slowly turned a brown-red color.

After warming to room temperature, the nmr spectrum exhibited aromatic H's and the following absorption was assigned to NCS β-lactam **10**: δ 7.31 (d, 1 H, J = 4 Hz), 5.44 (d, 1 H, J = 4 Hz), 0.58 (s, 3 H), 0.00 ppm (s, 3 H), along with a small singlet at δ 0.62 ppm assigned to imino lactam **3**. Examination of the nmr spectrum after 20 min showed no noticeable change. After 5 hr the δ 0.62 ppm singlet had increased in intensity relative to those at δ 0.58 and 0.00 ppm.

After standing overnight, bright yellow needles had precipitated. Filtration of the solution gave only **3**.

Low-Temperature Reduction of NCS β-Lactam 10. A solution of silole **1** (2.00 g, 7.62 mmol) and chloroform (14 ml) was cooled to 0°. To this CSI (1.08 g, 7.62 mmol) was added rapidly followed by removal of the cooling bath. After 2 hr an ir spectrum indicated all the CSI had reacted and exhibited only a band at 1812 cm^{-1} in the carbonyl region. The reaction mixture was cooled to −40° and thiophenol added (1.52 g, 15.2 mmol), followed by addition of a solution of pyridine (0.60 g, 7.62 mmol) and chloroform (4 ml) during a 0.5-hr period. The reaction mixture was slowly warmed to room temperature (*ca.* 4 hr), poured into chloroform (100 ml), and washed successively with 50-ml portions of saturated ammonium chloride, 1 sodium carbonate, water, and saturated sodium chloride. The organic layer was dried (calcium chloride) and chloroform removed under vacuum which gave a yellow oil which spontaneously crystallized. The resulting solid was washed with several portions of hot hexane which removed most of the diphenyl disulfide. The remaining solid was taken up in acetone, undissolved inorganic impurities were removed by filtration, acetone was removed under vacuum, and the resulting solid was recrystallized from chloroform–hexane which gave β-lactam **11** as a white solid (0.99 g, 43%). Further recrystallization gave pure **11**: mp 179–181°; nmr ($CDCl_3$) δ 7.37 (m, 10 H), 7.25 (br, 1 H), 7.08 (d, 1 H, J = 2.9 Hz), 4.69 (d, 1 H, J = 2.9 Hz), 0.55 (s, 3 H), −0.04 ppm (s, 3 H); ir (KBr) 3230 (m, NH), 3090 (w), 3000 (w), 2940 (w), 1746 and 1715 (s, C=O), 1255 and 791 cm^{-1} [m, $Si(CH_3)_2$]; ir ($CHCl_3$) ν_{CO} 1749 cm^{-1} (s); mass spectrum (70 eV) m/e (rel intensity) 305 (1), 304 (1.5), 263 (26), 262 (100).

Anal. Calcd for $C_{19}H_{19}NOSi$: C, 74.71; H, 6.27; N, 4.59. Found: C, 74.70; H, 6.24; N, 4.58.

Hydrogenation of 1,1-Dimethyl-2,5-diphenylsilole (1) over Palladium on Carbon. A suspension of silole 1 (2.50 g, 9.55 mmol), ethyl acetate (75 ml), and 105 palladium on carbon (0.40 g) was subjected to hydrogen gas. Progress of the hydrogenation was monitored by gas chromatography (10 ft × 0.25 in., 15% SE-30 on Chromosorb W, column temperature 250°, head pressure 40 psi) and stopped when the silole 1 peak disappeared (retention time 17.25 min). Two new peaks appeared in the ratio of 10 (retention time 13.75 min) to 1 (retention time 11.5 min). The catalyst was removed by filtration followed by removal of the ethyl acetate under vacuum which gave a yellow oil. Chromatography on silica gel with hexane resulted in separation of a residual amount of silole 1 and gave a mixture composed of 92% (from nmr) silacyclopentene (14) and 1,1-dimethyl-2,5-diphenylsilacyclopentane: nmr (CCl_4) for **14** δ 7.6–6.7 (m), 3.25–2.45 (m, 3 H), 0.30 (s, 3 H), −0.08 ppm (s, 3 H); irradiation at 421 Hz caused a dramatic change in the 3.25–2.45-ppm region; high-resolution mass spectrum calculated for $C_{18}H_{20}Si$, m/e 264.133; found, 264.132.

Conversion of Silacyclopentene (14) to Epoxide 16. A mixture containing 92% silacyclopentene (14) and 1,1-dimethyl-2,5-diphenylsilacyclopentane (0.10 g, 0.34 mmol) was added to a stirred solution of 85% *m*-chloroperbenzoic acid (0.065 g, 0.32 mmol) and chloroform (3 ml). The resulting solution was stirred overnight at room temperature, the precipitated *m*-chlorobenzoic acid was removed by filtration, and the resulting solution was washed successively with 10% sodium bicarbonate (2 × 5 ml), water (5 ml), and saturated sodium chloride (3 ml). This solution was dried (calcium chloride) and chloroform removed under vacuum which gave a light yellow oil (0.08 g). Preparative thick-layer chromatography (silica gel PF_{254}, 1 ether–hexane, 20 × 20 cm plate) led to observation of three bands: band 1, origin; band 2, 6.5 cm; band 3, 9.2 cm. Recovery of band 2 gave an oil which spontaneously crystallized. Three recrystallizations from hexane gave epoxide **16** as a white solid: mp 75–77°; nmr (CCl_4) δ 7.30–6.80 (m, 10 H), 3.37 (narrow m, 1 H), 2.40 (m, 3 H), 0.27 (s, 3 H), 0.05 (s, 3 H); ir (KBr) 3065 (w), 3030 (w), 2925 (w, m), 2855 (w), 1600 (m), 1498 (s), 1450 (m), 1407 (m), 1255 (m), 1221 (m), 1135 (w), 1081 (m), 1030 (w, m), 955 (w), 909 (m), 880 (w), 842 (s), 804 (s), 789 (s), 761 (s), 751 (m, s), 702 cm^{-1} (s); mass spectrum (70 eV) m/e (rel intensity) 280 (64), 265 (32), 206 (64), 189 (100), 165 (26); mass spectrum (16 eV) m/e (rel intensity) 280 (100), 206 (16), 189 (20), 165 (13); high-resolution mass spectrum calculated for $C_{18}H_{20}OSi$, m/e 280.1278; found, 280.1276.

Attempted Reaction of 1,1-Dimethyl-2,5-diphenylsilacyclopent-2-ene (14) with CSI. A solution of 9 silacyclopentene (**14**, 0.135 g, 0.510 mmol) and deuteriochloroform (0.3 ml) was placed in an nmr tube. Freshly distilled CSI (0.073 g, 0.516 mmol) was added to the contents of the tube which were shaken vigorously. An nmr spectrum immediately after addition showed that no reaction had occurred. The tube was then heated at 75° and spectra were recorded at 1.8- and 24-hr intervals. No change in the spectra was detected.

The purity of the CSI used in the above reaction was checked by the following procedure. A solution of 2-methyl-2-butene (0.70 g, 90.6 mmol) and deuteriochloroform (0.3 ml) was placed in an nmr tube and CSI (0.129 g, 0.91 mmol) added. The nmr showed no remaining starting olefin but only the nmr of 1-(chlorosulfonyl)-3,4-trimethyl-2-azetidinone:[14] nmr δ 3.32 (q, 1 H, J = 7 Hz), 1.79 (s, 3 H), 1.67 (s, 3 H), 1.33 ppm (d, 3 H, J = 7 Hz).

Acknowledgment. The authors are indebted to the U.S. Public Health Service, National Institutes of Health, for their generous support of this research (Research Grant GM 16689).

Registry No.—**1**, 7688-03-1; **3**, 53684-33-6; **5**, 19372-00-0; **6**, 53684-34-7; **7**, 22031-64-7; **8**, 53684-35-8; **9**, 14629-58-4; **10**, 53684-36-9; **11**, 53684-37-0; **14**, 53684-38-1; **16**, 53684-39-2; CSI, 1189-71-5; *trans*-cinnamonitrile, 1885-38-7; β-phenethyl alcohol, 60-12-8.

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Mercuric Ion Catalyzed Rearrangements of Ten-Membered-Ring Allenes[1]

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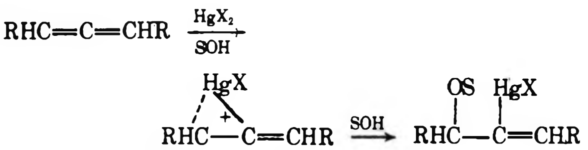
In contrast to most oxymercurations, the reactions of cyclodeca-1,2,5,8-tetraene, **3**, and cyclodeca-1,2,5-triene, **7**, with mercuric sulfate and acetic acid give only rearranged products. The major products from **3** are *cis,syn*-decalin-2-yl acetate, **4**, and tricyclo[4.4.0.0^{2,4}]deca-5,8-diene, **6**. Compound **7** gives only tricyclo[4.4.0.0^{2,4}]dec-5-ene, **8**. The ratio of products for **3** depends on solvent nucleophilicity.

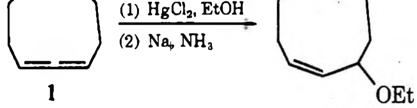
Oxymercuration is often used to effect Markovnikov addition of solvent to double bonds without rearrangement.[2-4] In the case of nonterminal allenes, mercuric ion generally adds to give a mercurinium ion that is attacked by solvent so that the mercury is ultimately attached to the center allene carbon (eq 1).[5-7] The mercury group can be



(1)

reductively removed[4] or is often lost during reaction under acidic conditions by an addition–elimination mechanism.[7] Allene oxymercuration represents an important part of a general technique for ring expansion and functionalization of medium-sized rings.[8]

The cases herein reported are the only known examples of rearrangement during oxymercuration of an allene. The most closely related system studied is cyclonona-1,2,6-triene (**1**) that was reported[9] to give only the normal adduct, **2**.



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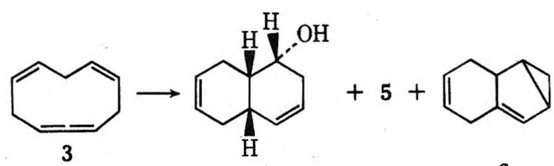
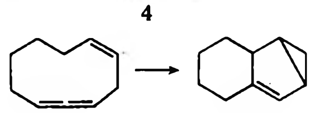
Results

Cyclodeca-1,2,5,8-tetraene (**3**) was prepared from cyclonona-1,4,7-triene[10] by the method which involves addition of a dibromo carbenoid and subsequent conversion to the allene using methyllithium.[8] Cyclodeca-1,2,5-triene (**7**) was prepared in a similar way from 1,4-cyclononadiene.[11]

Treatment of **3** with mercuric sulfate in acetic acid followed by reduction with lithium aluminum hydride did not lead to the expected allylic alcohol but to two rearranged alcohols, **4** and **5**, and a rearranged hydrocarbon, **6**. Similar



3 4 6



7 8

treatment of **7** gave only rearranged hydrocarbon **8**. The carbon skeleton and stereochemistry of **4** were assigned by reduction to the known *cis,syn*-decalin-2-ol.[12] The locations of the double bonds were determined by spreading out the proton magnetic resonance spectra with Eu(fod)$_3$ shift reagent[13] and then performing decoupling experiments. The changes in chemical shift of the various protons with added shift reagent (Table I) are consistent with the assigned structure **4**. Furthermore the H_3 methylene protons were shown to be coupled to H_2 and one vinyl proton (H_4) which locates one double bond. The H_1 proton was shown to be coupled with H_2 and the H_{10} methylene pair. Coupling was also demonstrated between the H_{10} protons and a vinyl proton (H_9) which locates the other double bond. (See Figure 1.)

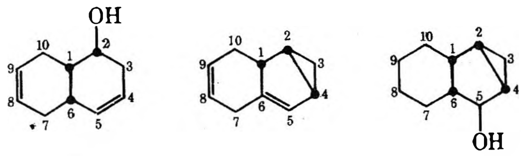
The structure of the minor alcohol product **5** was not fully elucidated, but hydrogenation followed by oxidation to the ketone gave *cis*-bicyclo[5.3.0]decan-2-one.

Reduction of either hydrocarbon **6** or **8** gave *cis*- and *trans*-decalin. Other reactions of **6** such as ozonolysis, oxymercuration, epoxidation, and hydroboration gave intrac-

Table I
Chemical Shifts for *cis,syn*-Bicyclo[4.4.0]deca-4,8-dien-2-ol (*cis,syn*-Decalin-2-ol) with Added Shift Reagent[a]

Added $Eu(fod)_3$	H_2	H_3	H_4 H_5	H_6 H_7	H_8 H_9	H_{10} H_1
0	4.0	2.5	(5.3–5.9)	(1.9–2.3)	(5.3–5.8)	(1.9–2.3)
5	5.2	3.0	(5.4–5.9)	(2.0–2.8)	(5.4–5.9)	(2.0–2.8)
25	7.9	5.1, 4.8	6.3 6.0	3.4 2.6	6.0 6.3	(4.0–4.7)
70	13.1	9.2, 8.0	7.0 6.6	4.6 3.3	6.6 7.0	(6.8–7.7)
100	16.5	11.6, 9.9	8.0 7.4	5.3 3.7	6.9 7.7	9.3, 9.4 8.6

[a] The protons are numbered according to the carbon to which they are attached (see Figure 1). The chemical shift is given in δ.



4 6 10

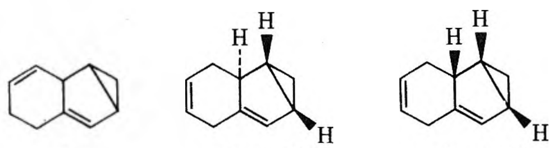
Figure 1. Numbering used for **4** and **6** and **10**.

Table II
Chemical Shifts for *cis,syn,cis*-Bicyclo[4.4.0.0^{2,4}]decan-*anti*-5-ol with Increasing Amounts of $Eu(fod)_3$ Shift Reagent[a]

H_5	H_6	H_4	H_1	H_2	*endo*-H_3	*exo*-H_3
3.9	*b*	*b*	2.7	*b*	0.6	0.5
5.9	*b*	*b*	3.6	*b*	1.1	0.8
10.0	6.4	5.8	5.8	3.5	2.2	1.8
11.6	7.4	6.7	6.7	4.0	2.8	2.1
12.6	8.2	7.5	7.2	4.4	3.1	2.3
15.9	10.4	9.8	8.8	5.4	4.0	2.8
17.0	11.2	10.6	9.3	5.7	4.3	3.1

[a] The protons in the six-membered ring are not shown. In the final entry they had separated into two four-proton groups at δ 4.3 and 3.1. [b] Buried in a large multiplet.

table material or complex product mixtures. The structure was assigned from its spectral data. The chemical shifts and coupling patterns of the cyclopropyl protons are similar to those of bicyclo[3.1.0]hex-2-ene[14] (see Experimental Section) which locates the cyclopropane ring and one double bond. The ultraviolet spectra, which shows only end absorption, rules out any conjugated isomers. This leaves two possible positions for the other double bond which are shown in structures **6** and **9**. For compound **9**, the chemical



9 *cis, anti*-**6** *cis, syn*-**6**

shifts for the five protons which are nonvinyl and noncyclopropyl should appear as a group of four protons near δ 2.2 and one proton near δ 3.1. The observed chemical shifts for the compound that has been assigned as **6** are quite different, *viz.*, one proton near 3.0, a rather sharp two-proton peak at 2.8, a proton at 2.5, and one hidden in the δ 1.4–2.0 group of cyclopropyl protons. The δ 2.8 pattern is presumably due to the doubly allylic protons (H_7). The other three protons are near the rather strongly anisotropic cyclopropyl group. Using the reported shielding effects for that group,[15] the calculated chemical shifts for the allylic methylene and methine protons are δ 2.1, 2.3, and 2.4 for the cis,anti isomer and 1.6, 2.1, and 2.8 for the cis,syn isomer. The cis,syn isomer agrees reasonably well with the observed values (*ca.*, 1.7, 2.5, and 3.0). In the calculated chemical shifts, it was assumed that in the absence of cyclopropane anisotropy, the methylene protons' chemical shifts would be like cyclohexene (δ 2.0) and that of the methine proton would be δ 0.3 down field of cyclopentene ($2.3 + 0.3 = \delta\ 2.6$).[16]

Structure **8** was initially assigned by analogy with **6** and from the nmr spectrum which showed two high-field cyclopropyl protons and one vinyl proton. Confirmation of the structure and assignment of stereochemistry was obtained by conversion of **8** to **10** (see Figure 1) by hydroboration. Treatment of **10** with $Eu(fod)_3$ shift reagent separated the protons at C_1 to C_6 from the other protons in the spectrum.

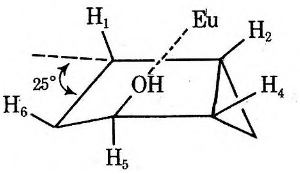
Proton H_5 appeared as a rather sharp singlet in agreement with previous studies of a similar system, *syn*-3-deuterium–*anti*-2-bicyclo[3.1.0]hexanol,[14] and with the model which showed dihedral angles close to 90° between H_5 and its neighboring protons. No clear decoupling could be done with H_5 but the $Eu(fod)_3$ shift studies showed that one of the two closest protons to H_5 was a cyclopropyl proton (H_4) since decoupling established that it was coupled with the high-field cyclopropyl protons. Similar decoupling located H_2 which in turn was shown to be coupled with the proton (H_1) that has a shift of 2.75 in the unshifted spectrum. That proton appears at unusually low field because of the rather strong anisotropy of the cyclopropane ring.[15] Decoupling also established the link between H_1 and the other "closest proton to H_5."

The cis,syn,cis stereochemistry for **10** has been assigned from the small coupling constants to H_5 and from the chemical shift changes when $Eu(fod)_3$ was added (Table II). Inspection of Drieding models indicates that only the assigned stereochemistry should have dihedral angles of about 90° between H_5 and both its neighbors. In addition, the distances between the europium (assumed to be 2.1 Å on the C–O axis[17]) and protons H_1, H_2, H_3, H_4, and H_6 could be fitted for that stereochemistry and not for the others. Using H_2 to calculate a proportionality constant for the equation $r^3 = k\Delta\delta$, the other distances were calculated. When the boatlike conformation of the five-membered ring (**11**) was used, all the calculated distances were within 0.1 Å of those measured from the model except *endo*-H_3 which differed by 0.3 Å. All of the other possible stereochemistries had at least one proton that was off by at least 1.0 Å. The only other stereochemistry that could concievably have near-zero couplings to H_5 is trans,anti,cis as shown in **12**. The chemical shifts for **12** do not correlate well, espe-

Table III
Products[a] Formed from *cis,cis*-Cyclodeca-1,2,5,8-tetraene (3)

		Relative percentages				
Conditions[b]	% yield	4	5	6	*epi*-4	13
HCO_2H, $HgSO_4$	19	63	14	11	<2	2[c]
HCO_2H	24	53	12	0	4[c]	14
HOAc, $HgSO_4$	52	43	3	54	<2	
HOAc, Hg-$(OAc)_2$	47	50	5	45	<2	
60% aq acetone, $HgSO_4$	67	88	6	6	<2	1[c]

[a] The products were reduced with lithium aluminum hydride prior to glc analysis. [b] Trifluoroethanol–mercuric sulfate gave a 75% yield of products of which 70% was **6**. The remainder was a mixture of trifluoroethyl ethers some of which may have arisen from reaction of **6** in this media. [c] Identified by retention time comparison only.



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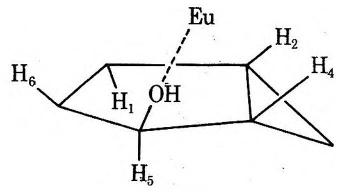

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cially H_1 which is off by *ca.* 1.8 Å. The stereochemistry established for **10** means that **8** must have the cis,syn stereochemistry and that the hydroboration takes place cis on the convex face as expected.

When the reactions were performed in deuterated acetic acid, deuterium was incorporated into the C_5 position of **4**. The location of the deuterium was determined using $Eu(fod)_3$ shift reagent as before (Table I). The mass specta and nmr spectra of hydrocarbons **6** and **8** showed that no deuterium was incorporated into that product.

For compound **3**, changing solvent dramatically changed the ratio of products (Table III). Thus in aqueous acetone the alcohols **4** and **5** are strongly favored whereas in trifluoroethanol hydrocarbon **6** predominates. The products were shown to be reasonably stable to the reaction conditions in aqueous acetone, acetic acid, and trifluoroethanol. If left for longer times, the products did not interconvert but **6** formed nonvolatile products. Hydrocarbon **6** was found to be quite unstable in formic acid so that the ratio shown in Table III probably underestimates considerably the amount of **6** that is actually formed.

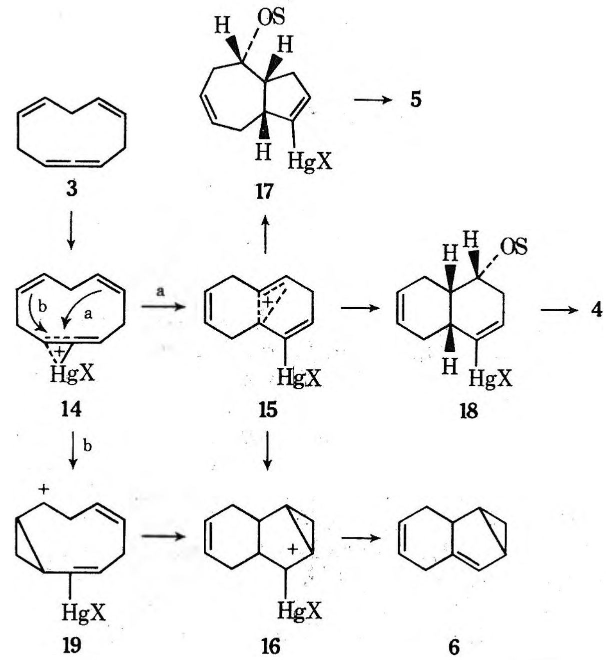
For compound **3**, mercuric sulfate and mercuric acetate were used as catalysts and gave similar results. With compound **7**, mercuric chloride gave somewhat higher yields than mercuric sulfate and mercuric acetate and mercuric trifluoroacetate a somewhat lower yield. A fivefold increase in catalyst increased the rate approximately fivefold for both **3** and **7**.

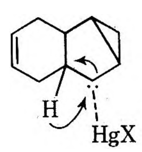
Allene **3** reacts with formic acid in the absence of mercuric catalyst, but at a much slower rate to give the same alcohols **4** and **5** (Table III) plus the epimer of **4** (*epi*-**4**) and *cis,cis,cis*-2,5,8-cyclodecatrienol (**13**). The structures of *epi*-**4** and **8** were determined by glc retention time and mass spectral comparison with an *epi*-**4** sample prepared from **4** and an authentic sample[18] of **8**. Without mercuric catalyst, no hydrocarbon **6** was observed.

Discussion

Scheme I accounts for the observed data. Earlier work[5–7] suggests initial formation of a mercurinium ion **14**. Transannular participation (path a) would give **15** which can be captured by solvent to give **17** or **18**. The mercury group can then be lost by an addition–elimination mechanism as described previously,[7] which is consistent with the incorporation of deuterium at C_5 in **4** when the reaction is run in deuterated acetic acid. Homoallyl–cyclopropyl carbinyl rearrangement of **15** leads to **16** which can be considered to be a "metal-complexed-carbene–metal-carbocation"[19] intermediate, **20**. Alternatively, homoallyl–cyclopropyl carbinyl rearrangement of **14** (path b) could give **19**, which could then undergo transannular rearrangement also leading to **16**. Species such as **16** are known to undergo hydride shifts as shown[19] (see **20**) which accounts for the lack of deuterium incorporation into **6**. Intermediate **16** could also be drawn as a delocalized ion (**21** or **22**) that could lead to **4** (*via* **18**) as well as **6**. A single species combining **15** and **21** is also possible (see below).

Scheme I





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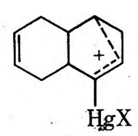

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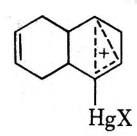

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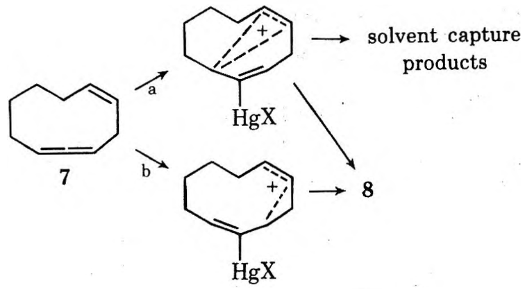
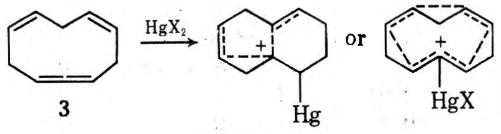
The change in product ratio with changing solvent correlates with solvent nucleophilicity. This supports Scheme I that postulates a competition between intramolecular rearrangement and solvent capture. Thus the solvent capture products **4** and **5** are dominant in the most nucleophilic solvent[20] used, 80% aqueous acetone, whereas hydrocarbon **6** prevails in the highly nonnucleophilic solvent trifluoroethanol[21] (see Table III). The product mixture is about equally split in acetic acid, the solvent with intermediate nucleophilicity. The product ratio in formic acid does not seem to fit into the solvent nucleophilicity correlation but this is probably because hydrocarbon **6** is not stable to that media. It is interesting that no **6** is observed in formic acid without mercuric salt added which supports the postulate that the mercury group plays a vital role in the formation of **6**.

The formation of hydrocarbon **8** from allene **7** could take place in the same way that hydrocarbon **6** forms from **3**. It is not completely clear why no solvent capture products

Scheme II



form. One possible explanation is that the conformation needed for path a in Scheme I is much more favorable for **3** than for **7**; however, models did not give a clearcut indication that this is the case. Another possibility is that the double bond strongly directs the initial attack of mercuric ion for **7**. Thus attack at one end of the allene **7** would lead to transannular participation (path a, Scheme II) which should give some solvent capture products whereas attack at the other end (path b) leads to **8**.[22] Earlier work suggests that homoallylic participation[23] should be favored relative to transannular participation.[24] The case for **3** is quite different since the system is symmetric so that addition at either end leads to a species that can simultaneously utilize both double bonds and might be thought of as a bishomopentadienyl cation, **23**, which can readily lead to either **15** or **19** and subsequently to the observed products. Conceivably a trishomotropilium species **24** could be formed. Such a species would be homoaromatic[25] but there is no evidence which demands such a species.



Experimental Section

General. Spectral measurements utilized Beckman IR-8, Cary Model 15, Varian Associates HA-100, Atlas CH7, and CEC 110B.[26] Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium or Chemalytics Inc. Analytical gas liquid chromatography (glc) utilized a Varian Aerograph Model 1200 instrument with flame ionization detector and the following columns: (A) 0.01 in. × 75 ft DEGS capillary, (B) 0.01 in. × 150 ft TCEP capillary, (C) 0.01 in. × 100 ft, Carbowax 1000 capillary, (D) 0.125 in. × 7 ft; 2.5% KOH–2.5% Carbowax 4000 on Chromosorb W, (E) 0.125 in. × 32 ft, 10% Carbowax 20M–1% XF1150 on 60–80 firebrick.

***cis,cis,cis*-1,4,7-Cyclononatriene**[27] was prepared from a mixture of 1,3,5- and 1,3,6-cyclooctatrienes as outlined earlier[10] except that the thermal rearrangement was carried out by heating in a flask under nitrogen at 180° for 5.5 hr.[28] The desired product was separated by adding 50 g of the product mixture to a solution of 120 g of silver nitrate, 120 ml of water, and 80 ml of 95% ethanol and stirring for 2 hr. The solid silver complex[29] was collected by filtration and washed thoroughly as follows: 2:1 ethanol–water (3 × 25 ml), water (2 × 40 ml), 95% ethanol (1 × 40 ml), and pentane (5 × 15 ml). Each washing was carried out by transferring the solid to a beaker, stirring the solid with the wash liquid, and collecting the solid by filtration.

The solid complex was added to 100 ml of concentrated ammonium hydroxide and 50 ml of water and then the mixture was extracted with pentane. Drying ($MgSO_4$) and removal of pentane gave 9.7 g of *cis,cis,cis*-1,4,7-cyclononatriene. Glc analysis on column A indicated that it was 97% pure. The spectra and melting point, 47–48° (lit.[10] 49.5–50.0°), agree with those reported.

***cis,cis,cis*-10,10-Dibromobicyclo[7.1.0]deca-3,6-diene.** A solution of 10 g (0.09 mol) of *cis,cis,cis*-1,4,7-cyclononatriene in 40 ml of pentane was stirred with a mechanical stirrer and chilled in an ice–salt bath, while 10 g of potassium tertiary butoxide was added under nitrogen (solution turns amber color), followed by 6.6 ml of bromoform which was added dropwise over 4.5 hr. At the end of the bromoform addition, 10 ml of water and 10 ml of pentane were added and the brown solid was filtered off. The filtrate was washed three times with water and once with saturated salt solution. After drying over sodium sulfate, the solvent was removed and the crude brownish solid was distilled under vacuum (bp 100° at 0.6 mm) yielding 6.5 g of the desired monoadduct. Crystallization from ether–pentane gave pure mono adduct: mp 57.5–58.5°; ir (CCl_4) 3010, 1470, 1110, 880, 710; nmr (CS_2, δ) 5.2–6.0 (m, 4), 2.9–3.6 (m, 1), 2.0–2.7 (m, 5), 1.5–1.9 (m, 2).

Anal. Calcd for $C_{10}H_{12}Br_2$: C, 41.11; H, 4.14. Found: C, 41.13; H, 4.19.

***cis,cis*-Cyclodeca-1,2,5,8-tetraene (3).** A solution of 3 g of the above dibromide in 8 ml of ether was stirred and chilled with Dry Ice–acetone cooling and 8 ml of 1.75 *M* methyllithium was added over 30 min under nitrogen. The temperature was then raised to −40° for 40 min and then 2 ml of water was added at 0°. The reaction mixture was washed with water until it was neutral to litmus. The ether layer was dried over magnesium sulfate. Removal of the solvent gave 1.8 g of yellowish liquid which was vacuum distilled which gave 1.1 g (78% yield) of the desired allene: ir ($CHCl_3$) 3000, 1965, 1445, 910, 880, 815, 700 cm^{-1}; nmr (CCl_4, δ) 5.3–5.7 (m, 4) 4.8–5.3 (m, 2), 2.5–2.9 (m, 6).

Anal. Calcd for $C_{10}H_{12}$: C, 90.91; H, 9.09. Found: C, 90.76; H, 8.94.

9,9-Dibromobicyclo[6.1.0]non-2-ene. A 42-g (0.374 mol) portion of potassium *tert*-butoxide, was placed in a flask under nitrogen and was cooled with an ice–salt bath. A solution of 53.4 g of 1,3-cyclooctadiene (0.48 mol) in 100 ml of dry pentane was added to the flask in one portion. Bromoform, (84 g, 29.6 ml, 0.332 mol) was added dropwise with stirring over a period of 1 hr (color changed from light yellow to brown). At the completion of the addition, the cooling bath was removed, the flask was allowed to come to room temperature, and stirring was contined at room temperature for 18–20 hr. Water was added (100 ml), followed by sufficient hydrochloric acid, to render the solution neutral. The organic layer was separated, and the aqueous layer was extracted with pentane (3 × 30 ml). The combined pentane solutions were washed with (3 × 30 ml) water, then dried over anhydrous magnesium sulfate and filtered, and the solvent was removed by rotary evaporation. The residue (98.9 g) was vacuumed distilled affording 54.3 g (58% yield based on bromoform) of slightly yellow liquid 9,9-dibromobicyclo[6.1.0]non-2-ene: bp 110–115° (3 mm) (lit.[30] bp 86° (0.3 mm)); ir (neat) 3020, 2950, 2890, 1450, 1420, 1165, 1085, 765, 740, 710, and 668 cm^{-1}; nmr (CCl_4, δ) 5.82 (m, 1), 5.30 (d, J = 10 Hz, 1), and 1.0–2.5 (m, 10).

Bicyclo[6.1.0]non-2-ene.[31] A solution of 15 g (0.65 mol) of sodium in 250 ml of liquid ammonia was prepared. Then 27.2 g of 9,9-dibromobicyclo[6.1.0]non-2-ene in 50 ml of dry ether was added dropwise over a period of 1.5 hr. The reaction was vigorous. Stirring and low temperature was maintained for another hour, then 23 g of ammonium chloride was slowly added to terminate the reaction. The liquid ammonia was allowed to evaporate. The reaction mixture was extracted into 100 ml of ether which was subsequently washed with water and 10% aqueous solution of HCl until rendered neutral. The ether solution was dried ($MgSO_4$), concentrated, and vacuumed distilled to give 6.1 g (52% yield) of clear liquid bicyclo[6.1.0]non-2-ene: bp 50° (5 mm); ir (neat) 3060, 3000, 2930, 2860, 1450, 1120, 1030, 850, 845, 700, and 600 cm^{-1}; nmr (CCl_4, δ) 5.3–5.9 (m, 2), 0.5–2.6 (m, 11), and −0.2 (q, J = 4 Hz, 1); mass spectrum m/e (rel intensity) 122 (20), 121 (5), 94 (26), 93 (56), 92 (5), 91 (22), 81 (56), 80 (78), and 79 (100).

1,4-Cyclononadiene.[11] Bicyclo[6.1.0]non-2-ene (6.1 g) was refluxed for 10 hr in a silicon oil bath (temperature range 150–170°) under nitrogen. Vacuum distillation gave (5.3 g, 89% yield) 1,4-cyclononadiene as a clear liquid: bp 90° (78 mm); ir (neat) 3030, 2940, 2880, 1465, 1440, 878, 815, 740, 720, and 708 cm^{-1}; nmr (CCl_4, δ) 5.2–5.6 (m, 4), 2.8 (m, 2), 2.2 (m, 4), and 1.5 (m, 4); mass spectrum m/e (rel intensity) 122 (4), 121 (16), 120 (4), 95 (4), 94 (20), 93 (36), 92 (8), 91 (24), 82 (4), 81 (52), 80 (60), 79 (100), 78 (12), and 77 (36).

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.32; H, 11.66.

10,10-Dibromobicyclo[7.1.0]dec-3-ene. The dibromo carbenoid addition was carried out in essentially the same way as above using 4.2 g (0.0374 mol) of potassium *tert*-butoxide, 3.48 g (0.0284 mol) of 1,4-cyclononadiene, 10 ml of pentane, and 5.02 g (0.0337 mol) of bromoform. This gave, after vacuum distillation, 4.0 g (48.7% yield) of slightly yellow liquid 10,10-dibromobicyclo[7.1.0]dec-3-ene: bp 110° (1.7 mm); ir (film) 3020, 2940, 2870, 2860, 1650, 1475, 1450, 1240, 1210, 1120, 1080, 1060, 1030, 1015, 975, 960, 900, 860, 830, 815, 780, 745, 735, and 705 cm^{-1}; nmr (CCl_4, δ) 5.15–5.81 (m, 2) and 0.79–2.63 (m, 12).

Anal. Calcd for $C_{10}H_{14}Br_2$: C, 40.85; H, 4.80; Br, 54.35. Found: C, 40.45; H, 4.62; Br, 54.89.

1,2,5-Cyclodecatriene (7). A solution of 1.09 g (0.0347 mol) of 10,10-dibromobicyclo[7.1.0]dec-3-ene in 2 ml of ether was cooled under nitrogen to −70° by a Dry Ice–Acetone bath and 2 ml of methyllithium (2 *M* in ether) was added over a period of 45 min. The temperature of the reaction was gradually brought up to 0° and 1 ml of water was added to terminate the reaction. The reaction mixture was extracted into ether which was washed repeatedly with dilute 10% aqueous HCl (5 × 5 ml) until neutral. The ether layers were dried over magnesium sulfate and then concentrated. Bulb-to-bulb vacuum distillation afforded 206 mg of allene (42% yield): bp 90° (10 mm); ir (neat) 3000, 2965, 2915, 2845, 1950, 1470, 875, 850, 825, 800, 780, 730, 710, and 685 cm^{-1}; nmr (CCl_4, δ) 5.14–5.90 (m, 4) and 0.9–3.1 (m, 10); mass spectrum *m/e* (rel intensity) 134 (5), 133 (10), 132 (3), 121 (4), 120 (25), 107 (5), 106 (20), 105 (40), 94 (24), 93 (40), and 92 (100); exact mass 134.108 (calcd for $C_{10}H_{14}$, 134.110)

Oxymercuration Reactions on Cyclodeca-1,2,5,8-tetraene (3). (a) Mercuric Sulfate and Acetic Acid. In a typical experiment, a mixture of 65 mg of the allene, 5 mg of mercuric sulfate, and 1 ml of glacial acetic acid was stirred at room temperature. The reaction was followed by glc (column D) and was normally complete after 30 min. At the end, 15 ml of ether was added and the reaction mixture was filtered to remove unreacted mercuric sulfate. The ether layer was washed twice with water and twice with saturated sodium bicarbonate solution and dried over magnesium sulfate. The dried ether solution was stirred at least 30 min with 65 mg of lithium aluminum hydride.[32] Then 20% Rochell salt solution was added and the ether layer was decanted off, washed with water, and dried over magnesium sulfate. Most samples were analyzed by glc at this stage (columns A and D). In some cases, the mixture was chromatographed on 5 ml of SilicAR using pentane to elute the hydrocarbon 6 and 20% ether–pentane to elute the alcohols 4 and 5. This gave 18.2 mg (28%) of **6**: ir (CCl_4) 3060, 3020, 2900, 2840, 1440, 1420, 1330, 1245, 1035, 1023, 1005, 940, 860, 660 cm^{-1}; uv, end absorption only; nmr (CCl_4, δ) 5.4–5.7, (m, 3), 2.3–3.1 (m, 4), 1.4–2.0 (m, 3), 0.5 (t of d, J = 8 and 4 Hz, 1), −0.1 (q, J = 4 Hz, 1).[33]

Anal. Calcd for $C_{10}H_{12}$: C, 90.91; H, 9.09. Found: C, 90.81; H, 8.94.

The alcohol fraction, 16.5 mg (23%), was recrystallized from ether–pentane to give pure **4**: mp 83.5–84.5°; ir (CS_2) 3020, 2900, 2840, 1080, 1040, 735, 670, 660; nmr (see Table I).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.18; H, 9.44.

(b) Stability of Products. A 10-mg sample of the acetate from part (a) above was stirred in 0.5 ml of acetic acid and 3 mg of mercuric sulfate for 5.5 hr. The reaction was followed by gas chromatography. There was no conversion to hydrocarbon **6**. The same stability test was done on hydrocarbon **6**. After 4 hr no conversion to acetate was observed. When the hydrocarbon was stirred in formic acid with mercuric sulfate, *ca.* 80% of the hydrocarbon disappeared, but no formate was observed to form.

(c) Other Solvents for Oxymercuration. The same conditions as given in part (a) were successfully used with trifluoroethanol, 85% formic acid, deuterated acetic acid, and 60% aqueous acetone. The speed of reaction was as in the order given with reaction being slowest in 60% aqueous acetone. Dioxane was also tried but gave no products after 2 hr.

(d) Mercuric acetate catalyst was used in place of mercuric sulfate in procedure a. Neither catalyst always went completely into solution.

(e) Reaction with 85% Formic Acid. The procedure was as in part (a) except with no catalyst. The reaction was at least ten times slower than the catalyzed conditions in part b.

Hydrogenation of 6 or 8. Either hydrocarbon 6 or 8 was hydrogenated over Adams catalyst in acetic acid at 1.5 atm of pressure overnight. Two of the products were found to have identical glc retention times (column E) and mass spectra as *cis*- and *trans*-decalin. A third product (10%) was not identified.

Hydrogenation of 4 was carried out in ether over Adams catalyst which gave *cis,syn*-bicyclo[4.4.0]decan-2-ol. The melting point 86–89° (lit.[12] 93°), infrared and nmr spectra, and melting point of the acid phthalate derivative, 169–170° (lit.[12] 176°), agreed with those of an authentic sample.[12]

Identification of 5. The crude mixture of alcohols 4 and 5 as hydrogenated as above and oxidized with Jones reagent. The retention times of the ketones corresponding to 4 and 5 were the same as *cis*-bicyclo[4.4.0]decan-2-one and *cis*-bicyclo[5.3.0]decan-2-one, respectively (columns B and C), and their mass spectra were the same as those for authentic samples.[34]

Reaction of Cyclodeca-1,2,5-triene (7). (a) Mercuric Acetate. In a typical experiment, 205 mg (1.53 × 10^{-3} mol) of allene 7 and 100 mg of tetralin standard in ether was concentrated under nitrogen. A solution of 2 ml of glacial acetic acid containing 96 mg (3.06 × 10^{-4} mol) of mercuric acetate was added (mole ratio of allene to catalyst was 5:1). The reaction was complete after 30 min (as indicated by glc) and was extracted into ether which was mixed with water then with 10% aqueous $NaHCO_3$ (5 × 4 ml). The ether layer was then dried over magnesium sulfate and concentrated by a gentle flow of nitrogen. The only product found was hydrocarbon 8 (110 mg based on internal standard tetralin, 55% yield). The hydrocarbon was isolated by liquid chromatography, on silicAR using dry pentane as elutant or by gas chromatography. Either procedure gave 8 that showed a single peak on glc: ir (CCl_4) 3080, 3060, 3025, 2980, 2920, 2845, 1950, 1800, 1480, 1440, and 1030 cm^{-1}; nmr (CCl_4, δ) 5.4 (s, 1), 2.6 (m, 1), 0.8–2.5 (m, 10), 0.6 (t of d, J = 4 and 7 Hz, 1), and 0.0 (q, J = 4; 1); mass spectrum *m/e* (rel intensity) 134 (25), 133 (7), 120 (4), 119 (21), 105 (18), 104 (29), 103 (4), 92 (18), 91 (36), 90 (100), 78 (18), 77 (22), and 76 (18); exact mass 134.108 (Calcd for $C_{10}H_{14}$, 134.110).

A plot of log A_0/A (A = concentration of allene) *vs.* mercuric acetate concentrations of 4, 6, 8, and 12 mg/ml gave a straight line plot.

(b) Product Stability. When 30 mg of 8 was stirred with 10 mg of tetralin standard, 4 mg of mercuric acetate, and 1 ml of acetic acid, the amount of 8 decreased slowly (27 mg left after 1 hr, 15 mg left after 12 hr). No volatile products were observed.

(c) Other Mercuric Catalysts. The reaction was carried out under the same conditions as above with mercuric sulfate, mercuric chloride, and mercuric trifluoroacetate which give yields of 53, 72, and 34%, respectively.[35]

(d) Mercuric acetate and deuterated acetic acid gave 8 with no deuterium incorporation.

***cis,syn,cis*-Tricyclo[4.4.0.0^{2,4}]decan-*anti*-5-ol (10).** A solution of 0.73 g (5.5 mmol) of allene, 110 mg (0.4 mmol) of mercuric chloride, and 10 ml of acetic acid was stirred at room temperature for 1 hr during which time the color changed from purple to brown and the reaction appeared to stop at about 60% reaction. An additional 100 mg of mercuric chloride was added which completed the reaction in 20 min. A 50-ml portion of ether was added and the mixture was extracted with saturated sodium bicarbonate until neutral. The solution was dried ($MgSO_4$) and concentrated to about 7 ml of solution (8 tends to polymerize easily when all solvent is removed). The hydroboration was carried out with 7 ml of 0.5 *M* diborane in THF according to the procedure of Zweifel and Brown.[37] Kugelrohr vacuum transfer at 0.1 mm gave 0.4 g of clear oil which glc indicated was 75% **10** (37% overall yield). Purification by glc (10% DEGS) gave pure **10**: ir (CCl_4) 3680, 3400, 3030, 2930, 2870, 1450, 1040, 1020, and 1000 cm^{-1}; nmr (CCl_4) 3.9 (s, 1), 2.7 (m, 1), 2.3 (s, OH), 1.0–2.0 (m, 11), 0.6 (m, 1), and 0.45 (m, 1).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.66; H, 10.71.

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Registry No.—**3**, 53716-34-0; **4**, 53716-35-1; **6**, 53776-70-8; **7**, 53716-36-2; **8**, 53716-37-3; **10**, 53716-38-4; *cis,cis,cis*-1,4,7-cyclononatriene, 696-86-6; *cis,cis,cis*-10,10-dibromobicyclo[7.1.0]deca-3,6-diene, 53716-39-5; 9,9-dibromobicyclo[6.1.0]non-2-ene, 2570-08-3; 1,3-cyclooctadiene, 1700-10-3; bicyclo[6.1.0]non-2-ene, 2570-07-2; 1,4-cyclononadiene, 27538-12-1; 10,10-dibromobicyclo[7.1.0]-dec-3-ene, 53716-40-8; mercuric sulfate, 7783-35-9; mercuric acetate, 1600-27-7.

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Heterogenized Homogeneous Catalysts. Hydrogenation of Methyl Sorbate by Polystyrene-Anchored Tricarbonylchromium

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The reaction of a swollen 1% divinylbenzene cross-linked polystyrene with hexacarbonylchromium gave polymer-anchored tricarbonylchromium moieties η^6 bonded to the polymer's phenyl rings. Using this heterogenized catalyst, methyl sorbate was converted selectively (96–97%) to (*Z*)-methyl 3-hexenoate with small amounts of methyl hexanoate and (*E*)-methyl 2-hexenoate in cyclohexane at 160° and 500 psi of hydrogen. The product distribution was sensitive to solvent and reaction temperature. No significant hydrogenation of cyclohexene or (*E,E,E*)-1,5,9-cyclododecatriene occurred at 150° and 500 psi of hydrogen in 24 hr. This heterogenized homogeneous catalyst system is discussed in relation to known homogeneous hydrogenation catalysts for methyl sorbate.

The anchoring of homogeneous catalysts to polymeric and glass supports has recently attracted increased attention.[1-8] Such "heterogenized" homogeneous catalysts can exhibit the unique selectivity and reactivity of their homogeneous counterparts while also increasing the ease of separation from the products and facilitating the recycling of the catalysts. However, diffusion into polymer gels can also play an important role in reactions using supported catalysts. In this paper we report the use of cross-linked polystyrene-anchored $-Cr(CO)_3$ moieties in selective methyl sorbate hydrogenations.

Methyl sorbate (methyl 2,4-hexadienoate) was chosen as a model substrate (1) because of its relation to commercially important dienoic and trienoic fatty acid esters, (2) because the resulting hydrogenation products can be analyzed readily by gas chromatography, and (3) because its hydrogenation has been previously studied using a variety of catalysts.[9-12] Hydrogenation of methyl sorbate, catalyzed by pentacarbonyliron,[9] gave a mixture of methyl 2-, 3-, and 4-hexenoate as well as methyl hexanoate. No assignment of the geometrical isomeric distribution was given. Cais, *et al.*,[10] and Frankel and Butterfield[11] showed a wide variety of η^6-arenetricarbonylchromium derivatives would selectively catalyze hydrogenation to methyl 3-hexenoate, but assignment of the geometrical isomer was not given. The same authors showed that η^6-arenetricarbonylchromium-catalyzed hydrogenations of dienes proceeded by 1,4-addition[13] and that isomerization of methyl 3-hexenoate to the 2-isomer occurred by a 1,3-hydrogen shift. The room temperature hydrogenation of sorbic acid by pentacyanocobaltate(II) gave (*E*)-2-hexenoic acid (82%), (*E*)-3-hexenoic acid (17%), and (*E*)-4-hexenoic acid (1%).[12] In methanol the selectivity to (*E*)-2-hexenoic acid increased to 96%.

η^6-(Ethylbenzene)tricarbonylchromium is a good electronic model for polystyrene-anchored tricarbonylchromium. Using it at 150° and 700 psi of hydrogen, methyl sorbate gave 90.1% methyl 3-hexenoate.[10] The product distribution in this study was different from that which we found using the heterogenized analog. Grubbs[14] has point-

Table I
Hydrogenation of Methyl Sorbate at 500 psi Catalyzed by Polystyrene-Anchored η^6-Phenyltricarbonylchromium

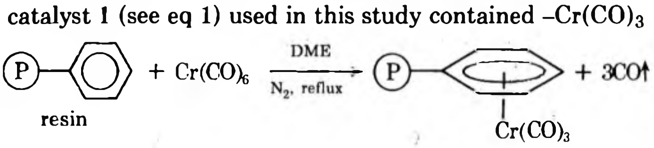
React. no.	Methyl sorbate, mmol	Catalyst, mmol[a]	Solvent (15 ml)	Temp, °C	React. time, hr	Total conversion, %	Product distribution, %[h] (Z)-Methyl 3-hexenoate	(E)-Methyl 2-hexenoate	Methyl hexanoate
1	15.2	0.51	Cyclohexane	150	24	100	65–58[i]	7–2[i]	34–40[i]
2[b]	15.2	0.49	Cyclohexane	150	24	100	80	7	12
3[b]	15.2	0.49	Cyclohexane	150	24	100	76	9	15
4[b]	15.2	0.49	Cyclohexane	150	24	100	80	5	15
5[b]	15.2	0.48	Cyclohexane	150	24	100	79	5	16
6[b]	15.2	0.48	Cyclohexane	150	24	100	82	4	14
7[b]	15.2	0.51	Cyclohexane	140	24	33	99.8	0.2	0
8[c]	15.2	0.51	Cyclohexane[c]	160	24	100	96.5	2.0	0.7
9[d]	15.2	0.51	Cyclohexane[d]	160	24	100	97.2	2.0	0.8
10[e]	15.2	0.51	Cyclohexane[e]	160	24	100	97.4	1.8	0.8
11	15.2	0.51	DMF	150	10	100	20	50	30
12[f]	15.2	0.51	DMF[f]	150	24	0	0	0	0
13[g]	15.2	0.51	DMF[g]	150	5	100	70.7	23.6	5.7
14	15.2	0.51	Cyclohexane	150	10	60	97.4	2.7	0
15	76.0	0.51	Cyclohexane	150	48	100	87.4	5.6	7.0

[a] Millimoles of $Cr(CO)_3$ units anchored within the resin charged to the reactor. [b] Runs 2–7 used the same catalyst recycled from run 1. Thus, in run 7 this catalyst was used in runs 1–6 previously. [c] Catalyst recycled from run 7. [d] Fresh catalyst used. [e] Catalyst recycled from run 9. [f] Catalyst recycled from run 11. [g] Fresh catalyst used. [h] Based on total conversion and determined by glc. [i] Results obtained from several runs spanned the range shown.

ed out that diffusion into the polymer beads is a rate-limiting factor in the hydrogenation of olefins catalyzed by polystyrene-anchored $(PPh_3)_3RhCl$.

Results and Discussion

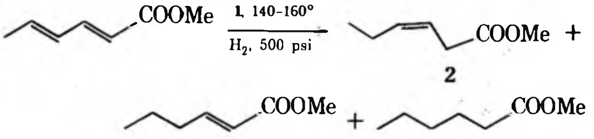
A swollen 1% divinylbenzene–styrene resin was complexed with $-Cr(CO)_3$ groups by refluxing with $Cr(CO)_6$ in dimethoxyethane under nitrogen. The resulting anchored catalyst 1 (see eq 1) used in this study contained $-Cr(CO)_3$



1 (1)

moieties attached to 20–25% of the polymer's benzene rings and distributed throughout the resin beads.

Methyl sorbate was quantitatively hydrogenated in cyclohexane or DMF solvents containing swollen beads of 1 at 140–160° and 500 psi of hydrogen for 24 hr. The product distribution was a function of temperature. The products were (*Z*)-methyl 3-hexenoate (2), (*E*)-methyl 2-hexenoate (3), and methyl hexanoate (4) (eq 2). At 160° the selectivity



(2)

to (*Z*)-methyl 3-hexenoate (2) was 96–98% which was higher than that observed using the η^6-ethylbenzene analog. At 150°, the selectivity was significantly lower with 2 (74–81%) still the major product. The product distribution at 150° was different in the initial reaction, but upon recycling the distribution stabilized to a different value. Once conditioned, the catalyst performs in a uniform manner for several recycling operations. Representative sample runs are given in Table I.

The catalyst conditioning phenomenon was studied by observing the ir spectrum of the polymer before and after its use in the initial reaction. Before use 1 shows intense metal carbonyl stretching frequencies at 1965 and 1880 cm^{-1}. After the initial hydrogenation, a new carbonyl absorption appears at 1635 cm^{-1}. Upon repeated recycling the 1965- and 1880-cm^{-1} band intensities steadily decreased but the polymer remained catalytically active. The 1635-cm^{-1} band remained, suggesting that methyl sorbate or a reaction product was being chemically bound into the resin. To further test this suggestion, the beads were swollen in benzene and toluene and extracted (soxhlet) for successive 4-hr periods. The 1635-cm^{-1} absorption's intensity remained unchanged. The decrease in the chromium-bound carbonyl bands was not due to leaching of $Cr(CO)_6$ (or other Cr derivatives) from the polymer because analysis confirmed the per cent Cr remained essentially unchanged during recycling. The presence of an inorganic CO bridging three Cr atoms (which would appear in the 1650-cm^{-1} range) was ruled out for lack of precedent. Most likely, methyl sorbate is complexed to resin-bound chromium and displaces CO.

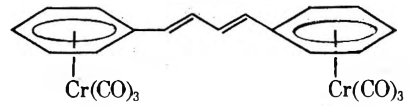
The product distribution at 140°, after 24 hr, and 30% conversion, was highly selective for 2 (<99%) and only a trace of 3 (0.2%) and no 4 was observed. Thus, at 140° the product distribution resembled those obtained at 160°. After much longer reaction periods only small amounts of 3 and 4 were ever observed.

At 150° in cyclohexane at conditions where Cais, *et al.*,[10] had reported η^6-(ethylbenzene)tricarbonylchromium catalyzed a 95% conversion of methyl sorbate in 7 hr, only 50% conversion in 24 hr was obtained using resin 1. This difference in rate can be attributed to diffusion into the resin. This diffusion limitation was expected to be serious in cyclohexane, because it is a poor solvent for swelling styrene–divinylbenzene resins. Significant retardation of the rate of hydroformylation of 1-pentene, catalyzed by anchored $(PPh_3)_3RhH(CO)$, *vs.* its homogeneous use (at 40–50°), has been observed in this laboratory.[15] Similarly, anchored $(PPh_3)_2Ni(CO)_2$ catalyzes the cyclooligomerization of butadiene at 112° at a rate about equal to that of the homogeneous catalyst at 90°.[15] In both of those cases, significant rate retardation occurred due to diffusion despite the fact that a good swelling solvent, benzene, was employed.

Dimethylformamide is a good swelling solvent. At 150° complete hydrogenation of methyl sorbate required only 5 hr using anchored catalyst **1**. Previously, it had been shown the rate of methyl sorbate hydrogenation, catalyzed by η^6-benzenetricarbonylchromium, markedly increased going from nonpolar cyclohexane to more polar methylene chloride.[10] Thus, the origin of the rate enhancement observed using DMF with **1** is not clear. Using DMF, the catalyst could not be recycled. After a single 10-hr reaction, the chromium content of **1** was reduced from 8.89% to 4.55%. The greenish-yellow DMF filtrate contained some $(DMF)_3Cr(CO)_3$ which could have participated in the catalytic reaction.[16] DMF was leaching $-Cr(CO)_3$ moieties from the resin by displacing the π-bound phenyl rings. The product distribution changed sharply in DMF. Esters **3** and **4** became the major products (50 and 30%, respectively) and only 20% of the product was **2**.

It was necessary to establish that the major product, using cyclohexane as the solvent, was actually the cis isomer **2** rather than the trans isomer. It was the trans isomer which was formed when pentacyanocobaltate(II) was employed.[12] This point was not established by Cais.[10] The nmr spectrum was not definitive since the coupling constant between the 3- and 4-vinyl protons could not be observed due to the coincidental chemical shifts of these protons. However, the ir spectrum of **2** did not correspond to that published for *trans*-methyl 3-hexenoate.[12,16] Most conclusive was the absence of a strong band in the 970-cm^{-1} region where the trans isomer absorbs. Bands at 700 and 750 cm^{-1} were present indicating the cis isomer had been obtained.

Bis-η^6-arenetricarbonylchromium compounds such as **5** and **6** greatly enhanced the hydrogenation rate in cyclohex-



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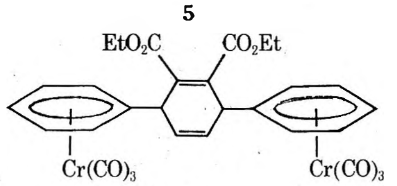

6

ane.[10] For example, with **6** a 99% conversion of methyl sorbate to **2** was obtained at 115° and 70 psi *vs.* the 150° and 700 psi of hydrogen required using η^6-benzenetricarbonylchromium.[10] Apparently, this special rate effect cannot be operative in resin **1** despite the fact that this resin must have phenyl-bound $Cr(CO)_3$ moieties in close proximity. The origin of this special effect may be in the conjugative interactions between rings in **5** and **6** rather than their relative proximity to one another.

Experimental Section

Chromium hexacarbonyl was purchased from Pressure Chemical Co. and was sublimed prior to use. Methyl sorbate (Pfaltz and Bauer) was purified by distillation at 90° (40 mm) and stored at −12° prior to use. Weekly checks of this material by vpc showed no oligomers were formed during storage. Cyclohexane and dimethoxyethane were dried over calcium hydride and distilled immediately before use. Dimethylformamide was dried over magnesium sulfate, distilled, and stored over Linde 4A molecular sieves. Polystyrene beads, cross-linked with 1% divinylbenzene, were purchased from Bio-Rad, Inc. They had a 12,000–14,000 mol wt exclusion limit when fully swollen in benzene.

Infrared spectra, recorded on a Beckman IR-33, were obtained in KBr pellets for the cross-linked beads and as thin films for methyl sorbate and its reaction products. Nmr spectra were recorded on a Hitachi–Perkin-Elmer R20B spectrometer using deuteriochloroform as the solvent and TMS as an internal standard.

Vpc curves were recorded on a Varian Aerograph Model 90-P. An 8-ft column consisting of 15% SE-30 or 20% Carbowax 20M deposited on Chromosorb P (non-acid-washed) at 180° was used to effect efficient product separation.

The stainless steel Hoke bomb, 150-ml capacity, used in these reactions was scraped clean, treated with mineral acids and organic solvents, and dried prior to each series of runs.

Preparation of Polystyrene-Anchored Tricarbonylchromium. A Strohmeier reactor, equipped with a 250-ml reaction flask containing a magnetic stirring bar, was charged with 4.0 g of cross-linked beads, 4.0 g of $Cr(CO)_6$, and 150 ml of dimethoxyethane.[17] After refluxing the mixture under nitrogen for 48 hr, the reaction was cooled to room temperature and filtered under nitrogen onto a sintered glass frit to collect the polymer beads. The beads were repeatedly swollen with benzene and collected by filtration in order to remove non-polymer-bound chromium complexes. After a final wash with petroleum ether (bp 30–60°), the beads were dried *in vacuo* for 48 hr. The presence of only polystyrene tricarbonylchromium moieties was confirmed by the infrared spectrum which showed two carbonyl stretching frequencies at 1965 and 1880 cm^{-1}. Elemental analysis showed 8.89% Cr, corresponding to *ca.* one $Cr(CO)_3$ unit for each four aromatic rings. The beads could be stored under nitrogen indefinitely. The beads occasionally had a green cast due to surface oxidation of the chromium during the above preparation. This in no way affected their activity or the results.

Hydrogenation of Methyl Sorbate. In a typical reaction, the Hoke bomb was charged, under nitrogen, with the catalyst, methyl sorbate, and solvent in amounts listed in Table I. After degassing *via* two freeze–thaw cycles, the bomb was pressurized with 500 psi of hydrogen and placed in a preheated oil bath where it was also shaken for the appropriate time. The bomb was then cooled to room temperature, the excess hydrogen was vented, and the solvent and products were separated from the catalyst by filtration under nitrogen. The bomb was rinsed with 3 × 5 ml of solvent and the rinse was used to wash the beads. The catalyst could then be recycled. After the first and fourth reactions a 10-mg aliquot of the catalyst was removed for chromium analysis. The total filtrate was concentrated and the products were separated by vpc. They eluted in the order methyl hexanoate, (*Z*)-methyl 3-hexenoate, (*E*)-methyl 2-hexenoate, and unreacted methyl sorbate. The products were identified by comparing their infrared and nmr spectra with published spectra.[11,12] The nmr spectra (CCl_4) follow: methyl hexanoate, δ 0.9 (3 H, t, CH_3CH_2), 1.55 (6 H, m, CH_2 groups at 3, 4, and 5 positions), 2.35 (2 H, t, CH_2 at 2 positions), 3.76 (3 H, s, CH_3O); methyl 3-hexenoate, δ 0.94 (3 H, t, CH_3CH_2), 2.05 (2 H, m, CH_2 at C-5), 3.05 (2 H, d, 7 H_2, CH_2 at C-2), 3.60 (3 H, s, CH_3O), and 5.5 (2 H, br t, J = 6–8 Hz, cis vinyl H's at C-3 and C-4 where $J_{3-4} \simeq 0$ due to almost identical chemical shifts); methyl 2-hexenoate, δ 1.0 (3 H, t, CH_3CH_2), 1.5 (2 H, m, CH_2), 2.2 (2 H, m, CH_2), 4.0 (3 H, s, CH_3O), 6.1 (1 H, d, 2-vinyl H, $J_{2,3}$ = 16 Hz), and 7.2 (1 H, m, 3-vinyl H).

Other Hydrogenations. Attempts were made to hydrogenate cyclohexene and (*E*,*E*,*E*)-1,5,9-cyclododecatriene at 150° for 24 hr (500 psi of H_2) using resin **1** as described for methyl sorbate. No significant hydrogenation was observed.

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Registry No.—**2**, 13894-62-7; **3**, 13894-63-8; **4**, 106-70-7; chromium hexacarbonyl, 13007-92-6; methyl sorbate, 689-89-4; polystyrene, 9003-53-6.

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Reaction of π-Allylnickel Bromide Complexes with Ketones and Aldehydes. Synthesis of α-Methylene-γ-butyrolactones

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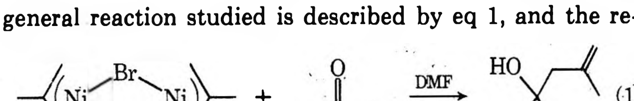
π-Allylnickel bromide complexes react with ketones and aldehydes to produce homoallylic alcohols. α diketones are the most reactive substrates, leading to α-keto homoallylic alcohols. Aldehydes and alicyclic ketones including some steroidal ketones are also reactive, while aliphatic acyclic ketones and α,β-unsaturated ketones react only sluggishly under forcing conditions. With conjugated ketones exclusive 1,2 attack results, even in the presence of added CuI. The reaction of α-(2-carbethoxyallyl)nickel bromide with ketones and aldehydes leads to α-methylene-γ-butyrolactones. Other carbonyl functional groups such as acid chlorides, esters, and amides, as well as nitriles and epoxides, are relatively unreactive. Thus π-allylnickel bromide complexes are less reactive and more selective than the corresponding allylzinc reagents toward carbonyl compounds, and are of potential synthetic utility.

π-Allylnickel halide complexes are becoming increasingly useful as carbon–carbon bond forming reagents for organic synthesis, and have been the subject of two recent reviews.[1,2] They react with a variety of organic halides under mild conditions to replace the halogen with the allyl group.[3] Complexes containing functional groups such as carbethoxy[4] or methoxy[5] in the allyl portion are readily prepared, and react similarly to produce more highly functionalized products. π-Allylnickel bromide complexes react with quinones under very mild (DMF, −50°) conditions to produce allylquinones in what is formally a 1,4 addition of the allyl complex to the quinone.[6] In contrast, other normally reactive carbonyl compounds such as benzaldehyde and cyclopentanone require considerably more vigorous (DMF, 50°) conditions to react, forming homoallylic alcohols, while benzophenone and methyl benzoate are unreactive.[3]

In an attempt to clarify some of the features of the reaction of π-allylnickel halide complexes with quinones, we initiated a general study of the interaction of these complexes with a variety of simple as well as conjugated carbonyl compounds. Our results indicate that these complexes are generally reactive toward ketones and aldehydes to produce fair to excellent yields of homoallylic alcohols under mild conditions. They are significantly *less* reactive than the corresponding allyllithium, -magnesium, or -zinc reagents, and offer a high degree of selectivity among normally quite reactive carbonyl compounds.[7]

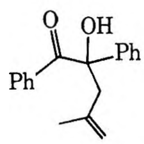
Results and Discussion.

A. Reactions of π-2-Methallylnickel Bromide. The general reaction studied is described by eq 1, and the re-



(1)

sults of this reaction with a wide variety of carbonyl compounds are collected in Table I. The most reactive substrates are α diketones and anthraquinone, which undergo exclusive attack of only one of the carbonyl groups, even in the presence of excess complex, to produce α-keto homoallylic alcohols (**1**, **2**, and **3**) in high yield. Phenyl ketones are



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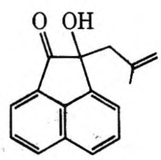

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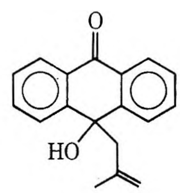

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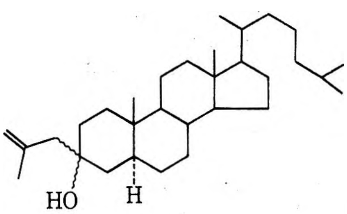

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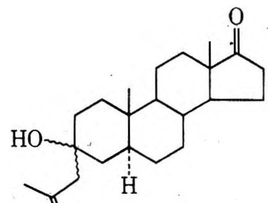

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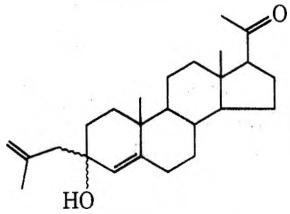

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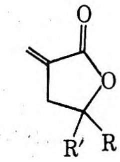


7a, R = Ph; R′ = H
b, R = n-C_6H_{13}; R′ = H
c, R = Ph; R′ = Me
d, R,R′ = $(-CH_2-)_5$
e, R = Ph; R′ = PhCO

more reactive than alkyl ketones as evidenced by the requirement of more severe conditions for 2,3-butanedione. In contrast allylmagnesium and allylzinc complexes frequently attack both carbonyl groups indiscriminately, lead-

Table I
Reaction of π-Allylnickel Bromide Complexes with Ketones and Aldehydes

Ni complex	Registry No.	Substrate	Registry No.	Ratio[a] of allyl/substrate	Time, hr	Temp, °C	Product	Registry No.	Yield, %[b]
2-Methallyl	12300-62-8	Benzil	134-81-6	1	30	25	1	53684-09-6	86
2-Methallyl		Acenaphthene-quinone	82-86-0	1	48	25	2	53684-10-9	84
2-Methallyl		2,3-Butanedione	431-03-8	1.2	24	50	2,4-Dimethyl-4-hydroxyhex-1-en-5-one	40519-29-7	78
2-Methallyl		Anthraquinone	84-65-1	1	48	25	3	53684-11-0	92
2-Methallyl		Cyclohexanone	108-94-1	1.7	24	50	1-(2-Methyl-2-propenyl)cyclohexanol	51800-40-9	79
2-Methallyl		5α-Cholestan-3-one	566-88-1	2.2	24	55	4(3α-CH) (3β-CH)	53730-91-9 53684-12-1	70[c]
2-Methallyl		5α-Androstane-3,17-dione	846-46-8	2	40	55	5(3α-CH) (3β-CH)	53684-13-2 53684-14-3	92[d]
2-Methallyl		2-Cyclohexen-1-one	930-68-7	2.3	96	55	1-(2-Methyl-2-propenyl)cyclohex-2-en-1-ol	5674-03-3	58
2-Methallyl		Progesterone	57-83-0	2.5	24	55	6	53684-15-4	77[e]
2-Methallyl		2-Acetonapthone	93-08-3	2.0	48	25	2-Methyl-4-hydroxy-4-(2-naphthyl)pent-1-ene	53684-16-5	80
2-Methallyl		2-Octanone	111-13-7	2.3	96	55	2,4-Dimethyldec-1-en-4-ol	53684-17-6	50
2-Methallyl		*n*-Heptaldehyde	111-71-7	1.2	24	50	2-Methyldec-1-en-4-ol	53684-18-7	71
1,1-Dimethylallyl	32650-02-5	Benzil		1.0	20	25	3,3-Dimethyl-1,2-diphenyl-2-hydroxypent-4-en-1-one	53684-19-8	28
							1,2-diphenyl-2-hydroxy-5-methylhex-5-en-1-one	5623-21-2	57
2-Carbethoxyallyl	12288-88-9	Benzaldehyde	100-52-7	2.0	24	25	7a	26613-71-8	85
2-Carbethoxyallyl		*n*-Heptaldehyde		2.0	28	25	7b	26798-41-4	76
2-Carbethoxyallyl		Acetophenone	98-86-2	2.0	24	55	7c	29043-98-9	83
2-Carbethoxyallyl		Cyclohexanone		2.0	24	25	7d	52978-85-5	80
2-Carbethoxyallyl		Benzil		2.0	24	55	7e	53684-20-1	68
2-Carbethoxyallyl		5α-Cholestan-3-one		2.0	24	55	8 (3α-O) (3β-O)	53684-21-2 53729-61-5	91[f,g]
2-Carbethoxyallyl		5α-Androstane-3,17-dione		2.0	24	55	9 (3α-O) (3β-O)	53684-22-3 53684-23-4	76

[a] Since the nickel complexes are dimeric, 1 mol of complex contains 2 mol of allyl ligands. The ratio refers to the molar ratio of allyl groups, not nickel complex, to substrate. [b] Reported yields refer to isolate products purified by layer chromatography or distillation. [c] Since a single epimer was obtained, unequivocal assignment of structure was not possible. [d] The compound is an unseparable 2:1 mixture of 3α and 3β hydroxy isomers from nmr spectra. [e] The yield is based on starting material consumed. About 50% progesterone was recovered. [f] The compound is a 1:1 mixture of 3α and 3β epimers. [g] The yield is based on starting material consumed. About 30% cholestanone was recovered.

ing to disubstitution.[8] Thus, the nickel complex offers a high yield approach to α-keto homoallylic alcohols (as well as to α, β, γ, δ conjugated enones by facile dehydration) without polysubstitution.

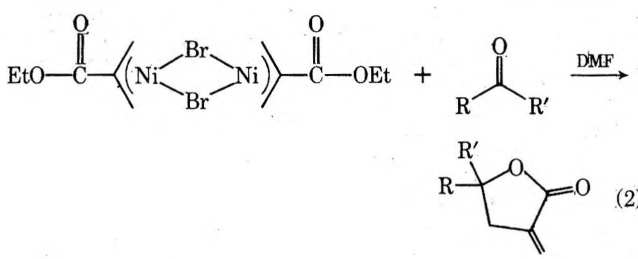
Alicyclic ketones such as cyclopentanone[3] and cyclohexanone also react well, although higher temperatures and excess nickel complex are required to ensure complete reaction. Some steroidal ketones are also reactive, with 5α-cholestan-3-one producing almost entirely (>90%) a single alcohol epimer (**4**) in excellent yield. In contrast, 5α-androstane-3,17-dione, while reacting exclusively at the more reactive[9] 3 keto group, produced a 2:1 mixture of the 3α and 3β hydroxy compounds (**5**). α,β unsaturated ketones are even less reactive, cyclohexenone reacting to only 55% in the presence of a large excess of nickel complex and under conditions sufficiently severe to cause thermal decomposition of the nickel complex. Benzalacetone and chalcone are similarly unreactive, leading to only 40–50% conversion under a variety of conditions. Surprisingly progesterone undergoes attack exclusively at the 3 keto (conjugated) group, while the 20 keto group is inert (**6**), in low (50%) conversion but fair (77%) yield. With α,β unsaturated ketones exclusive 1,2 attack is observed, even in the presence of added cuprous iodide. In contrast, both allylzinc[8] and allylmagnesium compounds are highly reactive toward α,β unsaturated ketones, and organomagnesium compounds add 1,4 to conjugated enones in the presence of added copper salts.[10] Again, π-allylnickel complexes are less reactive and more selective than the corresponding zinc and magnesium complexes.

While phenyl methyl ketones such as 2-acetonaphthone are sufficiently reactive to produce fair yields of homoallylic alcohols under moderate conditions, simple aliphatic ketones, such as 2-octanone, are relatively inert, reacting to only 50% conversion even in the presence of a large excess of nickel complex after 96 hr at 55°. This low reactivity of 2-octanone is demonstrated by the results of the reaction between π-2-methallylnickel bromide and a 1:1 mixture of cyclohexanone and 2-octanone. After 24 hr at 50°, the cyclohexanone had completely reacted, while the 2-octanone remained untouched. Thus the nickel complex was able to discriminate between two substrates of apparently comparable reactivity. Aldehydes are generally reactive, with both benzaldehyde[3] and *n*-heptaldehyde reacting in good yield under moderate conditions.

A number of substrates that readily undergo attack by allylzinc reagents[8] are essentially *unreactive* with π-allylnickel halide complexes. Acetonitrile and benzonitrile are inert, and have been used as solvents for π-allylnickel halide complex reactions.[11] Ethyl benzoate is also unreactive and is recovered unchanged after 165 hr at 55°.[3] Acid chlorides are also surprisingly inert. Both benzoyl chloride and lauryl chloride are recovered unchanged (except for some hydrolysis to the acid during isolation) after 72 hr at 25° in contact with the π-2-methallylnickel complex. Upon heating a DMF solution of benzoyl chloride and π-2-methallylnickel bromide at 50° for 24 hr, the complex decomposed, and a small amount of benzil was recovered along with large amounts of benzoyl chloride and benzoic acid. Finally, cyclohexene oxide failed to react with π-2-methallylnickel bromide even after several hours at 50°, while cyclopentene oxide and styrene oxide reacted to about 30–40%.[11]

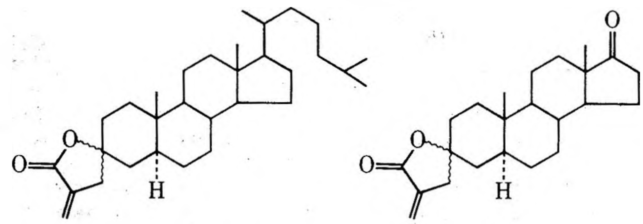
B. Reactions of π-1,1-Dimethylallylnickel Bromide. This complex is appreciably less reactive than the π-2-methallylnickel bromide complex. With benzil, one of the most reactive substrates studied, the reaction proceeded smoothly to produce an 85% yield of the homoallylic alcohol. The product is a 2:1 mixture of isomers resulting from attachment at the unsubstituted and the disubstituted terminus of the allyl group.[12] Other substrates such as cyclohexanone, cyclohexenone, and 2-acetonaphthone are unreactive under conditions of sufficient severity to decompose the nickel complex. These results indicate that polyalkylated allylic nickel complexes are likely to lack sufficient reactivity to be of any utility in the synthesis of homoallylic alcohols.

C. Reactions with π-(2-Carbethoxyallyl)nickel Bromide. The reaction of this complex with aldehydes or ketones leads to α-methylene-γ-butyrolactones (eq 2), a class



(2)

of compounds of current interest because of their activity as antitumor agents.[13] Although this complex is less reactive toward carbonyl groups than the π-2-methallylnickel bromide complex, aldehydes, α diketones, and alicyclic ketones do react to give α-methylene-γ-butyrolactones (7) in high yield. The steroidal ketones 5α-cholestan-3-one and 5α-androstane-3,17-dione react exclusively at the 3 keto (cyclohexanone) position to give a 1:1 mixture of epimeric lactones. Aliphatic ketones such as 2-octanone, and α,β un-



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saturated ketones such as benzalacetone and cyclohexenone, are essentially unreactive, as are styrene oxide, cyclohexene oxide, and cyclopentene oxide. α-Methylene-γ-butyrolactones can also be made by the reaction of ketones or aldehydes with zinc and α-(bromomethyl)acrylic esters.[14] These allylzinc complexes are considerably more reactive and less selective than the π-allylnickel halide complexes, and react equally well with aliphatic ketones and α,β-unsaturated ketones. Neither method is capable of producing the substitution pattern found in many of the naturally occurring sesquiterpene α-methylene-β-butyrolactones which show antitumor activity.[13a]

Conclusions

π-Allylnickel bromide complexes are generally reactive toward ketones and aldehydes to produce homoallylic alcohols. α-Methylene-γ-butyrolactones can be synthesized using the π-(2-carbethoxyallyl)nickel bromide complex. The nickel complexes are considerably less reactive than the corresponding zinc complexes, and considerably more selective. The nickel complexes are inert towards acid halides, nitriles, esters and epoxides, and are even able to discriminate between ketones of differing reactivity. The allylzinc reagents are very easy to make and, in syntheses in which no other reactive functional groups are present in the substrate, they are the reagents of choice. However, if a high degree of selectivity and the ability to discriminate between slightly different carbonyl groups is necessary, π-allylnickel bromide complexes warrant consideration.

Experimental Section

General. All melting points are uncorrected. Infrared (ir) spectra were measured with a Perkin-Elmer Model 337 or Model 267 spectrometer. Nuclear magnetic resonance (nmr) spectra were measured with a Varian Associates Model A-60A or a Jeol JNM-MH-100 nmr spectrometer with TMS internal standard. Mass spectra were measured with an Associated Electronic Industries MS-12 mass spectrometer. Layer chromatography was performed using Brinkman silica gel PF254 analytical and preparative plates, visualized by uv light. Microanalyses were performed by Midwest Microanalytical Laboratory, Indianapolis, Ind. All manipulations of the nickel complexes were carried out under an argon atmosphere.

Materials. DMF was distilled from calcium hydride under reduced pressure and stored under an argon atmosphere. Benzene (Fischer, reagent grade) was used without further purification. Nickel carbonyl was purchased from Matheson in 1-lb lecture bottles. All substrates were commercial materials purified by standard methods.

Preparation of the π-Allylnickel Bromide Complexes. A. π-2-Methallylnickel Bromide. This complex was prepared from 2-methallyl bromide[15] and nickel carbonyl by the method of Semmelhack and Helquist[16] on a 15-g scale with an 85% yield.

B. π-1,1-Dimethylallylnickel Bromide. This complex was prepared from 1,1-dimethylallyl bromide[15,17] and nickel carbonyl by the above method,[16] except the reaction was carried out at reflux rather than 70°.

C. π-(2-Carbethoxyallyl)nickel Bromide. The complex was prepared from 2-carbethoxyallyl bromide[18] and nickel carbonyl by the above method,[16] except the reaction was carried out at 40° rather than 70°. The crude material was dissolved in benzene and filtered under an argon atmosphere. The product was precipitated from the filtrate by addition of petroleum ether, removed by filtration, and dried under vacuum.

General Procedure for the Reaction of π-Allylnickel Bromide Complexes with Ketones and Aldehydes. Reactions were carried out in a 50-ml one-neck flask with a side arm capped with a serum cap, containing a magnetic stirring bar, and fitted with a stopcock. The reaction flask was flushed with argon, and placed in a nitrogen-filled glove bag along with a flask containing complex 1. The desired amount of 1 (1–2 mmol) was transferred into the reaction flask through the side arm (in the glove bag), the side arm was recapped with the serum cap, and the reaction flask was removed from the glove bag. The complex was dissolved in argon-saturated DMF (10 ml of solvent/mmol complex) giving a deep red solution. Liquid reactants (1.8–3.6 mmol) were directly added to the reaction flask, while solid reactants were dissolved in a minimum amount of DMF and added as solutions. Reactions requiring heat were immersed in an oil bath of the appropriate temperature. Upon completion, the reaction mixture was poured into a separatory funnel containing 50 ml of aqueous 3% HCl and 50 ml of ether, and was thoroughly shaken. The aqueous phase was washed with three 20-ml portions of ether, and the combined ether extracts were washed with three 50-ml portions of water to ensure complete removal of DMF. The organic phase was dried over anhydrous $MgSO_4$, and solvent was removed under vacuum. The crude product was purified by silica gel preparative layer chromatography or distillation.

Reactions with π-2-Methallylnickel Bromide. (a) 1,2-Diphenyl-2-hydroxy-4-methylpent-4-en-2-one (1). The nickel complex (0.25 g, 0.65 mmol) in 12 ml of DMF was added to benzil (0.27 g, 1.29 mmol) and the mixture was stirred at 25° for 35 hr. After routine isolation (Et_2O) and purification by column chromatography (Si gel, eluted with 3:1 hexane–ether) 0.28 g (86%) of a white, crystalline solid (mp 94.5–95.5°) was obtained: ir ($CHCl_3$) 2.85 (OH), 3.27, 3.34, 3.42, 5.95 (conj CO), 6.26, 6.33, 6.70, 6.91, 7.27, 7.60, 7.68, 8.15, 8.40, 8.90, 9.28, 9.75, 9.90, 10.42, 10.60, 11.00, 11.40, 14.30 μ; nmr ($CDCl_3$–TMS) δ 1.55 (d, J = 1.0 Hz, 3 H, vinyl CH_3), AB quartet, δ_A 2.90, δ_B 3.20 (J_{AB} = 14.0 Hz, 2 H, vinyl CH_2; diastereotopic), 4.05 (s, 1 H, OH), 4.63 (m, 1 H, vinyl CH), 4.88 (m, 1 H, vinyl H), 7.2–8.2 (m, 10 H, aromatic H). A portion was recrystallized from ether–trimethylpentane and submitted for analysis.

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.91; H, 6.86.

(b) 1-(2-Methyl-2-propenyl)-1-hydroxy-2-oxoacenaphthene (2). The nickel complex (0.42 g, 1.08 mmol) in 15 ml of DMF was added to the acenaphthene quinone (0.33 g, 1.82 mmol) and the resulting mixture was stirred at 25° for 48 hr. After routine isolation ($CHCl_3$) and purification by recrystallization from ether–trimethylpentane 0.36 g (84%) of a white crystalline solid (mp 110–111°) was obtained: ir ($CHCl_3$) 2.7–3.1 (br, OH), 3.25–3.41 (br, CH), 5.85 (CO), 6.10, 6.15, 6.22, 6.70, 6.80, 7.00, 7.27, 7.45, 7.64, 7.97, 8.50, 9.00, 9.35, 9.92, 10.20, 10.55, 11.10, 11.33, 11.56, 11.95, μ; nmr ($CDCl_3$–TMS) δ 1.41 (s, 3 H, vinyl CH_3), 2.76 (s, 2 H, vinyl CH_2), 3.60 (s, 1 H, OH), 4.58 (m, 2 H, vinyl H), 7.70 (m, 6 H, aromatic H).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.45; H, 5.92.

(c) 2,4-Dimethyl-4-hydroxyhex-1-en-5-one. The nickel complex (0.37 g, 0.96 mmol) in 10 ml of DMF was added to the 2,3-butanedione (0.14 g, 1.65 mmol) and the resulting mixture was stirred at 50° for 24 hr. After routine isolation and purification by evaporative distillation (40° (0.1 mm)) 0.18 g (78%) of a colorless liquid was obtained: ir (neat) 2.87 (br, OH), 3.22, 3.36, 3.42 (CH), 5.83 (C=O), 6.07, 6.88, 7.22, 7.35, 8.55, 8.60, 9.00, 9.90, 10.30, 10.72, 11.20 μ; nmr ($CDCl_3$–TMS) δ 1.38 (s, 3 H, CH_3), 1.72 (d, J = 1 Hz, 3 H, vinyl CH_3), 2.21 (s, 3 H, CH_3CO), 2.44 (s, 2 H, vinyl $-CH_2-$), 3.60 (br, s, 1 H, OH), 4.80 (m, 2 H, vinyl H); mass spectrum parent *m/e* 142.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.32; H, 9.90.

(d) 9-(2-Methyl-2-propenyl)-9-hydroxy-10-oxoanthracene (3). The nickel complex (0.28 g, 0.72 mmol) in 15 ml of DMF was added to the anthraquinone (0.27 g, 1.30 mmol) and the resulting mixture was stirred at 25° for 48 hr. After routine isolation ($CHCl_3$) and purification by recrystallization from chloroform–benzene 0.32 g (92%) of an off-white crystalline solid (mp 174–175°) was obtained: ir ($CHCl_3$) 2.80 (OH), 3.28, 3.32, 3.38, 5.98 (CO), 6.26, 6.87, 7.51, 7.60, 7.79, 7.92, 9.00, 9.80, 10.80, 11.05, 12.60, 14.30 μ; nmr ($CDCl_3$–TMS) δ 0.90 (s, 3 H, vinyl CH_3), 2.64 (s, 2 H, vinyl CH_2), 3.14 (s, 1 H, OH), 3.82 (m, 1 H, vinyl H), 4.50, (m, 1 H, vinyl H), 7.2–8.2 (m, 8 H, aromatic H). The relatively highfield absorption of the methyl allyl group is due to shielding by the ring current effect in the aromatic portion of the molecule.

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.72; H, 6.23.

(e) 1-(2-Methyl-2-propenyl)cyclohexanol. Cyclohexanone (0.098 g, 1.00 mmol) was added to the nickel complex (0.33 g, 0.85 mmol) and the resulting mixture was stirred for 24 hr at 50°. After routine isolation and evaporative distillation (80° (0.5 mm)) 0.12 g (70%) of a colorless liquid was obtained: ir (neat) 2.90 (OH), 3.42, 3.52, 6.10, 6.93, 7.30, 7.95, 8.21, 8.50, 8.62, 8.78, 9.22, 9.40, 10.30, 11.20 μ; nmr (CCl_4–TMS) δ 1.48, (br, s, 10 H, ring CH_2), 1.80 (d, J = 1.0 Hz, 3 H, vinyl CH_3), 2.11 (s, 2 H, vinyl CH_2), 4.68 (m, 1 H, vinyl H), 4.84 (m, 1 H, vinyl H). This material was identical in all respects to authentic material prepared by a Reformatsky[7] type reaction.

(f) 5α-Cholestan-3-(2-methyl-2-propenyl)-3-ol (4). A solution of π-2-methallylnickel bromide (0.32 g, 0.83 mmol) in 10 ml of DMF was added to a suspension of 5α-cholestan-3-one (0.29 g, 0.75 mmol) in 10 ml of DMF, and the resulting mixture was stirred at 55° for 40 hr. After routine isolation and purification by preparative layer chromatography (Si gel, 5:1 pentane–ether, three developments, R_f 0.70) 0.23 g (70%) of a white crystalline solid (mp 120–121°) was obtained: ir ($CHCl_3$) 2.72, 2.80, 2.82 (OH), 3.34, 3.38, 3.42, 3.50 (CH), 6.10, 6.82, 6.92, 7.22, 7.40, 8.10, 8.65, 9.00, 9.30, 9.60, 11.00, 12.60, 14.10 μ; nmr ($CDCl_3$–TMS) δ 0.64 (s, 3 H, C_{18} methyl), 0.73 (s, 3 H, C_{19} methyl), 0.85 (d, 6 H, J = 6.0 Hz, C_{26} methyls), 0.86 (d, 3 H, J = 6.0 Hz, C_{20} methyl), 0.98–1.90 (m, 31 H, ring and chain $-CH_2-$, $-CH-$), 1.81 (d, 3 H, J = 1.0 Hz, vinyl CH_3), 2.11 (s, 2 H, vinyl CH_2), 4.80 (m, 2 H, vinyl H).

Anal. Calcd for $C_{31}H_{54}O$: C, 84.09; H, 12.29. Found: C, 84.09; H, 12.22.

The nmr of the crude material showed about 10% of the other hydroxy isomer, but amounts insufficient for characterization were recovered from the chromatography plate.

(g) 5α-Androstan-3-(2-methyl-2-propenyl)-3-hydroxy-17-one (5). A solution of π-2-methallylnickel bromide (0.39 g, 1.01 mmol) in 10 ml of DMF was added to 5α-androstan-3,17-dione (0.29 g, 1.00 mmol) in 10 ml of DMF and the mixture was stirred at 55° for 40 hr. After routine isolation and purification by preparative layer chromatography (Si gel, 3:1 ether–pentane, three developments, R_f 0.80) 0.32 g (92%) of a white crystalline solid (mp 155–158°) was obtained: ir ($CHCl_3$), 2.80 (OH), 3.41, 3.50 (CH), 5.80 (CO of cyclopentanone), 6.10, 6.80, 6.89, 7.11, 7.28, 8.00, 8.92, 9.20, 9.90, 11.08 μ. The nmr spectrum of this material shows it to be a 2:1 mixture of 3α hydroxy and 3β hydroxy isomers. This mixture was not separable in our hands. The spectrum of the mixture is nmr ($CDCl_3$–TMS) δ 0.79 (s, 2 H, C_{19} methyl of 3α hydroxy isomer), 0.88 (s, 4 H, C_{18} methyl of both isomers, and C_{19} methyl of 3β hydroxy isomer), 1.00–2.40 (m, 22 H, ring $-CH_2-$ and $-CH-$), 1.83 (d, 3 H, J = 1.0 Hz, vinyl CH_3), 2.18 (s, 1.33 H vinyl CH_2 of α hydroxy isomer), 2.30 (s, 0.67 H, vinyl CH_2 of β hydroxy isomer), 4.88, (m, 2 H, vinyl H).

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.00; H, 10.62.

The C_{19} methyl absorption of 5α-androstane appears at δ 0.79, while that of 5α-androstan-3β-hydroxy-17-one appears at δ 0.84.[19]

(h) 1-(2-Methyl-2-propenyl)cyclohex-2-en-1-ol. Cyclohexenone (0.096 g, 1.00 mmol) was added to the nickel complex (0.44 g, 1.13 mmol) in 15 ml of DMF and the resulting mixture was stirred for 96 hr at 55°. After routine isolation and purification by evaporative distillation (50° (0.1 mm)) 0.10 g (58%) of a colorless liquid was obtained: ir (neat) 2.90 (OH), 3.25, 3.32, 3.41, 3.50, 3.52 (CH), 6.23, 6.28, 6.62, 6.75, 6.90, 7.20, 7.91, 8.08, 8.56, 9.30, 9.80, 10.40, 11.22, 13.10, 13.50, 14.40 μ; nmr (CCl_4–TMS) δ 1.66 (br s, 4 H, ring CH_2), 1.80 (d, J = 1.0 Hz, 3 H, vinyl CH_3 of allyl), 1.84 (m, 2 H, ring vinyl CH_2), 2.21 (s, 2 H, vinyl CH_2 of allyl), 2.60 (s, 1 H, OH), 4.75 (m, 2 H, vinyl H of allyl), 5.68 (s, 2 H, ring vinyl H). This material was identical in all respects to authentic material prepared by a Reformatsky type reaction.[7]

(i) 4-Pregnen-3-(2-methyl-2-propenyl)-3-hydroxy-20-one (6). A solution of π-2-methallylnickel bromide (0.32 g, 0.83 mmol) in 10 ml of DMF was added to a suspension of progesterone (0.20 g, 0.65 mmol) in 10 ml of DMF and the resulting mixture was stirred at 55° for 48 hr. After routine isolation and purification by preparative layer chromatography (Si gel, 2:1 pentane–ether, R_f 0.60) 62 mg (77% based on starting material consumed) of a white crystalline solid (mp 161–162°) was obtained: ir ($CHCl_3$) 2.70, 2.80, 2.90 (OH), 3.35, 3.37, 3.42, 5.89 (C=O), 6.90, 7.22, 7.30, 7.40, 8.20, 8.90, 9.30, 9.58, 10.80, 11.00, 11.80, 12.60, 14.20, 14.80 μ; nmr ($CDCl_3$–TMS) δ 0.61 (s, 3 H, C_{18} methyl), 1.03 (s, 3 H, C_{19} methyl), 0.9–2.4 (m, 20 H, ring $-CH_2-$ and $-CH-$), 1.82 (d, 3 H, J = 1.0 Hz, vinyl methyl), 2.10 (s, 3 H, CH_3CO on C_{17}), 2.26 (s, 2 H, vinyl CH_2), 4.82 (m, 2 H, vinyl H on methallyl chain), 5.18 (s, 1 H, C_4 vinyl H).

Anal. Calcd for $C_{25}H_{38}O_2$: C, 81.03; H, 10.34. Found: C, 81.14; H, 10.18.

From spectra this is a single epimer, and unequivocal assignment of structure was not possible. Progesterone (0.14 g) was recovered from R_f 0.40 band, indicating ~50% conversion for this reaction.

(j) 2-Methyl-4-hydroxy-4-(2-naphthyl)pent-1-ene. The nickel complex (0.36 g, 0.93 mmol) in 15 ml of DMF was added to the 2-acetonaphthone (0.16 g, 0.93 mmol) and the resulting mixture was stirred at 25° for 48 hr. After routine isolation and purification by preparative layer chromatography (alumina, 6:1 benzene–ether, two developments, R_f 0.61) 0.18 g (80%) of a colorless oil was obtained: ir (neat) 2.90 (OH), 3.28, 3.36, 3.42 (CH), 6.10, 6.25, 6.66, 6.90, 7.28, 7.45, 7.86, 8.95, 9.20, 9.40, 10.70, 11.20, 11.72, 12.30, 13.40 μ; nmr ($CDCl_3$–TMS) δ 1.40 (d, J = 1.0 Hz, 3 H, vinyl CH_3), 1.52 (s, 3 H, CH_3COH), 2.35 (s, 1 H, OH), AB quartet δ_A 2.40, δ_B 2.69, (J_{AB} = 14.0 Hz, 2 H, vinyl CH_2), 4.73 (m, 2 H, vinyl H), 7.2–7.9 (m, 7 H, aromatic); mass spectrum, parent m/E 226, 208 (P − H_2O), 171 (P − methallyl), 155 (naphthyl − CO^+), 127 (naphthyl$^+$).

Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.62; H, 8.02.

(k) 2,4-Dimethyldec-1-en-4-ol. The 2-octanone (0.13 g, 1.00 mmol) was added to the the nickel complex (0.44 g, 1.13 mmol) in 10 ml of DMF and the resulting mixture was stirred at 55° for 96 hr. After routine isolation and purification by evaporative distillation (75° (0.1 mm)) 0.087 g (50%) of a colorless liquid was obtained: ir (neat) 2.90 (OH), 3.39, 3.41, 3.51 (CH), 6.10, 6.86, 7.28, 7.92, 9.00, 9.80, 11.22, 12.40 μ; nmr (CCl_4–TMS) δ 0.95 (m, 3 H, CH_3–C), 1.10 (s, 3 H, CH_3COH), 1.32, (br s, 10 H, $-CH_2-$), 1.82 (s, 3 H, vinyl CH_3) 2.15 (s, 2 H, vinyl CH_2), 4.78 (m, 2 H, vinyl H). A portion was collected from glpc (6 ft × 0.25 in. 10% Carbowax 4000 on Chromosorb P 80/100 AWDMCS, 155°, 2.6 mm) for elemental analysis.

Anal. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.41; H, 13.03.

(l) 2-Methyldec-1-en-4-ol. *n*-Heptaldehyde (0.19 g, 1.65 mmol) was added to the nickel complex (0.37 g, 0.96 mmol) and the resulting mixture was stirred at 50° for 24 hr. After routine isolation and evaporative distillation (0.1 mm, 70°) 0.20 g (71%) of a colorless liquid was obtained: ir (neat) 2.93 (OH), 3.22, 3.34, 3.38, 3.48 (CH), 6.06 (C=C), 6.72, 6.83, 7.25, 8.85, 9.20, 9.40, 9.70, 10.33, 11.10 μ; nmr (CCl_4–TMS) δ 0.86 (m, 3 H, CH_3), 1.36 (m, 10 H, $-CH_2-$), 1.78 (s, 3 H, vinyl CH_3), 2.08 (m, 2 H, vinyl $-CH_2-$), 3.60 (m, 1 H, CHOH), 4.80 (m, 2 H, vinyl H); mass spectrum, parent m/e 170. This material was identical to authentic material prepared by a Reformatsky type reaction.[7]

Reaction with π-1,1-Dimethylallylnickel Bromide. (a) With Benzil. The nickel complex (0.24 g, 0.58 mmol) in 15 ml of DMF was added to the benzil (0.23 g, 1.16 mmol) and the resulting mixture was stirred for 20 hr at 25°. After routine isolation and purification by preparative layer chromatography (Si gel, 10:1 pentane–ether, three developments) two major products were obtained.

Compound 1: R_f 0.78; 77 mg (28%) of white solid; ir ($CHCl_3$) 2.85 (OH), 3.26, 3.28, 3.31, 3.38, 3.41, 3.51 (CH), 5.95 (CO), 6.12, 6.29, 6.35, 6.71, 6.77, 6.81, 6.92, 7.08, 7.22, 7.35, 7.52, 7.67, 7.81, 7.90, 8.20, 8.41, 9.18, 9.29, 9.70, 10.00, 10.50, 10.80, 11.80, 12.42, 12.70, 13.50, 14.00, 14.58, 15.30 μ; nmr ($CDCl_3$–TMS) δ 1.09 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 3.05 (s, 1 H, OH), 4.95–5.40 (m, 2 H, C=CH_2), 6.0–6.50 (m, 1 H, =CH), 7.10–7.60 (m, 10 H, aromatic); mass spectrum, parent m/e 280, 263 (P − OH), 175 (P − PhCO), 106 (PhCHO), 78 (PhH).

This material is 3,3-dimethyl-1,2-diphenyl-2-hydroxypent-4-en-1-one from attack on one of the carbonyl groups by the *most* substituted position of the allyl group.

Compound 2: R_f 0.50; 154 mg (57%) of white solid; ir ($CHCl_3$) 2.90 (OH), 3.29, 3.35, 3.42, 3.50 (CH), 5.96 (C=O), 6.25, 6.35, 6.70, 6.90, 7.26, 7.40, 8.10, 8.50, 9.00, 9.36, 9.80, 10.60, 13.20, 14.10, 14.38, 14.40 μ; nmr ($CDCl_3$–TMS) δ 1.41 (s, 3 H, vinyl CH_3), 1.66 (s, 3 H, vinyl CH_3), 3.00 (m, 2 H, vinyl CH_2), 5.12 (m, 1 H, vinyl H), 7.18–7.80 (m, 10 H, aromatic); mass spectrum, parent m/e 280, 263 (P − OH), 212, 175 (P − PhCO), 105 ($PhCO^+$). This material is 1,2-diphenyl-2-hydroxypent-4-en-1-one.

Reactions with π-(2-Carbethoxyallyl)nickel Bromide. Because this complex was less reactive and thermally less stable than the other complexes studied, it was necessary to use excess complex, heat the reaction mixtures to 50°, and separate the desired α-methylene-γ-butyrolactones from the diester resulting from coupling of the allyl ligands.

(a) α-Methylene-γ-phenyl-γ-butyrolactone (7a).[14,20] Benzaldehyde (0.12 g, 1.16 mmol) was added to the nickel complex (0.62 g, 1.16 mmol) in 15 ml of DMF and the resulting mixture was stirred at 25° for 24 hr. After routine isolation and purification by preparative layer chromatography (Si gel, 2:1 pentane–ether, two developments, R_f 0.36) 0.17 g (85%) of a white crystalline solid (mp 55–56°) was obtained: ir ($CHCl_3$) 3.22, 3.25, 3.31, 3.36, 3.40 (CH), 5.64 (lactone C=O), 6.00 (C=C), 6.66, 6.84, 6.96, 7.13, 7.26, 7.68, 7.81, 8.00, 8.50, 8.86, 9.25, 9.77, 10.00, 10.20, 10.55, 10.70, 12.30, 13.25, 14.30 μ; nmr ($CDCl_3$–TMS) δ 2.6–3.7 (m, 2 H, β-CH_2), 5.50 (d of d, J's = 6.6 and 8.0 Hz, 1 H, PhCHO), 5.66 (d of d, J's = 2.6 and 3.0 Hz, 1 H, =CH), 6.23 (d of d, J's = 2.6 and 3.0 Hz, 1 H, =CH), 7.35 (s, 5 H, Ph).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.68; H, 5.94.

(b) α-Methylene-γ-n-hexyl-γ-butyrolactone (7b). *n*-Heptaldehyde (0.10 g, 0.90 mmol) was added to the nickel complex (0.47 g, 0.90 mmol) in 15 ml of DMF and the resulting mixture was stirred at 25° for 28 hr. After routine isolation and purification by preparative layer chromatography (Si gel, 2:1 pentane–ether, two developments, R_f 0.58) 0.13 g (76%) of a colorless liquid was obtained: ir (neat) 3.39, 3.41, 3.50 (CH), 5.69 (lactone C=O), 6.01 (C=C), 6.82, 6.92, 7.16, 7.24, 7.82, 7.99, 8.70, 8.95, 9.90, 10.65, 11.38, 12.28, 13.62 μ; nmr ($CDCl_3$–TMS) δ 0.90 (m, 3 H, CH_3), 1.30 (m, 10 H, $-CH_2-$), 2.14–3.37 (m, 2 H, β-CH_2), 4.50 (m, 1 H, γ-CH), 5.62 (d of d, J's = 2.6 and 3.0 Hz, 1 H, C=CH), 6.16 (d of d, J's = 2.6 and 3.0 Hz, 1 H, C=CH); mass spectrum, parent m/e 182.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.63; H, 9.67.

(c) γ-Methyl-α-Methylene-γ-phenyl-γ-butyrolactone (7c). Acetophenone (0.15 g, 1.27 mmol) was added to the nickel complex (0.64 g, 1.27 mmol) in 15 ml of DMF and the mixture was stirred at 55° for 24 hr. After routine isolation and purification by preparative layer chromatography (Si gel, 2:1 pentane–ether, two developments, R_f 0.60) 0.20 g (83%) of a colorless liquid was obtained: ir (neat) 3.23, 3.27, 3.29, 3.36, 3.42 (CH), 5.67 (lactone C=O), 6.00 (C=C), 6.24, 6.67, 6.90, 7.14, 7.24, 7.80, 7.92, 8.25, 8.95, 9.18, 9.49, 10.45, 10.80, 11.20, 12.60, 13.00, 14.30 μ; nmr ($CDCl_3$–TMS) δ 1.68 (s, 3 H, CH_3), 3.13 (d of d, J's = 1.0 and 3.0 Hz, 2 H, β-CH_2), 5.69 (d of d, J's = 1.0 and 3.0 Hz, 1 H, C=CH), 6.18 (d of d, J's = 1.0 and 3.0 Hz, 1 H, C=CH), 7.20 (s, 5 H, Ph); mass spectrum, parent m/e 188.

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.35; H, 6.23.

(d) α-Methylene-γ-spirocyclohexane-γ-butyrolactone (7d). Cyclohexanone (0.13 g, 1.30 mmol) was added to the nickel complex (0.69 g, 1.30 mmol) in 15 ml of DMF and the mixture was stirred at 25° for 24 hr. After routine isolation and purification by preparative layer chromatography (Si gel, 2:1 pentane–ether, two developments, R_f 0.55) 0.17 g (80%) of a colorless liquid was obtained: ir (neat) 3.40, 3.50 (CH), 5.67 (lactone C=O), 6.01 (C=C), 6.15, 6.90, 7.16, 7.28, 7.62, 7.84, 7.92, 8.08, 8.35, 8.75, 9.05, 9.65, 10.35, 10.60, 11.20, 11.35, 11.50, 12.25, 13.35 μ; nmr ($CDCl_3$–TMS) δ 1.63 (m, 10 H, cyclohexyl CH_2), 2.74 (t, J = 3.0 Hz, 2 H, β-CH_2), 5.62 (d of t, J's = 2.5 and 0.3 Hz, 1 H, C=CH), 6.17 (d of t, J's = 3.0 and 0.3 Hz, 1 H, C=CH); mass spectrum, parent m/e 166.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.23; H, 8.53.

(e) γ-Benzoyl-α-methylene-γ-phenyl-γ-butyrolactone (7e). The nickel complex (0.60 g, 1.18 mmol) in 20 ml of DMF was added to benzil (0.36 g, 1.72 mmol) and the mixture was heated at 50° for 24 hr. After routine isolation and purification by preparative layer chromatography (Si gel, 7:1 pentane–ether, two developments, R_f 0.30) followed by recrystallization from hexane–ether 0.32 g (68%) of a white crystalline product (mp 64–65°) was obtained: ir ($CHCl_3$) 3.25, 3.28, 3.30, 3.40 (CH), 5.61 (lactone C=O), 5.92 (ketone C=O), 6.25, 6.30, 6.65, 6.89, 7.80, 8.60, 9.25, 9.55, 9.92, 10.50, 11.50, 12.00 μ; nmr ($CDCl_3$–TMS) δ 3.00 (d, J = 16 Hz, 1 H, β-CH_2), 4.24 (d, J = 16 Hz, 1 H, β-CH_2), 5.64 (m, 1 H, vinyl H), 6.24 (m, 1 H, vinyl H), 7.42 (m, 8 H, aromatic), 8.00 (m, 2 H, aromatic).

Anal. Calcd for $C_{18}H_{14}O_3$: C, 76.68; H, 5.07. Found: C, 76.89; H, 5.07.

(f) α-Methylene-γ-(3-spiro-5α-cholestane)-γ-butyrolac-

tone (8). The nickel complex (0.40 g, 0.75 mmol) in 15 ml of DMF was added to 5α-cholestan-3-one (0.30 g, 0.78 mmol) and the resulting mixture was stirred for 24 hr at 25°. After routine isolation the mixture was purified by preparative layer chromatography (Si gel, 10:1 pentane–THF, two developments) and gave three major bands.

Band 1: R_f 0.61; 0.091 g of white solid; unreacted 5α-cholestan-3-one by ir, nmr, and melting point.

Band 2: R_f 0.53; 0.104 g (42%) of white crystalline solid; mp 155–156.5°; ir ($CHCl_3$) 3.41, 3.48 (CH), 5.68 (lactone C=O), 6.01 (C=C), 6.78, 6.82, 6.90, 7.11, 7.20, 7.28, 7.35, 7.49, 7.56, 7.70, 8.05, 8.25, 8.50, 8.60, 8.75, 8.90, 9.10, 9.90, 10.20, 10.55 μ; nmr ($CDCl_3$–TMS) δ 0.65 (s, 3 H, C_{18} methyl), 0.85 (s, 3 H, C_{19} methyl), 0.86 (d, 6 H, J = 6.0 Hz, C_{25} methyls), 0.90 (d, 3 H, J = 6.0 Hz, C_{20} methyl), 2.79 (t, 2 H, J = 2.4 Hz, β-CH_2 in lactone), 5.58 (t, 1 H, J = 2.4 Hz, C=CH), 6.20 (t, 1 H, J = 2.4 Hz, C=CH). This is the isomer in which the lactone oxygen is β, resulting from attack on the α face, as evidenced by the deshielding of the C_{19} methyl[21] peak as well as the peak of the lactone β-CH_2 group,[5] relative to the other isomer.

Anal. Calcd for $C_{31}H_{50}O_2$: C, 81.88; H, 11.08. Found: C, 82.01; H, 11.11.

Band 3: R_f 0.45; 0.123 g (49.5%) of white crystalline solid; mp 209–210°, ir ($CHCl_3$) 3.39, 3.47 (CH), 5.68 (lactone C=O), 6.01 (C=C), 6.80, 6.90, 6.95, 7.11, 7.21, 7.32, 7.69, 7.80, 7.90, 8.08, 8.25, 8.80, 8.91, 9.65, 10.05, 10.30, 10.51, 11.00, 11.10 μ; nmr ($CDCl_3$–TMS) δ 0.65 (s, 3 H, C_{18} methyl), 0.80 (s, 3 H, C_{19} methyl), 0.86 (d, J = 6.0 Hz, 6 H, C_{25} methyls), 0.90 (d, J = 6.0 Hz, 3 H, C_{20} methyl), 2.67 (t, J = 2.6 Hz, 2 H, β-CH_2 in lactone), 5.58 (t, J = 2.6 Hz, 1 H, C=CH), 6.20 (t, J = 2.6 Hz, 1 H, C=CH). This is isomer in which the lactone oxygen is α, resulting from attack of the β face, as evidenced by the chemical shift of the C_{19} methyl and the lactone β-CH_2 group relative to the other isomer.

Anal. Calcd for $C_{31}H_{50}O_2$: C, 81.88; H, 11.08. Found: C, 81.68; H, 11.24.

(g) α-Methylene-γ-(3-spiro-5α-androstan-17-one)-γ-butyrolactone (9). The nickel complex (0.98 g, 1.94 mmol) in 15 ml of DMF was added to 5α-androstane-3,17-dione (0.30 g, 1.10 mmol) and the resulting mixture was heated at 50° for 22 hr. After routine isolation, the desired product was separated from the diester (resulting from coupling of the allyl ligand) by passing through a short column of Si gel. The diester was eluted with 10:1 pentane–THF, and the product lactone eluted with chloroform: yield 0.26 g (76%) of white crystalline solid; ir ($CHCl_3$) 3.40, 3.48, 3.50, 5.67 (lactone CO), 5.75 (cyclopentanone CO), 6.00 (C=C), 6.86, 6.95, 7.10, 7.25, 7.30, 7.59, 7.75, 7.89, 8.05, 8.25, 8.50, 8.78, 9.40, 9.60, 9.71, 9.85, 10.10, 10.51, 11.00, 12.00, 12.20 μ; nmr ($CDCl_3$–TMS) δ 0.83 (s, 6 H, C_{18} and C_{19} CH_3), 1.0–2.0 (m, 20 H, ring CH_2), 2.20 (m, 2 H, CH_2CO), 2.80 (m, 2 H, lactone β-CH_2), 5.65 (m, 1 H, vinyl H), 6.22 (m, 1 H, vinyl H). (Inseparable mixture of epimers.)

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.30; H, 9.12.

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Synthesis of Olefins. Cross Coupling of Alkenyl Halides and Grignard Reagents Catalyzed by Iron Complexes

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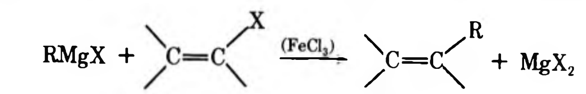
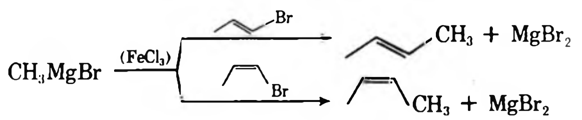
Grignard reagents are coupled with alkenyl halides such as 1-bromopropene and β-bromostyrene in the presence of catalytic amounts of iron(III) complexes to afford alkenes. This cross-coupling reaction can be employed as a synthetic route for alkenes, in which primary, secondary as well as tertiary alkyl groups like isopropyl, cyclohexyl, and *tert*-butyl Grignard reagents are utilized. The reaction is stereospecific since *trans*-1-bromopropene affords only *trans*-butene-2 with methylmagnesium bromide and iron(III) pivalate. Furthermore, the rearrangement of branched alkyl groups such as *tert*-butyl has not been observed with an iron catalyst. Among various iron(III) complexes examined, tris(dibenzoylmethido)iron(III) is the most effective from the standpoint of rates and deactivation. Product and spectral studies suggest that the active catalyst is a labile iron species derived by reduction of iron(III) *in situ* by the Grignard component. High rates of cross coupling are limited by deactivation of the catalyst due to an aging process attributed to aggregation of the active iron species. Several mechanistic schemes are considered for cross coupling including (a) oxidative addition of alkenyl halide to a low valent alkyliron species followed by reductive elimination of the cross-coupled product and (b) assistance by reduced iron in the concerted displacement of halide at the alkenyl center by the Grignard reagent.

Olefins are produced from the cross-coupling reaction 1 between Grignard reagents and alkenyl halides in the presence of catalytic amounts of ferric chloride.[1] Thus, *n*-propylmagnesium bromide and vinyl bromide in tetrahydrofuran (THF) afford pentene-1. *cis*- and *trans*-1-propenyl bromide are converted stereospecifically into *cis*- and *trans*-butene-2 in the presence of methylmagnesium bromide and 10^{-4} *M* ferric chloride.



(1)



(2a)

(2b)

Catalysis of the cross coupling reaction 1 occurs with a reduced iron species, since it can be shown in separate experiments[2] that iron(II, III) chlorides rapidly oxidize alkylmagnesium halides to afford a soluble form of iron, together with alkane and alkene. This soluble iron species is capable of catalyzing the cross-coupling reaction, but its effectiveness is decreased markedly simply on standing. Deactivation of the iron catalyst has been attributed to aggregation of the reduced iron species. In this report, we wish to examine the use of other iron complexes as more effective catalysts, particularly with respect to aging, and to extend the utility of the cross-coupling reaction to Grignard reagents containing secondary and tertiary alkyl groups.

Results

Examination of Iron(III) Complexes as Catalyst Precursors. The cross-coupling reaction between 1-bromopropene and methylmagnesium bromide was used as a model for testing the effectiveness of various iron(III) complexes under a standard set of conditions given in Table I. The optimum concentration of the iron(III) complexes for these screening experiments was determined by varying the concentration of ferric chloride from 2×10^{-5} *M*, where the rate was too slow, to 4×10^{-3} *M*, at which point aging (to be discussed later) severely restricted the production of butene-2. All of these studies were carried out by adding an excess of neat 1-bromopropene to a standard solution of methylmagnesium bromide and iron(III) complex which had previously been stirred for 5 min.

Table I
Iron(III) Complexes as Catalyst Precursors[a]

Run	Iron(III) complex[b]	Conversion, %[c]
1[d]	$FeCl_3$	25
2[e]	$Fe[O_2CC(CH_3)_3]_3$	73
3[e]	$Fe(CH_3COCHCOCH_3)_3$	90
4[e]	$FeCl_3(PPh_3)$	27
5[e]	$Fe(CF_3COCHCOCF_3)_3$	25
6[f]	$Fe(CH_3COCHCOCH_3)Cl_2$	57
7[f]	$Fe(CH_3COCHCOCH_3)_2Cl$	>99
8[f]	$Fe[(CH_3)_3CCOCHCOC(CH_3)_3]_3$	>99
9[f]	$Fe(PhCOCHCOPh)_3$	>99

[a] In THF containing 0.12 *M* CH_3MgBr, 0.35 *M* bromopropene. [b] 4.11×10^{-4} *M*. [c] % completion of reaction within 45 min at 25°; 100% implies all CH_3MgBr consumed. [d] THF, 34 ml. [e] THF, 17 ml. [f] THF, 8.5 ml.

Butene-2 accounted for more than 97% of all the products formed in the reaction, with small amounts (1–2%) of propene as a side product. Traces of isobutylene derived from the 2-bromopropene impurity in the starting material, as well as methane and ethane produced during the generation of the catalyst (*vide infra*), were the only other products observed.

The data in Table I clearly show that the conversion (rate) into butene-2 is highly dependent of the structure of the iron(III) compound.[3] Fe(III) complexes containing β-diketonate ligands in all or most of the coordination sites of iron(III) were the most effective. The color changes occurring during the course of reaction are noteworthy. The iron(III) complexes in THF solution varied from red to orange. Addition of the colorless Grignard reagent caused an immediate change to clear yellow, whereupon the reaction mixture gradually turned darker until at the end of the reaction it became clear gray-black, with a slight tendency toward yellow depending on the iron(III) compound employed. However, with tris(dibenzoylmethido)iron(III) the wine-red solution of iron(III) became lime-green immediately upon addition of the Grignard reagent and then gradually turned more gray as the reaction proceeded. The solutions in all cases are unstable to air and water. They lose color and activity slowly when exposed to air and quite rapidly with water, giving clear homogeneous solutions.

Kinetics. Two related types of kinetic behavior are observed in the cross-coupling reaction depending on the

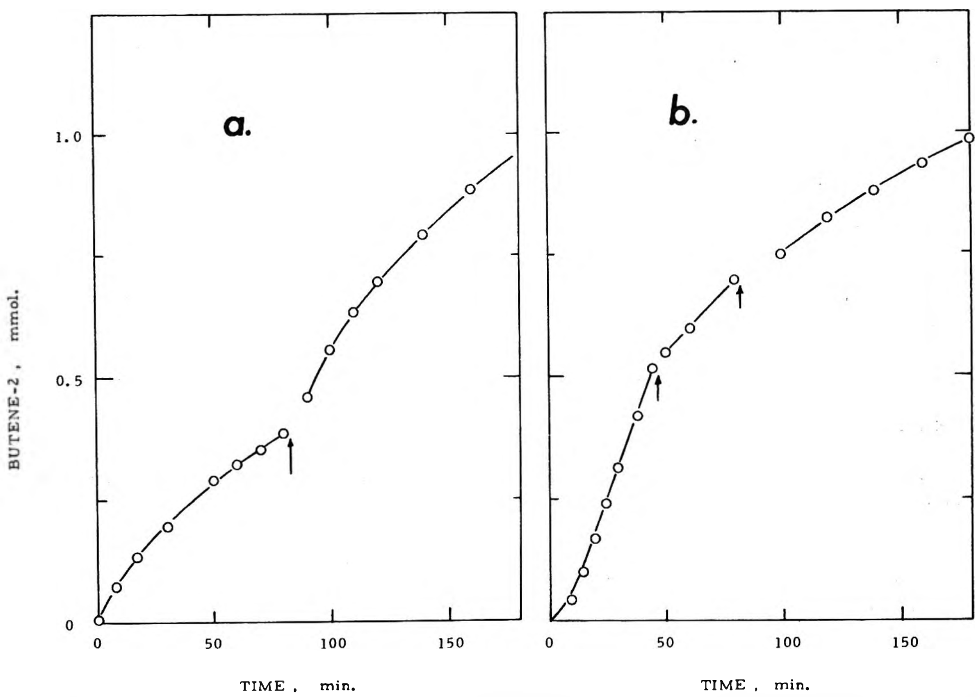


Figure 1. Formation of butene-2 from the cross-coupling reaction with 3.5×10^{-3} mmol of $Fe(DPM)_3$ using (a) 1.5 mmol of CH_3MgBr and 0.5 mmol of $BrCH{=}CHCH_3$; additional 0.5 mmol of 1-bromopropene added at arrow; (b) 0.5 mmol of CH_3MgBr and 1.5 mmol of $BrCH{=}CHCH_3$; additional 0.26 mmol of CH_3MgBr added at arrow.

iron(III) complex. With the active catalyst derived from tris(dipivaloylmethido)iron(III), $Fe(DPM)_3$, the rate of formation of butene-2 is zero order in Grignard reagent after a very short initial period. In the presence of excess 1-bromopropene, this reaction stops abruptly when the methylmagnesium bromide is consumed. The reaction continues unabated when more Grignard reagent is added as shown in Figure 1. The reaction is first order in 1-bromopropene in the presence of excess methylmagnesium bromide, and it can be carried to higher conversions by adding more 1-bromopropene after the first aliquot has been consumed. $Fe(DBM)_3$ shows similar behavior to $Fe(DPM)_3$.

Iron(III) pivalate, $Fe(Pv)_3$, is less active than either $Fe(DBM)_3$ or $Fe(DPM)_3$, and the conversion of methylmagnesium bromide is not complete even in the presence of a large excess of 1-bromopropene. Furthermore, the addition of more Grignard reagent to the reaction mixture has no effect. More butene-2 is formed only if additional $Fe(Pv)_3$ is added.

Aging the Catalyst. We attributed the foregoing difference in the kinetic behavior between $Fe(DBM)_3$ and $Fe(Pv)_3$ to the irreversible deactivation of the catalytic species during the course of reaction. To test this hypothesis, we varied the time of mixing the iron(III) complex with methylmagnesium bromide before the addition of 1-bromopropene. If the time of mixing was less than 5 min, which was carried out by reversing the order of addition of methylmagnesium bromide and 1-bromopropene (*i.e.*, $t_{mix} \cong 0$), we otained more or less the same results as those in Table I. All of the Fe(III) complexes except one showed a diminished conversion into butene-2 when the aging time was extended beyond 15 min as shown in Table II. The single exception to this trend is $Fe(DBM)_3$, which we also noted as being anomalous in its color changes during the reaction. Indeed, the aging time with $Fe(DBM)_3$ could be extended to as long as an hour without serious deleterious effects. Further aging produced a sharp retardation of about 90% which then appeared to remain reasonably constant.

The effects of temperature on aging the catalyst derived

Table II
Effect of Aging on the Catalyst Activity[a]

Run	Fe(III) complex[b]	Aging time, min	Conversion,[c] %	Retardation,[d] %
10[e]	$FeCl_3$	40	2.1	92
11[f]	$Fe(Pv)_3$	15	9.2	87
12[f]	$Fe(acac)_3$	15	40	56
13[f]	$FeCl_3(PPh_3)$	15	12	56
14[f]	$Fe(facac)_3$	15	10	60
15[g]	$Fe(acac)Cl_2$	15	12	79
16[g]	$Fe(acac)_2Cl$	15	6	94
17[g]	$Fe(DPM)_3$	15	4	94
18[g]	$Fe(DBM)_3$	15	>99	0

[a] In THF solutions containing 0.12 *M* CH_3MgBr and 0.35 *M* $BrCH{=}CHCH_3$. [b] 4.11×10^{-4}, Pv = pivalate, acac = acetylacetonide, facac = hexafluoroacetylacetonide, DPM = dipivaloylmethide, DBM = dibenzoylmethide. [c] % reaction at 45 min. [d] Relative to results in Table I. [e] THF, 34 ml. [f] THF, 17 ml. [g] THF, 8.5 ml.

in situ from $Fe(acac)_3$ is illustrated in Figure 2. At 25°, the catalytic activity falls off rapidly as the time of mixing is increased. However, the rate of conversion at 1° reaches a maximum at about 25 min. The decreased conversions beyond 30 min are similar to those found at 25°. Thus, a decrease in temperature serves only to displace the curve in Figure 2 to longer times. We interpret the slower rates of reaction observed at short mixing times and low temperatures to the rather slower rate of reduction of $Fe(acac)_3$ by Grignard reagent at this temperature. Deactivation or aging appears to be a subsequent step which is only slightly affected by cooling.

We attribute the lower conversions obtained from other iron(III) complexes listed in Table I to a similar deactivation of the catalytic species. Aging is largely irreversible, since the addition of more Grignard reagent or bromoalkene is without noticeable effect. Higher conversions to butene-2 under such conditions can only be achieved by the addition of more iron(III) complex.

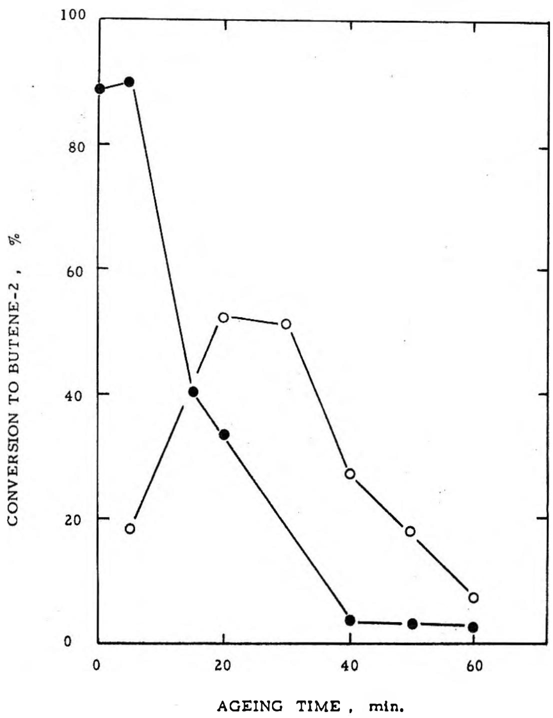


Figure 2. Effect of aging time on the conversion of 0.35 *M* 1-bromopropene and 0.12 *M* methylmagnesium bromide to butene-2 at 25° (●) and 1° (O) using 4.1×10^{-4} *M* $Fe(acac)_3$.

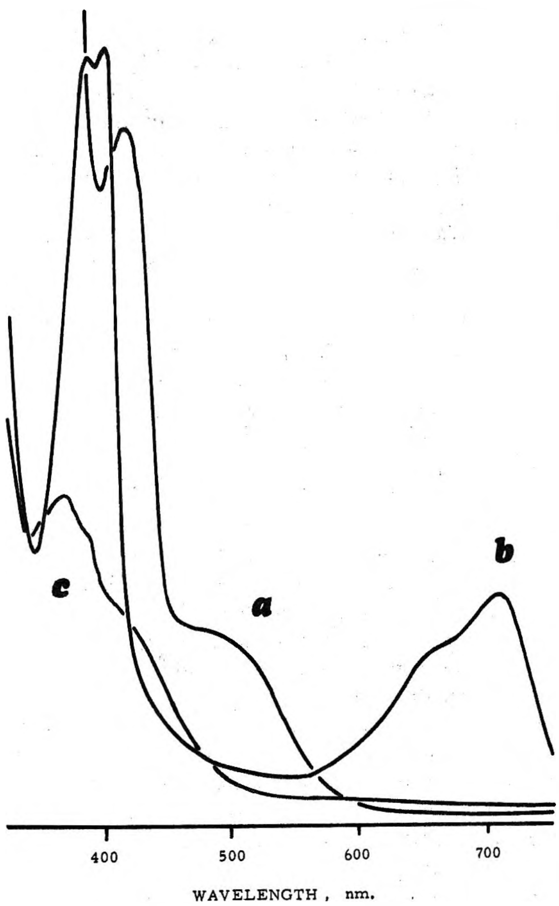


Figure 3. (a) Visible absorption spectrum of 1×10^{-3} *M* $Fe(DBM)_3$ in 0.7 ml of THF; (b) after addition of 0.2 *M* isopropylmagnesium bromide in 1.0 ml of THF to a; (c) after addition of 0.3 mmol of $BrCH{=}CHCH_3$ to b.

If aging of the catalytic species is due to aggregation, a change in coordination around iron by a free ligand in solution could retard deactivation. Several neutral ligands listed in Table III were added to iron(III) complexes to test this hypothesis. The results in Table III indicate that triphenylphosphine does indeed reduce the aging effect on $Fe(Pv)_3$, but unfortunately it also reduces the catalytic activity. Bisdiphenylphosphinoethane shows a similar effect on $Fe(acac)_3$.

Table III
Effect of Neutral Ligands on Aging[a]

Fe(III) complex[b]	Ligand[c]	Aging time, min	Conversion, %	Retardation, %
$Fe(Pv)_3$	PPh_3	5	35	46
$Fe(Pv)_3$	PPh_3	15	19	
$Fe(Pv)_3$	DPPE	5	53	91
$Fe(Pv)_3$	DPPE	15	5	
$Fe(acac)_3$	PPh_3	5	63	86
$Fe(acac)_3$	PPh_3	45	8	
$Fe(acac)_3$	DPPE	5	28	69
$Fe(acac)_3$	DPPE	45	4	

[a] In 18 ml, THF containing 0.11 *M* CH_3MgBr and 0.33 *M* $BrCH{=}CHCH_3$. [b] 3.9×10^{-4} *M* Fe(III). [c] 3.9×10^{-4} *M* free ligand; DPPE = $Ph_2PCH_2CH_2PPh_2$.

Table IV
Reduction of Iron(III) by Methylmagnesium Bromide[a]

Iron(III) complex	CH_3MgBr, (10^2 mmol)	CH_3-MgBr/Fe(III)	CH_4, (10^2 mmol)	C_2H_6, (10^2 mmol)	n[b]
$Fe(acac)_3$	20	4	6.15	1.16	1.7
$Fe(acac)_3$	30	6	3.41	3.29	2.0
$FeCl_3(PPh_3)$	30	6	4.53	2.48	1.9
$Fe(acac)_3$	50	10	1.40	3.54	1.7
$Fe(acac)_3$	125	25	1.96	2.66	1.5

[a] In THF solutions containing 5×10^{-2} *M* iron(III). [b] $n = (CH_4 + 2C_2H_6)/5$.

Studies on the Catalytic Iron Species. The foregoing results indicate that the catalytic species produced from the reaction of iron(III) complexes and methylmagnesium bromide is highly labile and strongly discourage attempts at isolation. The formation of methane and ethane suggested the following stoichiometric relationship:

$$Fe(III) + nCH_3MgBr \longrightarrow Fe(III\text{-}n) + XCH_4 + YC_2H_6 \quad (3)$$

where $n = X + 2Y$. The determination of the value for n according to eq 3 could provide information about the oxidation state of the reduced iron species, which is assumed to be the active catalyst. The experimental determination of n in Table IV was carried out by carefully measuring the amounts of methane and ethane evolved during the reaction of $Fe(acac)_3$ with various amounts of methylmagnesium bromide. We tentatively conclude from the results in Table IV that $Fe(acac)_3$ is reduced to an Fe(I) species.[4]

We attempted to exploit the color changes during the cross-coupling reaction to observe possibly the formation of metastable reduced iron species. In those catalytic systems in which yellow solutions were visually observed, no relevant information could be gleaned since the visible spectrum of the iron(III) complex merely disappeared and no distinctive bands appeared. On the other hand, the reaction of $Fe(DBM)_3$ with Grignard reagent is accompanied by the appearance of a new band at approximately 700 nm.

The absorption spectrum of $Fe(DBM)_3$ in THF solution exhibits two principal bands at 408 nm (ϵ 7550) and 520 (shoulder) as shown in Figure 3. Addition of isopropylmagnesium bromide to this solution immediately causes a new

Table V
Absorption Spectra of Reduced Iron Species from $Fe(DBM)_3$ and Grignard Reagent[a]

Grignard Reagent	Absorption spectrum, nm Band I (ε)	Band II (ε)
CH_3MgBr	360 (130,000)[b]	703 (4300)[b]
$(CH_3)_2CHMgBr$	379	708
	393	
c-$C_6H_{11}MgBr$	379	709
	394	
C_6H_5MgBr	386	706

[a] In THF solution. [b] Based on total conversion of $Fe(DBM)_3$.

Table VI
Reduction of $Fe(DBM)_3$ and $Fe(DBM)_2$ by Methylmagnesium Bromide in THF

Iron complex[a]	Absorption spectrum, λ_{max}, nm (ε)
$Fe(DBM)_3$	409(7550), 500(sh)
$Fe(DBM)_3$ + CH_3MgBr	360(130,000)
	704(4300), 655(sh)
$Fe(DBM)_2$	514(4200)
$Fe(DBM)_2$ + CH_3MgBr	360[b]
	702(4800),650(sh)

[a] In solutions approximately 10^{-3} *M* Fe and 0.2 *M* CH_3MgBr. [b] Not determined.

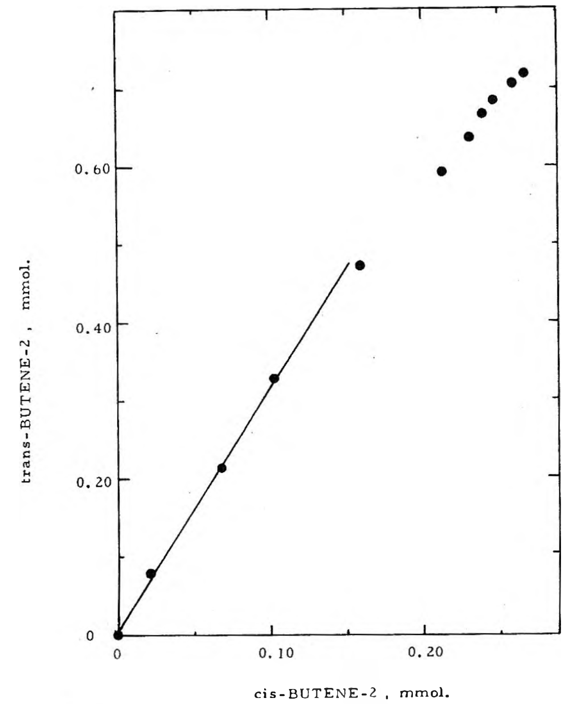


Figure 4. Correlation of the rates of formation of *cis*- and *trans*-butene-2 from 0.12 *M* methylmagnesium bromide and 0.35 *M* *cis*/*trans*-1-bromopropene using 4.1 × 10^{-4} *M* $Fe(acac)_3$.

band to appear at 708.5 nm with a shoulder at about 650 nm, and the band at shorter wavelength is shifted to 378 and 393 nm as a doublet. The color is rapidly bleached by 1-bromopropene, but the spectrum does not revert to that of $Fe(DBM)_3$, showing mainly a band at 355 mm but of roughly the same molar intensity. The color change is not simply due to olefinic π coordination to the iron complex, since pentene-1 in large excess had no effect on the spectrum.

$Fe(DBM)_3$ reacts similarly with other Grignard reagents listed in Table V. In each case, the band at 700 nm retains the same features shown in Figure 3, and it is largely unaffected by the Grignard reagent used. Moreover, the absorptions in the short wavelength region of the spectrum also show pronounced similarities, with the slight exception of the spectrum resulting from methylmagnesium bromide. The absence of significant differences in the absorption spectra of the reduced iron species,[4] presumably Fe(I) or Fe(0), suggest that R groups from the Grignard reagent may not be tightly coordinated, but more studies are required to establish this point.

The possibility existed that the spectrum was not that of an Fe(I) or Fe(0) species but the spectrum of an Fe(II) species. In order to resolve this problem, we independently prepared a sample of bis(dibenzoylmethido)iron(II) dihydrate. The visible absorption spectrum of $Fe(DBM)_2$ in THF has a principal band at 514 nm which is clearly at variance with those of either $Fe(DBM)_3$ or the supposed Fe(I) species. Moreover, addition of methylmagnesium bromide to $Fe(DBM)_2$ resulted in a species whose absorption spectrum is the same as that derived from $Fe(DBM)_3$ under similar conditions (Table VI). These spectral results coupled with the stoichiometric value of n in eq 3, are consistent with Fe(I) or Fe(0) species being the catalyst derived from $Fe(DBM)_3$ or $Fe(DBM)_2$ and Grignard reagent.

Stereospecificity of the Cross-Coupling Reaction Catalyzed by Iron. The coupling of methylmagnesium bromide and 1-bromopropene is stereospecific when induced by ferric chloride.[1] The demonstration of a similar stereospecificity was desirable for the more effective iron(III) complexes examined in this study. Thus, a sample of pure *trans*-1-bromopropene afforded only *trans*-butene-2 when treated with methylmagnesium bromide in the presence of $Fe(Pv)_3$. Similarly, when a mixture of *cis*- and *trans*-1-bromopropene is completely converted into butene-2 with $Fe(Pv)_3$ it affords the same mixture of cis and trans isomers as that contained in the reactant.

The stereospecificity of the reaction and the absence of rearrangement allowed the mixture of *cis*- and *trans*-butene-2 to be used to determine the relative rates of coupling of the isomers. The formations of *cis*- and *trans*-butene-2 are correlated as shown in Figure 4. The competition at low conversions is kinetically pseudo zero order in bromopropene, and the slope is related to the ratio of second-order rate constants k_t/k_c by eq 4. With several iron(III) com-

$$k_t/k_c = \text{slope}\ [\text{cis}]_0/[\text{trans}]_0 \quad (4)$$

plexes listed in Table VII, *trans*-bromopropene is about eight times more reactive than the cis isomer.[5]

Coupling of Alkenyl Halides and Grignard Reagents. We extended the cross coupling of primary alkylmagnesium halides with vinyl and propenyl bromides to include secondary and tertiary alkyl and aryl Grignard reagents as well as β-bromostyrene as reactants. $Fe(DBM)_3$ was used to promote all of the cross-coupling reactions listed in Table VIII. In at least two examples, the reported yields are based on materials isolated from reactions carried out on a preparatory scale. All other yields were determined by quantitative gas chromatography, but were not necessarily optimized.

Every reaction proceeded through the same or similar color changes, going from the wine red of $Fe(DBM)_3$ to an opaque blue-green on addition of the Grignard reagent. This solution then cleared instantly and gradually turned deep amber when the bromo olefin was added. The reactions are exothermic, and those carried out on a preparative scale generated sufficient heat to cause THF to reflux if the solutions were not cooled prior to the addition of bromopropene.

Table VII
Relative Reactivities of *cis*- and *trans*-Bromopropene[a]

Iron(III) complex	Concn, *M*	Relative rate k_t/k_c
$FeCl_3$	4×10^{-4}	7.4
$Fe(Pv)_3$	4×10^{-4}	6.4
$Fe(acac)_3$	4×10^{-4}	7.8

[a] In THF solutions containing 0.35 *M* bromopropene (69% *cis*, 31% *trans*) and 0.12 *M* CH_3MgBr at 25°.

Table VIII
Synthesis of Olefins by the Cross-Coupling Reaction with $Fe(DBM)_3$[a]

Grignard reagent (RMgBr)	Alkenyl bromide (R'Br)	Products, %[b]			
		R–R'	RH	R(–H)	R–R
Ethyl	BrCH=CHCH$_3$[c]	58	12	29	1
Phenyl	BrCH=CHPh	32	*d*		10
Ethyl	BrCH=CHPh	59	8	6	5
Isopropyl	BrCH=CHCH$_3$[c]	60	9	10	3
Cyclohexyl	BrCH=CHCH$_3$[c]	54 45[e]	*d*	*d*	*d*
tert-Butyl	BrCH=CHCH$_3$[c]	27[e]	*d*	*d*	*d*

[a] In 8.5-ml THF solutions containing 0.12 *M* RMgBr, 0.35 *M* bromo olefin, and 4×10^{-4} *M* $Fe(DBM)_3$. [b] Based on RMgBr added. Reaction terminated after 45 min at 25° and products determined be gas chromatography. [c] Mixture of cis and trans isomers. [d] Present but not quantitatively analyzed. [e] Isolated yield.

The cross-coupling reactions listed in Table VIII occurred with no indication of rearrangement of the alkyl group. Thus, isopropylmagnesium bromide and cis/trans 1-bromopropene afforded only 4-methylpentene-2 as cis and trans isomers. Hexene-2, expected from the rearrangement of the isopropyl group to the *n*-propyl group, was not present (<0.5%). Similarly, the coupling of *tert*-butylmagnesium bromide and 1-bromopropene afforded only 4,4-dimethylpentene-2, and no isomeric 5-methylhexene-2 resulting from the possible rearrangement of the *tert*-butyl group to an isobutyl group during the reaction. Isomerization of the bromo olefin was not examined in these studies. We presume from the results of the earlier experiments, however, that the mixture of cis and trans olefins arose directly from the isomeric 1-bromopropenes employed as reactants.

Discussion

The cross-coupling reaction of Grignard reagents and alkenyl halides has several interesting features which merit some discussion, including the nature of the catalytic iron species, the specificity, and the stereochemistry of the coupling. Any mechanistic formulation of this process must take each of these factors into consideration.

The unstable character of the catalytic iron species shown by this study unfortunately precludes a detailed description of the mechanism at this juncture. Our studies do show, however, that the added iron(III) complexes are rapidly reduced by the Grignard component to the catalytically active species. The contrary notwithstanding, we tentatively suggest that a monomeric iron(I) species is the active catalyst.[4] Aggregation of the active iron species may be responsible for the deactivation observed on aging the catalyst. In only one case, $Fe(DBM)_3$, were we able to obtain independent spectral evidence for a reduced iron species as a discrete entity formed during the reaction with Grignard reagent.

The kinetic results show that the cross-coupling reaction is largely independent of the concentration of alkylmagnesium halide. The rate is roughly first order in alkenyl halide and iron catalyst. There are essentially two catalytic cycles which can be considered in order to account for our observations and to form the basis for discussion and further study. Schemes I and II basically differ in the nature of the propagation sequence.[6]

Scheme I

Initiation $$Fe(III) + 2RMgX \longrightarrow Fe(I) + R_{ox} \quad (5)$$

Propagation $$Fe(I) + RMgX \rightleftharpoons RFe(I)^- + MgX^+ \quad (6)$$

$$RFe(I)^- + R'Br \longrightarrow RR'Fe(III) + Br^- \quad (7)$$

$$RR'Fe(III) \longrightarrow RR' + Fe(I), \text{etc.} \quad (8)$$

Termination $$nFe(I) \longrightarrow [Fe(I)]_n \quad (9)$$

$$Fe(I) \xrightarrow{(ox)} Fe(III) \quad (10)$$

The catalytic amounts of iron required for the cross coupling according to the postulate in Scheme I are continually recycled between several oxidation states in a manner demonstrated for the gold-catalyzed coupling of alkyl groups from alkyl halides and Grignard reagents.[7] Analogous mechanisms have been suggested for similar reactions catalyzed by copper, nickel, and rhodium.[7-9]

In Scheme I, the iron(III) complex added as a catalyst precursor is initially reduced in eq 5 by Grignard reagent. Alkene, alkane, and alkyl dimers are the usual products of oxidation R_{ox} of the Grignard component.[10] The aspects of the ensuing propagation sequence in Scheme I which require further elaboration are (a) the oxidation of the reduced iron species in eq 7 and (b) the reduction of iron in eq 8.

A reaction such as that shown in eq 7 between a reduced metal species and an organic halide is formally represented as an oxidative addition.[11] Since it represents the metal complex essentially as a nucleophilic species, conversion into an anionic complex by coordination with Grignard reagent in eq 6 would facilitate the process.[12,13] Oxidative addition of alkyl halides to reduced iron species were described in previous studies.[10] Moreover, the ability of alkenyl halides to enter into oxidative addition reactions like the related aryl halides has been recently described for nickel(0) and platinum(II) complexes.[14,15]

The completion of the catalytic cycle in Scheme I requires the reduced iron species to be regenerated in a subsequent step. Reductive elimination of the alkyl and alkenyl groups as a cross-coupled product in eq 8 would fulfill this requirement. An analogous reductive elimination from trialkylgold(III) species in eq 11 has recently been demonstrated.[16]

$$RAu^{III}(CH_3)_2PPh_3 \longrightarrow RCH_3 + CH_3Au^{I}PPh_3 \quad (11)$$

Scheme I differs significantly from the alternative mechanism in Scheme II in one regard, namely the propagation step. The substitution process in Scheme II requires the reduced iron species to effect substitution by a coordination mechanism. No oxidation or reduction of the iron is required for the one-step process in eq 12, in contrast to the stepwise mechanism presented in eq 7 and 8. Such a con-

Scheme II

Propagation $$Fe(I) + R'Br \rightleftharpoons Fe(R'Br) \quad (6)$$

$$Fe(R'Br) + RMgX \longrightarrow RR' + MgXBr + Fe(I), \text{etc.} \quad (12)$$

Table IX
Comparison of Alkyl and Alkenyl Halides in Iron-Catalyzed Reactions with Methylmagnesium Bromide[a]

Organic halides	Products, %[b]					
	CH_4	C_2H_6	C_2H_4	C_3H_8	C_4H_{10}	C_4H_8-2
Ethyl bromide	48	6	41	16	8	0
1-Bromopropene[c]	Trace	Trace	0	0	0	100[c]
Ethyl bromide + 1-Bromopropene	22	7	8	3	0.4	52[c]

[a] In 8.5-ml THF solution containing 0.12 *M* CH_3MgBr, 0.35 *M* organic halide, and 4×10^{-4} *M* $Fe(DBM)_3$. [b] Based on CH_3MgBr charged. [c] Mixture of *cis* and *trans* isomers.

certed reaction could readily accommodate the retention of stereochemistry observed in the coupling process.[1,17] It gains important support from the lack of alkyl rearrangement during the coupling reaction of isopropyl and *tert*-butylmagnesium bromides. The latter are especially pertinent in view of the extensive rearrangement observed by Kumada, *et al.*, during the related nickel-catalyzed coupling of alkylmagnesium halides with aryl halides.[18] Thus, isopropylmagnesium chloride and various haloarenes with nickel(II) afford not only the expected cumenes, but also significant amounts of the corresponding *n*-propyl isomers are formed depending on the ligand attached to nickel. A stepwise mechanism was postulated in which eq 13 and 14

$$L_2Ni(X)Ar + RMgX \longrightarrow L_2Ni(R)Ar + MgX_2 \quad (13)$$

$$L_2Ni(R)Ar + ArX \longrightarrow RAr + L_2Ni(X)Ar, \text{ etc.} \quad (14)$$

constitute the propagation cycle. They suggested that isomerization of the isopropyl group occurred by β-elimination–readdition from the diorganonickel(II) intermediate in eq 15.

$$ArL_2NiCH(CH_3)_2 \rightleftharpoons ArL_2Ni(H)(\text{//}\!-CH_3) \rightleftharpoons ArL_2NiCH_2CH_2CH_3 \quad (15)$$

Alkyl isomerization and β elimination of other alkyl groups σ bonded to metals have been reported and appear to be rather general properties of transition metal alkyls.[19-21] We would have expected a similar rearrangement and/or elimination during the cross-coupling process if it occurred by Scheme I, especially with the *tert*-butyl moiety which is particularly prone to such an alkyl isomerization and elimination.[20,21]

Further support for a concerted mechanism is obtained by a competition experiment in which the cross-coupling reaction between methylmagnesium bromide and 1-bromopropene is carried out in the presence of ethyl bromide. Alkyl halides such as ethyl bromide have been shown independently to react with Grignard reagents in the presence of iron(III) complexes under conditions similar to the cross coupling reaction.[10] The products such as those given in Table IX for the reaction between ethyl bromide and methylmagnesium bromide are derived from methyl- and ethyliron intermediates which undergo facile reductive elimination by disproportionation and coupling.[10] Such organoiron species cannot be involved in the cross-coupling reaction of 1-bromopropene, since no cross-over product particularly pentene-2 in eq 18 was formed in the competition reaction given in Table IX.

$$CH_3MgBr + \begin{cases} CH_3CH{=}CHBr \\ CH_3CH_2Br \end{cases} \xrightarrow{Fe(DBM)_3} \begin{cases} \rightarrow CH_3CH{=}CHCH_3 & (16) \\ \rightarrow CH_4, C_2H_6, C_2H_4, \text{etc.} & (17) \\ \not\rightarrow CH_3CH{=}CHCH_2CH_3, & (18) \end{cases}$$

Organoiron species capable of undergoing reductive elimination, however, are present during the cross-coupling process. Thus, the yields of alkane, alkene, and alkyl dimers, as products of oxidation of the Grignard component in Table VIII, are too high to be derived solely by the reduction of the catalytic amounts of iron(III) in the initial phases of the process. They undoubtedly arise from an organoiron species in a higher oxidation state than those presented in eq 6. For example, it is possible that the organoiron species in eq 7 and 8 in Scheme I may be involved by a competing exchange followed by reductive elimination (eq 19). Alternatively, similar organoiron species may be de-

$$RR'Fe(III) + RMgX \rightleftharpoons R'MgX + R_2Fe(III) \longrightarrow Fe(I) + R_{ox} \quad (19)$$

rived by an entirely independent pathway. In either case, the information on hand is insufficient to use such side reactions to distinguish the two mechanistic schemes.

The lines of evidence used above are not sufficient to distinguish Scheme I from Scheme II rigorously, since exceptions to each are known. However, we hope that further studies in progress will help to resolve some of these points.

Experimental Section

Materials. Magnesium was kindly provided by Dow Chemical Co. as triply sublimed metal. Tetrahydrofuran (THF) was supplied in generous quantity by E. I. du Pont and purified by first treating it with potassium benzophenone ketyl, freeze–pump–thaw degassing this solution, and vacuum transferring the purified THF prior to use. 1-Bromopropene (Aldrich Chemical Co.) was purified by shaking with a saturated $NaHCO_3$ solution, drying with calcium hydride, and distilling the remaining mixture of cis and trans isomers from the 2-bromopropene impurity on a Teflon annular spinning band column. Pure *trans*-1-bromopropene was supplied by Chemical Samples Co. All other commercially available reagents were purified by published methods before use unless otherwise noted.[22]

Grignard Reagents. All Grignard reagents were prepared in the usual manner by adding a solution of alkyl halide in THF to an excess of magnesium shavings and allowing the reaction to go to completion under reflux. The molarity of the Grignard reagents was determined by one of two methods. If the hydrolysis product of the Grignard reagent was a gas, a known volume of the Grignard reagent was hydrolyzed with a 10% sulfuric acid solution, and the alkane liberated as a gas was determined by quantitative gas chromatography. If the hydrolysis product of the Grignard reagent was not a gas, a known volume of Grignard reagent was added to a known excess amount of standard sulfuric acid. The unconsumed acid was then back-titrated with standard sodium hydroxide solution.

Iron(III) Complexes. Ferric chloride was commercially available (Fisher Scientific) and dehydrated by azeotropic distillation with benzene prior to use.

Ferric pivalate was generously provided by E. I. du Pont Co. and used without further purification.

Ferric acetylacetonate was commercially available material (Shepard Chemical) and purified by recrystallization from absolute ethanol; visible spectrum: λ_{max} 354, 436 nm.

Ferric chloride–triphenylphosphine [$FeCl(PPh_3)$] was prepared by the method of Singh and Rivest as follows.[23] Iron enneacarbonyl $Fe_2(CO)_9$ (1.8 g, 4.8 mmol) was placed in a 200-ml two-necked round-bottom flask in a dry bag filled with nitrogen. Under a flow of nitrogen, 3.0 g (11.4 mmol) of triphenylphosphine in $CHCl_3$ (100 ml) was added to the flask, which was fitted with a reflux condenser and a fritted disk filter tube with receiver. The mixture was refluxed for 15 hr. After cooling and filtering, the filtrate was concentrated to about 25-ml total volume on a rotary evaporator. The concentrated filtrate was shaken with *n*-hexane and a dark yellow viscous mass separated. After decanting the supernatant liquid, the residue was treated with absolute ethanol whereupon a yellow solid formed. Recrystallization from absolute ethanol yielded a stable yellow powder (13% yield), mp 156–158°. Although the experimental melting point is approximately 40° higher than that reported, the compound was identified by its infrared spectrum: Ph_3–P, 1107; Fe–Cl, 372; Fe–P, 522 cm^{-1} (Perkin-Elmer 621 using silver chloride and polyethylene windows).

Ferric hexafluoroacetylactonate [$Fe(HFA)_3$] was prepared by the method of Juvet and Durbin in the following manner.[24] Hexafluoroacetylacetone (HFA, Eastman Kodak) was shaken several times with concentrated sulfuric acid to dehydrate it prior to use. After removal of the acid the HFA was added directly to 1.06 g (2.26 mmol) of finely divided ferric nitrate in a small flask fitted with a drying tube. The mixture was heated gently to 60° for about 5 min. On cooling, the product was extracted into carbon tetrachloride, removed by rotary evaporation, and subsequently recrystallized from carbon tetrachloride. $Fe(facac)_3$ was obtained as red needles in 48% yield: mp 48–50° (reported 49°);[25] infrared spectrum 1615 (C=O), 1645 (C=C); 1438, 1113 (C–H); 1255, 1220 (C–F_3); 663 cm^{-1} (C–CF_3);[25] visible spectrum λ_{max} 367 nm.

$Fe(acac)Cl_2$ was prepared by the method of Puri and Methrotra as follows.[26] To a solution of ferric chloride in benzene (50 ml) was added an equivalent amount of acetylacetone, at which point the solution became red. The solution was allowed to reflux for 24 hr in a 130° oil bath. After cooling, the solid product was collected by filtration of the reaction mixture and recrystallized as a red powder by adding hot hexane to a hot solution of the product in benzene: mp 165–170° dec; visible spectrum λ_{max} 328 nm; Cl (as AgCl) calcd 31.4; found 33.2.

$Fe(acac)_2Cl$ was prepared in the following manner.[26] To a solution of ferric chloride in benzene was added a greater than 2:1 excess of acetylacetone, at which point the mixture became red. The mixture was refluxed for 40 hr and the solid collected on cooling; the filtrate was saved. The collected solid was determined by chloride analysis to be $Fe(acac)Cl_2$. After removal of the benzene from the dark red mother liquor by rotary evaporation, the remaining oil was recrystallized by adding hot hexane to a hot benzene solution of the product. The product was obtained as dark red needles: 34% yield; mp 191–196°; visible spectrum λ_{max} 350 nm, 442; Cl (as AgCl) calcd 12.2, found 11.4.

$Fe(DPM)_3$ was prepared by the method of Hammond and coworkers as follows.[27] To an aqueous solution containing an excess of ferric sulfate and an excess of sodium acetate was added an ethanolic solution (20 ml) of dipivaloylmethane (1.82 g, 9.90 mmol). Reaction was immediate and an orange-red powder formed in solution, which was subsequently collected by filtration. Additional product could be precipitated from the mother liquor by adding large amounts of water. Sublimation at 130–140° yielded an orange powder, mp 163.5–164°, yield 33%.

$Fe(DBM)_3$ was prepared in the following manner.[28] To an aqueous solution of 0.6 g of ferric chloride was added an ethanolic solution of dibenzoylmethane (1.85 g, 2.76 mmol). An immediate reaction afforded a red solid which was completely precipitated by the addition of 50% aqueous ammonia. The solid was filtered, washed with water, and dried. Recrystallization by addition of hot hexane to a hot benzene solution of product gave a 70% yield of red needles: mp 240° dec; visible spectrum λ_{max} 408 nm, 500 (sh).

$Fe(DBM)_2 \cdot 2H_2O$ was prepared by analogy to the work of Emmert as follows.[29] To a degassed aqueous solution of excess ferrous sulfate was added 2.24 g (3.34 mmol) of dibenzoylmethane in ethanol. At this point the green solution immediately turned pink. On addition of 20 ml of 5% sodium hydroxide, the product precipitated as a bluish purple solid which readily oxidized in solution and more slowly in air. The solid was collected by filtration under a blanket of nitrogen and dried at 40° *in vacuo* for 15 hr. The product was recrystallized by adding hot, degassed hexane to a hot solution of product in degassed benzene, visible spectrum λ_{max} 513 nm. Although $Fe(DBM)_2 \cdot 2H_2O$ was not characterized directly by additional physical methods, comparing it to reports by other workers on analogous compounds leaves little doubt as to its identity.[30,31] Visible spectra were taken on a Cary 14 instrument using Pyrex air-tight 1-cm or 1-mm cells specially made in the Indiana University glass shop.

Procedure for Studying Activity of Fe(III) Catalysts. A 200-ml two-neck flask was equipped with a stirring bar and a rubber septum and dried in the oven. It was taken hot from the oven and placed on a vacuum line where it was evacuated until cool. After filling the flask with nitrogen, butane was added as an internal standard. Aliquots of methylmagnesium bromide and iron(III) complex in THF were added and allowed to mix for 5 min. An excess of neat 1-bromopropene was then added and the head gases analyzed for products 45 min from this point; *cis*- and *trans*-2-butene were identified by gas chromatography using commercial pure samples.

For reactions requiring no aging, into a nitrogen-filled, dry, two-necked, 200-ml, round-bottom flask was placed a solution of Fe(III) in THF and neat 1-bromopropene. To this was then added methylmagnesium bromide in THF. The butene products were analyzed 45 min from this point by gas chromatography using butane as an internal standard.

Procedure for Experimental Determination of *n* in Equation 3. A three-necked, 100-ml, round-bottom flask was fitted with a stirring bar, a stopper, a septum, and a sealed angular piece of glass tubing containing 0.05 mmol of the solid Fe(III) compound. The vessel was then carefully evacuated and filled with nitrogen so that none of the Fe(III) compound fell into the flask. After filling, a portion of head gas was removed and 25 ml of dry THF and 20 ml of propane standard were added. Methylmagnesium bromide (2 ml) was added and allowed to equilibrate, and the head gas sampled. The flask was turned so the Fe(III) compound dropped into solution and again was allowed to equilibrate and the head gas sampled for methane and ethane.

$Fe(DBM)_3$ Catalyzed Reaction of Methylmagnesium Bromide with 1-Bromopropene and Ethyl Bromide. To a nitrogen-filled, dry, two-necked, 200-ml, round-bottom flask containing 5 ml (1 mmol) of methylmagnesium bromide in THF was added 3.5 ml (3.5×10^{-3} mmol) of $Fe(DBM)_3$ in THF and the two were allowed to mix for 5 min. Ethyl bromide (0.25 ml, 3 mmol) was added, followed by 0.25 ml (3 mmol) of 1-bromopropene. Products were determined 45 min from this point by gas chromatography after quenching with 5 ml of 0.2 *N* sulfuric acid. Reversing the order of addition of ethyl bromide and 1-bromopropene had no effect on the product distribution.

$Fe(DBM)_3$ Catalyzed Reaction of Methylmagnesium Bromide and Ethyl Bromide. To a nitrogen-filled, dry, two-necked, 200-ml, round-bottom flask containing 5 ml (1 mmol) of methylmagnesium bromide in THF was added 3.5 ml (3.5×10^{-3} mmol) of $Fe(DBM)_3$ in THF and the mixture stirred for 5 min. Ethyl bromide (0.25 ml, 3 mmol) was added and the products were analyzed by gas chromatography 45 min from this point, following the quench with 5 ml of 0.2 *N* sulfuric acid.

Metathesis of Methylmagnesium Bromide and Ethyl Bromide. In a dry nitrogen-filled, two-necked, round-bottom flask 5 ml (1 mmol) of methylmagnesium bromide in THF and 0.25 ml (3 mmol) of ethyl bromide were allowed to mix for 45 min. The head gases were analyzed by gas chromatography following the quenching with 5 ml of 0.2 *N* sulfuric acid. No ethane was observed and 98% of the materials could be accounted for.

Procedure for Studying the Effect of Free Ligand on Fe(III) Catalysts. Into a nitrogen-filled, dry, two-necked, 200-ml, round-bottom flask was placed 7 ml (7×10^{-3} mmol) of the Fe(III) complex in THF and 1 ml (7×10^{-3} mmol) of free ligand in THF. After these components were mixed for 5 min, 10 ml (2 mmol) of methylmagnesium bromide in THF was added and stirred for the desired time of aging. Then 0.5 ml (6 mmol) of 1-bromopropene was added, and after 45 min the head gases were analyzed for 2-butenes by gas chromatography using a butane standard.

Procedure and Conditions for Various Cross-Coupling Reactions. In a nitrogen-filled, dry, 200-ml, round-bottom flask was placed 5 ml (1 mmol) of Grignard reagent in THF. To this mixture was added 3.5 ml (3.5×10^{-3} mmol) of $Fe(DBM)_3$ in THF and the two were mixed for 5 min. Alkyl bromide (3 mmol) was added, and products were analyzed 45 min from this point as below.

Ethylmagnesium Bromide and 1-Bromopropene. The 2-pentene cross-coupled product was identified quantitatively by gas chromatography (6 ft, 15% dibutyl tetrachlorophthalate column) using a pure commercial sample (Chemical Samples Co.) and propane as internal standard.

Phenylmagnesium Bromide and β-Bromostyrene. The *trans*-stilbene cross-coupled product was identified by gas chromatography (5 ft, 5% SE-30 column) using a pure commercial sample and adamantane as the internal standard.

Ethylmagnesium Bromide and β-Bromostyrene. Butenylbenzene as the cross-coupled product was identified and quantitatively analyzed by gas chromatography (10 ft, 15% Apiezon column) using a pure sample prepared by the base-catalyzed isomerization of 1-phenylbutene-2 (Phillips Petroleum Co.) and purified by distillation. Octane was used as internal standard.

Isopropylmagnesium Bromide and 1-Bromopropene. The 4-methyl-2-pentene cross-coupled product was identified and analyzed quantitatively by gas chromatography (10 ft, 15% Carbowax column) using a pure commercial sample (Chemical Samples Co.) and heptane as internal standard. *cis*- and *trans*-hexene-2 (Aldrich Chemical Co.) are well-separated from 4-methyl-2-pentene on a 6 ft, 15% dibutyl tetrachlorophthalate column, and no evidence could be found for their presence in the reaction mixture. Since authentic alkenes were available, quantitative ga chromatography was effected by the internal standard method after careful calibration under conditions which reproduced the reaction as closely as possible.

General Preparative Procedures. To approximately 45 mmol of Grignard reagent in THF was added 0.15 mmol of $Fe(DBM)_3$ in THF. After mixing for 5 min 10 ml (12 mmol) of 1-bromopropene was added and the solution cooled in an ice bath to prevent the THF from refluxing. After 60 min, the mixture was filtered to give a dark liquid and a white solid. The solid was dissolved in hydrochloric acid and the liquid, which had been concentrated by a factor of 2 by distillation, was extracted with large amounts of 5% hydrochloric acid and an organic solvent. The organic solvent was then removed and the product collected by fractional distillation.

Cyclohexylmagnesium Bromide and 1-Bromopropene. A preliminary determination of the product was made by gas chromatography (10 ft, 15% Carbowax column) which indicated a 60–65% yield of propenylcyclohexane, 54% of which was recovered from a pentane extract: bp 80–90° (90 mm); mass spectrum *m/e* 124 (M^+); nmr methyl protons (doublet) δ 1.30 (J = 7 Hz), ring protons (multiplet) 5.48; integration olefinic/alkyl 1:6.8. *Anal.* Calcd for C_9H_{20}: C, 87.01; H, 12.99. Found: C, 86.91; H, 12.87.

***tert*-Butylmagnesium Bromide and 1-Bromopropene.** A preliminary examination by gas chromatography (6 ft, 15% dibutyl tetrachlorophthalate) identified the 4,4-dimethyl-2-pentene cross-coupled product using a pure sample as the basis for the identification (Chemical Samples Co.). Gas chromatographic analysis indicated a yield of about 55%, of which 27% was isolated from an octane extract: mass spectrum *m/e* 98 (M^+); nmr δ *tert*-butyl protons (singlet) 1.00, methyl protons (doublet) 1.60 (J = 4.5 Hz), olefinic protons (multiplet) 5.38; integration *tert*-butyl/methyl/olefinic 8.6:2.9:1. The reaction mixture was examined by gas chromatography for the presence of the isomeric 5-methylhexene-2 which is readily separated from 4,4-dimethylpentene-2 on a 10 ft, 15% Carbowax 5M column. Authentic 5-methylhexene-2 was prepared from the cross coupling of isobutylmagnesium bromide and 1-bromopropene with $Fe(DBM)_3$.

Note Added in Proof. A radical-chain mechanism has recently been proposed for the coupling reaction between π-allylnickel bromide and organic halides [L. S. Hegedus and L. L. Miller, *J. Amer. Chem. Soc.*, **97,** 459 (1975)]. Alkyl radicals were postulated as principal chain-carrying species to account for the loss of stereochemistry during the coupling of (*S*)-2-iodooctane. A different chain mechanism is apparently operative with β-bromostyrene since coupling proceeds with retention of stereochemistry. The latter is similar to the stereochemical observations in the iron-catalyzed couplings reported here. The strongly reducing environment, however, strongly discourages the use of similar tests for inhibition [I. H. Elson, D. Morrel, and J. K. Kochi, *J. Organometal. Chem.*, 84, C7 (1975)] in our system.

Acknowledgment. We wish to thank the National Science Foundation for partial financial support of this work.[32]

Registry No.—$FeCl_3$, 7705-08-0; $Fe[O_2CC(CH_3)_3]_3$, 53418-62-5; $Fe(CH_3COCHCOCH_3)_3$, 14024-18-1; $FeCl_3(PPh_3)$, 21144-09-2; $Fe(CF_3COCHCOCF_3)_3$, 17786-67-3; $Fe(CH_3COCHCOCH_3)Cl_2$, 18533-50-1; $Fe(CH_3COCHCOCH_3)_2Cl$, 14689-46-4; $Fe[(CH_3)_3C-COCHCOC(CH_3)_3]_3$, 14876-47-2; $Fe(PhCOCHCOPh)_3$, 14405-49-3; methylmagnesium bromide, 75-16-1; *cis*-1-bromopropene, 590-13-6; *trans*-1-bromopropene, 590-15-8; ethyl bromide, 74-96-4; ethylmagnesium bromide, 925-90-6; phenylmagnesium bromide, 100-58-3; β-bromostyrene, 103-64-0; isopropylmagnesium bromide, 920-39-8; cyclohexylmagnesium bromide, 931-50-0; *tert*-butylmagnesium bromide, 2259-30-5.

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(5) These results are somewhat at variance with the earlier study in ref 1.
(6) Coordination around iron hereinafter will be largely unspecified unless required for the discussion. Oxidation numbers are only included as a bookkeeping device [J. Halpern, *Accounts Chem. Res.*, **3,** 386 (1970)] and are not necessarily intended to denote actual changes in oxidation states (*cf.* C. K. Jorgensen, "Oxidation Numbers of Oxidation States," Plenum Press, New York, N.Y., 1969).
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A Study of the Alkylation of Enamines Derived from Sterically Hindered Amines[1]

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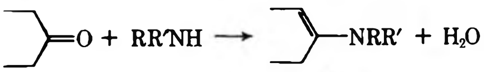
Alkylation by alkyl halides and oxonium salts of enamines derived from a series of sterically hindered amines was studied. Cyclohexanone enamines of diisobutylamine, *n*-butylisobutylamine, and 2,2-dimethylpyrrolidine were found in some cases to give improved yields of C-alkylated products. Application to enamines of mono- and disubstituted acetaldehydes led to a useful procedure for the C-alkylation of such aldehydes by simple alkyl halides.

One of the most elegant methods for carbon–carbon bond formation is the enamine synthesis developed by Stork and coworkers.[2] The mild conditions under which enamines can be prepared, reacted with electrophiles, and the products hydrolyzed to α-substituted aldehydes and ketones have led to extensive utilization of enamines for the synthesis of polyfunctional molecules.[3] The principal reactions occurring during an enamine synthesis are the following (E^+ is a generalized electrophile).

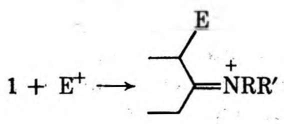
preparation



(1)

1

electrophilic attack



(2)

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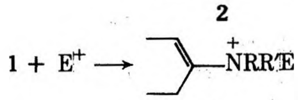
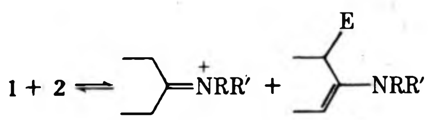


(3)

3

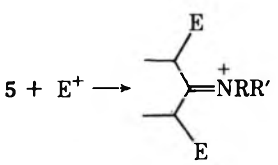
proton transfer



(4)

4 5

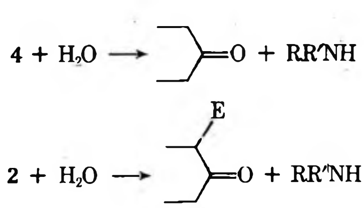
polysubstitution



(5)

6

hydrolysis



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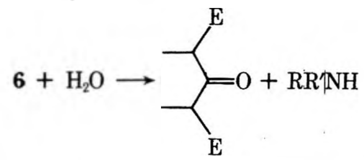
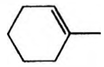


In general, polysubstitution (reaction 5) and electrophilic attack at nitrogen (reaction 3) lower the yield of the monosubstitution product **7**, whose preparation is usually the goal of the synthesis. With electrophilic olefins or acyl halides, attack at nitrogen is reversible and does not interfere with the desired C-alkylation or acylation. Moreover, reagent stoichiometry, reaction solvent, and choice of amine component can be manipulated to minimize polysubstitution.[2] With alkyl halides, however, the synthesis is, in general, satisfactory only for the most strongly electrophilic members of the class, such as the allylic and benzylic halides and the α-halocarbonyl compounds. Alkylation of ketone enamines with simple unactivated alkyl halides tends to give complex mixtures of unalkylated, monoalkylated, dialkylated, and N-alkylated products. Methylation appears to be especially bad in this respect. For example, Stork reports that the pyrrolidine enamine of cyclohexanone gives with methyl iodide 30% recovered starting material, 44% 2-methylcyclohexanone, and considerable 2,6-dimethylcyclohexanone.[2] Alkylation of aldehyde enamines by unactivated halides is even less satisfactory, with N-alkylation and aldol condensation usually the only reactions observed.[4,5] Our objective in undertaking the work reported here was to see if appropriate modification of the amine component would remove some of these limitations.

Results and Discussion

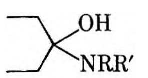
In considering ways to modify the amine component, we could find no good rationale for planning modifications that might reduce the amount of polysubstitution. The amount of reaction 5 which occurs is likely to be a function not only of the relative alkylation rates for unsubstituted and monosubstituted enamines but also of the various acid–base equilibria involved (reaction 4). The degree of polysubstitution might then show a complex dependence on the structure of the amine component. For this reason, we focused our efforts on modifications which might reduce the amount of N-alkylation. It seemed to us that the rates of C- and N-alkylation (reactions 2 and 3) should respond differently to the bulk of alkyl groups R and R′ attached to nitrogen. Very bulky groups might repress N-alkylation completely. However, in designing a suitably hindered amine, two additional factors had to be considered. First, with highly hindered amines the preparation of enamine **1** could become impracticably difficult. Reaction 1 must pass through a carbinolamine intermediate **8**, whose concentra-

Table I

Alkylation of Cyclohexanone Enamines  **NRR′ by Oxonium Salts[a]**

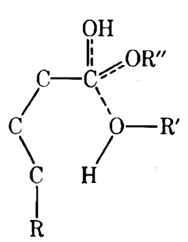
Entry no.	Enamine R	Enamine R′	Registry no.	Alkylating agent	Yields, % Cyclohexanone	Yields, % 2-Alkylcyclohexanone	$-E_s{}^c$ $(R + R')^b$
1	$-(CH_2)_4-$		1125-99-1	$Et_3OBF_4{}^f$	6	25	
2[c]	*i*-Bu	*i*-Bu	49651-43-6	Et_3OBF_4	12, 18	69, 79	2.48
3	*i*-Bu	*n*-Bu	53516-45-3	Et_3OBF_4	5	79	1.94
4	*i*-Bu	*n*-Pr	53516-46-4	Et_3OBF_4	20	70	1.91
5	*i*-Bu	Et	53516-47-5	Et_3OBF_4	5	52	1.62
6	*n*-Bu	*n*-Bu	10468-25-4	Et_3OBF_4	6	45	1.40
7	Isopentyl	Isopentyl	53516-48-6	Et_3OBF_4	8	37	1.31
8	$-CH_2CH_2OMe$	$-CH_2CH_2OMe$	53516-49-7	Et_3OBF_4	4	27	2.15
9	*i*-Bu	Me	53516-50-0	Et_3OBF_4	3	8	1.24
10	$-(CH_2)_4-$			$Me_3OBF_4{}^g$	19	5	
11[d]	*i*-Bu	*i*-Bu		Me_3OBF_4	19	66	
12[d,e]	*i*-Bu	*i*-Bu		Me_3OBF_4	9	74	
13[d,e]	*i*-Bu	*n*-Bu		Me_3OBF_4	16	66	
14[d,e]	*n*-Bu	*n*-Bu		Me_3OBF_4	10	17	

[a] The enamine was treated with 1.25 mol of oxonium salt in dichloromethane for 2 hr at room temperature. Yields were determined by gas chromatography. [b] See text. [c] Two runs. [d] Small amounts of 2,6-dimethylcyclohexanone (1–3%) were also formed. [e] Nitromethane as reaction solvent. [f] Registry number, 368-39-8. [g] Registry number, 420-37-1.

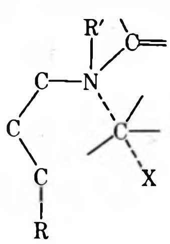


8

tion at equilibrium (or rate of formation) will influence the overall rate of enamine formation. Bulky groups on nitrogen would be expected to lower the stability of **8** and to have an adverse effect on reaction **1**. Second, approach to the β-carbon of enamine **1** could become so hindered that C-alkylation would be unusably slow with all but the most powerfully electrophilic alkylating agents. Indeed, Opitz in his attempts to alkylate aldehyde enamines of dicyclohexylamine found that these enamines could not be C-alkylated at all by unactivated halides (*e.g.*, *n*-propyl iodide) and were alkylated only in rather low yields by more electrophilic agents.[5] In order to repress N-alkylation without unduly retarding either C-alkylation or the preparation of the enamine itself, we sought an alkyl group capable of exerting a rather specific steric hindrance at the nitrogen atom. The isobutyl group seemed to offer considerable promise for this purpose. First, as a primary alkyl group, it ought not to interfere too greatly with the formation of the enamine itself. Then, the principle bulk of the isobutyl group, being concentrated at the branched β-carbon atom, appeared sufficiently removed from the site of C-alkylation not to interfere with that process. Finally, this same branching at the β-carbon might well offer substantial hindrance to the sterically demanding N-alkylation reaction. With regard to the last point, Newman, in studying the data on acid-catalyzed esterification of hindered acids, suggested that the rate-retarding effect of an alkyl group was related to the number of atoms (six-number) located six atoms away from carbonyl oxygen.[6] The similarity between transition states for acid-catalyzed esterification (or the related hydrolysis) and N-alkylation suggested that an isobutyl group with a six-number of six, should be effective at retarding the latter reaction.

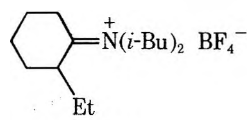


transition state for esterification (R′ = alkyl; R″ = H) or hydrolysis (R′ = H; R″ = alkyl)



transition state for N-alkylation

In our first attempt to reduce these considerations to practice, the diisobutylamine enamine of cyclohexanone was prepared by azeotropic distillation of the components in xylene. Complete reaction required several days at reflux, reflecting, no doubt, steric hindrance in the amine component. In order to obtain rapid and complete reaction of the enamine, it was alkylated with an excess of triethyloxonium tetrafluoroborate in dichloromethane. After removal of solvent and hydrolysis with water, a disappointingly low yield of 2-ethylcyclohexanone, along with a small amount of cyclohexanone, was at first obtained. However, we noticed that during hydrolysis a heavy oil separated, which solidified upon cooling. Examination by nmr revealed that this solid was not the expected N-alkylated salt but was instead the iminium salt **9**. Apparently **9** had sur-

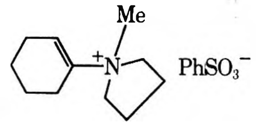


9

vived treatment with boiling acid virtually unchanged, making it one of the most stable acyclic iminium salts known. The hydrolytic stability of **9** is probably due to its reluctance to form a carbinolamine intermediate. Refluxing **9** with sodium acetate–acetic acid buffer, however, did bring about smooth hydrolysis to 2-ethylcyclohexanone.[7] Repetition of the alkylation reaction with hydrolysis by acetate buffer then produced 2-ethylcyclohexanone in 79% yield, accompanied by 18% cyclohexanone. Encouraged by the outcome of this experiment, we prepared a series of cyclohexanone enamines and studied their alkylation with both triethyl- and trimethyloxonium tetrafluoroborates. Results are summarized in Table I. As pyrrolidine enamines have proven most satisfactory for alkylations,[2] the pyrrolidine enamine of cyclohexanone was also alkylated under the same conditions (entries 1 and 10). Clearly, the results of Table I show that the use of certain sterically hindered amines, notably diisobutyl- and *n*-butylisobutylamine, can greatly increase the yields of C-alkylated products. Control experiments established that the gas chromatographic procedure used to determine yields led to a 90–95% recovery of ketonic products; therefore, the unaccounted for portion of the starting material probably represents N-alkylation.[8] That the improvement observed in the C/N-alkylation ratio is related to the steric bulk of the amine component is suggested by comparison of the C-alkylation yields with the $E_s{}^c$ values for the *N*-alkyl groups. $E_s{}^c$ values, a more quantitative measure of steric effect than six-number, are Taft's original steric parameters,[9] modified by Hancock[10] to remove a hyperconjugative component in the reference reaction (ester hydrolysis). The sum of the $E_s{}^c$ values for the two *N*-alkyl groups is given in the last column of Table I. With one exception, the yields of C-alkylated products fall off monotonically with decreasing sum of the $E_s{}^c$ values.[11] The single exception, bis(2-methoxyethyl)amine (entry 8), may reflect a not unexpected polar effect on the relative rates of C- and N-alkylation.[12]

Two other points in Table I deserve comment. First, because trimethyloxonium tetrafluoroborate is insoluble in dichloromethane, this reagent was also utilized as a solution in nitromethane. The yield of 2-methylcyclohexanone was slightly higher for alkylation in homogenous medium (compare entries 11 and 12) but not significantly so. Second, in all of the reactions in Table I, varying amounts of cyclohexanone were recovered. Indeed, this was a common feature of almost all the alkylations we carried out. A careful check of the starting enamines by infrared spectroscopy showed less than 1–2% cyclohexanone present. A more likely source of cyclohexanone is acid, either present in the oxonium salt to start with or generated by hydrolysis from adventitious water. Such acid will convert a corresponding amount of enamine to iminium salt which, being inert to alkylation, will appear as cyclohexanone in the final product mixture. Furthermore, any process (monoalkylation excepted), such as dialkylation, which releases a proton to the medium will in a similar manner tie up an equivalent amount of the starting enamine.[14] Dialkylation did not occur to an appreciable extent in these reactions (however, *vide infra*), but other proton-releasing processes such as elimination of ethylene from the triethyloxonium ion might well compete with alkylation. Finally, the possibility that cyclohexanone arose from incomplete reaction was ruled out by several observations. The reactions were all strongly exothermic, necessitating cooling during mixing. For entry 11 the insoluble trimethyloxonium salt dissolved within minutes after addition of the enamine. Moreover, reactions run for 18 hr at room temperature or for 2 hr at reflux exhibited no significant difference in the amount of cyclohexanone produced.

With a view to broadening the utility of the hindered enamines, their alkylation by the more generally accessible alkyl halides was examined. The results are shown in Table II. For methylation, the *n*-butylisobutyl enamine seemed to offer a slight advantage over the pyrrolidine enamine, but none of the enamines examined were really very satisfactory. The diisobutyl enamine appeared to react very sluggishly with methyl and ethyl iodides, and considerable unreacted cyclohexanone was recovered. While some N-alkylation may be occurring in the reactions with methyl iodide, the chief difficulty is that sizable amounts of dialkylated ketone are produced, along with an equivalent amount of unalkylated ketone. Apparently, for all the enamines studied, methyl iodide reacts at comparable rates with unalkylated and monoalkylated enamine. Some attempts were made to improve the methylation yield. Opitz reported that addition of dicyclohexylethylamine, a highly hindered proton acceptor, improved the yields of monoalkylated products obtained from the pyrrolidine enamines of cyclic ketones.[15] In our case, however, addition of dicyclohexylethylamine did not increase the yield of 2-methylcyclohexanone obtained from the *n*-butylisobutyl enamine. Likewise, substitution of methyl benzenesulfonate for methyl iodide only reduced slightly the yields of monoalkylated products obtained from the sterically hindered enamines. With cyclohexanone pyrrolidine enamine, methyl benzenesulfonate gave little (<10%) 2-methylcyclohexanone. The principal product was the N-methylated salt **10**.



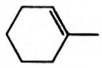
10

For ethylation, the *n*-butylisobutyl enamine was alkylated by ethyl iodide in acetonitrile in relatively good yield (Table II, entry 9). Alkylation of cyclohexanone pyrrolidine enamine has been reported to give a maximum of 54% of 2-ethylcyclohexanone,[15] so the use of the more hindered enamine appears to be of some advantage here. Experiments with ethyl iodide suggested that acetonitrile was a more satisfactory solvent than benzene (compare entries 8 and 9), and this solvent was used for most subsequent alkylations. With the less reactive *n*-butyl iodide, the yield of C-alkylated product again declined, and the hindered enamine was only slightly better than the pyrrolidine enamine, which Stork reported gave a 44% yield of 2-butylcyclohexanone accompanied by 23% recovered cyclohexanone.[2] In alkylations with the more electrophilic allyl bromide and ethyl bromoacetate, the *n*-butylisobutyl enamine gave yields inferior to those obtained with the pyrrolidine enamine.

During the course of our investigation the question arose as to whether the observed product distribution resulted from a kinetically controlled reaction. For example, several groups of workers have reported that N-alkylated products obtained from nonallylic halides can, under sufficiently vigorous conditions, isomerize to C-alkylated products.[16–18] Allylic halides represent a special case, as intramolecular N → C alkyl group transfer can occur *via* a [3,3] sigmatropic rearrangement.[4,5,16,19,20] To investigate whether N-alkylation is reversible at temperatures as low as those employed in our work, sulfonate **10** was subjected to prolonged treatment with sodium iodide in refluxing acetonitrile. Subsequent hydrolysis produced no detectable amount of either cyclohexanone or 2-methylcyclohexanone. Had iodide-promoted N-dealkylation of **10** occurred, the cyclohexanone pyrrolidine enamine and methyl iodide thus produced should have recombined to form some C-alkylated product. The absence of such a product in the reaction mixture suggests that N-alkylation is not significantly reversible at the temperatures employed by us and that the products we obtained were those of kinetic control.[21] It is likely that similar kinetic control occurs in ethylation and butylation, but there is less certainty regarding the reactions with allyl bromide and ethyl bromoacetate, the former because sigmatropic rearrangements might intervene and the latter because the enhanced reactivity of α-substituted esters might facilitate reversal of N-alkylation.

The difficulties encountered in achieving selective monomethylation of cyclohexanone with methyl iodide prompt-

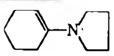
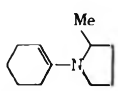
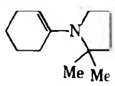
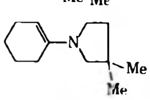
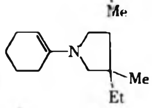
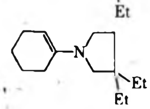
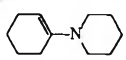
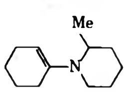
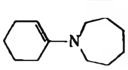
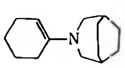
Table II

Alkylation of Cyclohexanone Enamines  **NRR′ by Alkyl Halides**

Entry no.	Enamine R	Enamine R'	Alkyl halide (mol)	Registry no.	Solvent	Reaction Time, hr[a]	Yields, %[b] Cyclohexanone	2-Alkylcyclohexanone	2,6-Dialkylcyclohexanone[c]
1[d]	–(CH$_2$)$_4$–		MeI (2)	74-88-4	PhH	19	20	41	17
2	*i*-Bu	*i*-Bu	MeI (2)		PhH	17	31	46	5
3	*i*-Bu	*n*-Bu	MeI (2)		PhH	12	18	56	11
4	*i*-Bu	*n*-Bu	MeI (1.3)		MeCN	16	14	56	14
5	*i*-Bu	*n*-Pr	MeI (2)		PhH	11	28	47	5
6	Isopentyl	Isopentyl	MeI (2)		PhH	12	12	38	8
7	*i*-Bu	*i*-Bu	EtI (2)	75-03-6	PhH	21	71	19	
8	*i*-Bu	*n*-Bu	EtI (2)		PhH	22	53	39	
9	*i*-Bu	*n*-Bu	EtI (2)		MeCN	17	14	70	
10	*i*-Bu	*n*-Bu	*n*-BuI (2)	542-69-8	MeCN	20	14	55	
11	–(CH$_2$)$_4$–		CH$_2$=CHCH$_2$Br (1.25)	106-95-6	MeCN	13	15	71	
12	*i*-Bu	*n*-Bu	CH$_2$=CHCH$_2$Br (1.25)		MeCN	13	12	57	
13	–(CH$_2$)$_4$–		BrCH$_2$CO$_2$Et (1.15)	105-36-2	PhH	4	15	55	
14	*i*-Bu	*n*-Bu	BrCH$_2$CO$_2$Et (1.15)		PhH	20	14	41	

[a] At reflux. [b] Determined by gas chromatography. [c] Only methylations (entries 1–6) were examined for 2,6-dialkylcyclohexanone. [d] Reaction at room temperature for 18 hr or at reflux for 1 hr gave results essentially identical with those obtained in this experiment.

Table III
Methylation of Cyclohexanone Enamines Derived from Cyclic Amines[a]

Entry no.	Enamine	Registry no.	Reaction time, hr	Yield, %[b] Cyclohexanone	2-Methylcyclohexanone	2,6-Dimethylcyclohexanone	Mono/di[c]
1[d]			1	16	37	16	2.3
2		53516-51-1	3	16	49	20	2.5
3[d]		53516-52-2	4	18	60	9	6.7
4[d]		53516-53-3	2	18	50	22	2.3
5		53516-54-4	6	16	49	21	2.3
6		53516-55-5	6	20	54	14	3.9
7		2981-10-4	2	5	8	2	4.0
8		53516-56-6	4	13	30	13	2.3
9		23430-63-9	2	16	49	24	2.0
10		53516-57-7	12	31	32	26	1.2

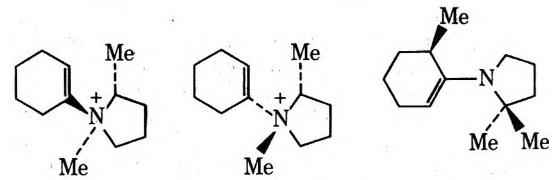
[a] All reactions were run with 2 equiv of methyl iodide in refluxing acetonitrile. [b] Determined by gas chromatography. [c] Ratio of monoalkylated to dialkylated ketone. From duplicate runs we estimate at ±15% uncertainty (average deviation) in these ratios. [d] Average of two runs.

Table IV
Alkylation of Aldehyde Enamines, $R_1R_2C{=}CHNR_3R_4$[a]

Entry no.	R_1	R_2	R_3	R_4	Registry no.	Alkylating agent	Reaction time, hr	Yield, %[b]
1	H	H	*i*-Bu	*n*-Bu	53516-58-8	*n*-$C_5H_{11}I$[c, i]	6	3
2	H	Et	*i*-Bu	*n*-Bu	53516-59-9	MeI	15	58
3	H	Et	*i*-Bu	*n*-Bu		EtI	20	41
4	H	Et	*i*-Bu	*n*-Bu		*n*-BuI	20	34
5	H	Et	*i*-Bu	*n*-Bu		*n*-BuBr[j]	18	6
6	H	*n*-Pr	*i*-Bu	*i*-Bu	42298-81-7	MeI[d]	12	66[e]
7	H	*n*-Pr	*i*-Bu	*i*-Bu		EtI[d]	15	7[f]
8	H	*n*-Pr	*i*-Bu	*i*-Bu		Et_3OBF_4[g]	18	52[e]
9	H	*n*-Pr	*i*-Bu	*n*-Bu	53516-60-2	EtI[d]	24	32[e]
10	H	*n*-Pr	*i*-Bu	*n*-Bu		EtI	10	78[e]
11	H	*n*-Pr	*i*-Bu	*n*-Bu		*n*-BuI	20	24[h]
12	H	Ph	*i*-Bu	*n*-Bu	53516-61-3	MeI	18	80
13	H	Ph	*i*-Bu	*n*-Bu		EtI	18	73
14	Me	Me	*i*-Bu	*n*-Bu	53516-62-4	MeI	20	64

[a] Unless otherwise indicated, all alkylations were conducted with 2 equiv of alkylating agent in refluxing acetonitrile. [b] Of monoalkylated aldehyde, as determined by gas chromatography. [c] 0.9 equiv. [d] In refluxing benzene as solvent. [e] A small amount (less than 10%) of unalkylated aldehyde was recovered. [f] Unalkylated aldehyde (33%) was recovered. [g] In refluxing dichloromethane with 1.1 equiv of oxonium salt. [h] Average of two runs. [i] Registry number, 628-17-1. [j] Registry number, 109-65-9.

ed us to extend our investigation of steric control somewhat further. In particular, we prepared a series of cyclic amines having alkyl groups or chain branching near the nitrogen. The corresponding cyclohexanone enamines were then alkylated with methyl iodide. The results of these experiments are summarized in Table III. With the pyrrolidine enamines, a single methyl group α to nitrogen reduced the fraction of N-alkylated products (compare entries 1 and 2) but had only a slight effect on the monoalkylated/dialkylated ketone ratio. However, two methyl groups in a 2,2 relationship not only suppressed N-alkylation but also increased the monoalkylation/dialkylation ratio (entry 3). These observations may be explained as follows. In the enamine from 2-methylpyrrolidine, N-methylation will lead to either or both of the quaternary ammonium salts 11 and 12.



11 12 13

In both cases alkyl groups are forced into an unfavorable 1,2-cis relationship on the five-membered ring. Although N-alkylation will be thus retarded, C-alkylation (both mono- and dialkylation) will be considerably less effected, because the enamine has available a number of conformations in which there is no interference between an incoming alkylating agent and the single methyl group on the pyrrolidine ring. When two α-methyl groups are present, however, not only will N-alkylation be difficult, as in the monomethyl case, but also the mono-C-alkylated enamine will now be forced into conformation 13, in which further C-alkylation is hindered by the pyrrolidine ring methyls. Placing the *gem*-alkyl groups on the more remote β position of the pyrrolidine ring (entries 4–6) is still effective in suppressing N-alkylation, but, with the possible exception of entry 6, these groups are now too far from the site of C-alkylation to have any effect on this process. The monoalkylation/dialkylation ratio does appear to increase somewhat for the *gem*-diethyl grouping (entry 6), which may reflect a small interaction with the incoming alkylating agent.

It is appropriate to reiterate here, however, a point made earlier, that the amount of dialkylation depends both on relative rates of alkylation and on acid–base equilibria. If, for example, monoalkylated enamine were a much stronger base than unalkylated enamine, it would be present during the alkylation largely as the corresponding iminium salt 2 and thus unavailable for further alkylation. Very probably polar effects in the amine component would influence basicity and nucleophilicity in parallel fashion (e.g., base-strenghtening polar effects should also increase alkylation rates), and some net cancellation might be expected. Steric effects would not necessarily show such a parallelism, which is one reason we attribute much of the changes in monoalkylation/dialkylation ratios to this source. The energy changes involved are, in any case, very small and susceptible to more than one explanation.

As in the case of the pyrrolidines, α-methylation of the piperidine ring has a retarding effect on N-alkylation (compare entries 7 and 8). The change for the piperidines, while more striking than for the pyrrolidines, is still not sufficient to block N-alkylation completely. For the two hexamethylenimine enamines examined (entries 9 and 10), a definite decrease in the monoalkylation/dialkylation ratio occurred when the β positions of the parent amine were connected by an ethano bridge. A good explanation for this has so far eluded us, the problem being complicated by the large number of conformations available to the seven-membered ring. Finally, comparison of the results for the parent five-, six-, and seven-membered cyclic amines (entries 1, 7, and 9) shows that hexamethylenimine gives the highest and piperidine the lowest yields of monoalkylated ketone, in agreement with studies by other workers.[18,22] Stork reported that in benzene the pyrrolidine enamine is slightly better than the hexamethylenimine,[2] perhaps pointing up the subtlety of the factors influencing these alkylations.

Having found that in a number of cases the use of sterically hindered amines offered distinct advantages in alkylation of ketone enamines, it became of great interest to examine the utility of these amines for the corresponding synthesis of aldehydes, where N-alkylation is usually a severe, if not fatal, drawback. We confined our investigation to enamines of diisobutyl- and *n*-butylisobutylamine, for which we expected the least amount of N-alkylation. Our results are given in Table IV, and they clearly show that we have in hand, for the first time, a practical method for C-alkylation of mono- and disubstituted acetaldehyde enamines by unactivated alkyl halides. Optimum conditions for alkylation appeared to involve reaction of the *n*-butylisobutyl enamine with alkyl iodide in refluxing acetonitrile. Under comparable conditions the diisobutyl enamine appeared to react more slowly than the corresponding *n*-butylisobutyl enamine (compare entries 7 and 9), possibly reflecting increased steric hindrance in the former. Acetonitrile was definitely superior to benzene as a reaction solvent (compare entries 9 and 10), while in the one case studied (entries 4 and 5), the more reactive iodide gave a better yield than the corresponding bromide.[23] Unfortunately, alkylation of acetaldehyde enamine itself (entry 1) did not afford usable yields of the homologated aldehyde, a failure traceable, perhaps, to the marked instability of the starting enamine. With the exception of acetaldehyde, enamines were obtained from all aldehydes in fair to good yields by standard procedures[24] or modifications thereof (see Experimental Section), making the overall transformation of an aldehyde into its α-alkylated derivative *via* the sterically hindered enamine an attractive synthetic procedure.

Conclusion

As a result of our studies, we feel that the use of a sterically hindered amine component in the enamine alkylation reaction can improve and extend the usefulness of this already quite versatile procedure for carbon–carbon bond formation. For ketones, our model studies with cyclohexanone indicate that, where permitted by other functional groups in the molecule, methylation or ethylation can be effected in good yields by reaction of the diisobutyl or *n*-butylisobutyl enamines with trialkyloxonium salts. For alkylations by alkyl halides, the *n*-butylisobutyl enamine with an alkyl iodide in acetonitrile gives somewhat better yields of monoalkylated ketone than the more usual pyrrolidine enamine. Enamines of 2,2-dimethylpyrrolidine may also have some utility in such alkylations, especially where 2,6-dialkylation is a major complication. Undoubtedly, our most useful finding is that aldehyde enamines of *n*-butylisobutylamine can be C-alkylated, often in quite good yields, by alkyl iodides in refluxing acetonitrile. Since we first communicated this finding,[1] an *n*-butylisobutyl enamine has been advantageously employed to achieve direct C-alkylation of isobutyraldehyde with propargylic halides,[20] circumventing the formation of allenic products, which arise from the more usual enamines by initial N-alkylation and subsequent N → C sigmatropic rearrangement.[19] Many other applications of these hindered enamines may be envisaged, including their use for acylations, for serial dialkylation of aldehyde enamines, to prepare functionalized aldehydes, and to suppress N-alkylation of medium ring ketone enamines.

Experimental Section[25]

Preparation of Amines. Methylisobutylamine. Isobutyraldehyde (36 g, 0.5 mol) was added dropwise with stirring and ice cooling to aqueous methylamine (42 ml of a 12 *M* solution). After standing at room temperature for 1 hr, 1 g of 10% ruthenium on charcoal was added, and the reaction mixture was hydrogenated on the Parr apparatus at 70° and 60 lb of pressure until hydrogen uptake ceased. The catalyst was removed by filtration; the filtrate was strongly basified with sodium hydroxide pellets and extracted with ether. The ether extract was dried over magnesium sulfate and distilled to give methylisobutylamine: 13.4 g (31%); bp 74–75° (lit.[26] bp 76–78°).

Ethylisobutylamine. Isobutyraldehyde (72 g, 1 mol) was added dropwise with stirring and ice cooling to a solution of ethylamine (45 g, 1 mol) in 300 ml of ether. After stirring 1 hr at room temperature, the ether phase containing the Schiff's base was separated and dried first over potassium carbonate and then over magnesium sulfate. The decanted ether phase was added dropwise to a well-stirred suspension of lithium aluminum hydride (19 g, 0.50 mol) in 300 ml of anhydrous ether. Stirring was continued for an additional 2 hr, and then excess hydride was destroyed by slow addition of 50% sodium hydroxide solution (68 ml). After stirring overnight, the mixture was filtered, and the filtrate was fractionated to give ethylisobutylamine: 46.1 g (46%); bp 97–98° (lit.[27] bp 97–98°).

***n*-Propylisobutylamine** was prepared from isobutyraldehyde and *n*-propylamine in the same manner as ethylisobutylamine (46% yield): bp 120–121° (lit.[27] bp 123–125°).

***n*-Butylisobutylamine.** This amine could be prepared *via* the Schiff's base as for ethylisobutylamine (62% yield) but the following was more convenient. Isobutylamine (440 g, 6 mol) was stirred and heated to reflux. *n*-Butyl bromide (274 g, 2 mol) was added at a rate sufficient to maintain reflux without external heating. After addition of the bromide was complete, the reaction mixture was refluxed for 7 hr. The precipitated salts were dissolved by addition of water (100 ml) followed by aqueous sodium hydroxide (100 g of NaOH in 300 ml of water). The upper phase was separated and repeatedly treated with KOH pellets until no more aqueous phase separated. The crude amine was stirred 1 hr over crushed KOH pellets, decanted, and fractionally distilled to give *n*-butylisobutylamine: 179 g (69%); bp 147–152° (lit.[28] bp 150–151°).

3,3-Dimethylpyrrolidine. 2,2-Dimethylsuccinic acid was converted to the corresponding succinimide (57% yield) by the *Organic Syntheses* procedure for succinimide.[29] The resulting 2,2-dimethylsuccinimide (10.5 g, 0.083 mol) dissolved in 250 ml of anhydrous ether was added dropwise with stirring and ice cooling to lithium aluminum hydride (8 g, 0.21 mol) in 50 ml of anhydrous ether. The reaction mixture was allowed to warm to room temperature and then refluxed for 24 hr. Excess hydride was destroyed by slow addition of 50% sodium hydroxide solution (28 ml). Filtration and fractionation of the filtrate gave 3,3-dimethylpyrrolidine: 5.5 g (67%); bp 115–116° (lit.[30] bp 114–115°).

3-Ethyl-3-methylpyrrolidine. By the procedures used for preparation of 3,3-dimethylpyrrolidine, 2-ethyl-2-methylsuccinic acid was converted to the imide (44% yield), and this was reduced by lithium aluminum hydride to the pyrrolidine (75% yield): bp 145–147° (lit.[31] bp 140°).

3,3-Diethylpyrrolidine was prepared in a similar fashion from 2,2-diethylsuccinic acid (yield of imide 59%, yield of amine 54%): bp 66–68° (15 mm) (lit.[30] bp 169–170°).

2,2-Dimethylpyrrolidine was prepared by lithium aluminum hydride reduction of 5,5-dimethyl-2-pyrrolidone.[32]

2-Methylpyrrolidine was prepared by lithium aluminum hydride reduction of 5-methyl-2-pyrrolidinone.[33]

Other amines were purchased from commercial sources.

Enamines. Enamines of cyclohexanone and of some aldehydes were prepared by the usual azeotropic procedures[2,24] using 1 mol of carbonyl component per 300 ml of benzene, toluene, xylene, or (for isobutyraldehyde) no solvent.[24c] Enamines prepared in this manner are summarized in Table V. For enamines of monosubstituted aldehydes, the Mannich–Davidson procedure[24b] was modified by using ether as solvent and 1 mol of amine per mole of aldehyde. We have independently confirmed the report of Wittig and Mayer[34] that with aliphatic amines it is necessary to use only 1 mol of amine rather than the usual 2 mol. The following general procedure was employed. A mixture of 0.2 mol of amine, 50 ml of ether, and 28 g of anhydrous potassium carbonate was mechanically stirred under a nitrogen atmosphere while 0.2 mol of freshly distilled aldehyde was added dropwise with ice cooling. After stirring overnight, the mixture was filtered, and the filtrate was fractionally distilled. Enamines prepared in this manner included the *n*-butylisobutyl enamines of valeraldehyde [bp 63–67° (1.5 mm); 71% yield] and acetaldehyde [bp 26–27° (1 mm); 26% yield].

All enamines were characterized by ir (strong band in the 1630–1660-cm^{-1} region, absent or very weak carbonyl band) and nmr (vinyl CH at 4.2–4.65). The purity of some enamines was checked by gas chromatography, and some enamines were subjected to elemental analysis (see Table V).

Alkylation of Enamines by Alkyl Halides. The following general procedure was used. Enamine (20 mmol) was refluxed under nitrogen with alkyl halide (40 mmol) in 20 ml of the appropriate dry solvent. The course of the reaction was followed by periodic titration of an aliquot with hydrochloric acid using Methyl Red indicator. When reaction was judged complete, a buffer solution consisting of 1 g of sodium acetate, 2 ml of acetic acid, and 10 ml of water was added, and the resulting mixture was refluxed under ni-

Table V
Preparation of Enamines by Azeotropic Distillation

Carbonyl component	Amine[a]	Registry no.	Solvent	Reaction time, hr	Yield, %	Bp, °C	Pressure, mm
Cyclohexanone	$(i\text{-Bu})_2NH$ (2)	110-96-3	Xylene	144	59	73–75	2
Cyclohexanone	i-BuNH-n-Bu (1.5)	20810-06-4	Xylene	96	76	67–69	2
Cyclohexanone	i-BuNH-n-Pr (1.4)	39190-66-4	Xylene	120	73	87–89	5
Cyclohexanone	i-BuNHEt (1.4)	13205-60-2	Toluene	72	44	91–92	9
Cyclohexanone	i-BuNHMe (1.5)	625-43-4	Benzene	72	68	73–74	5
Cyclohexanone	$(n\text{-Bu})_2NH$ (2)	111-92-2	Xylene	72	79	96–99	2
Cyclohexanone	$(i\text{-}C_5H_{11})_2NH$ (2)	544-00-3	Xylene	96	80	84–87	2
Cyclohexanone	$(MeOCH_2CH_2)_2NH$ (2)	111-95-5	Xylene	216	92	81–83	3
Cyclohexanone	2-Methylpyrrolidine (1.1)	765-38-8	Toluene	40	80[b]	102–103	3
Cyclohexanone	3,3-Dimethylpyrrolidine (1.1)	3437-30-7	Benzene	1	77[b]	110–112	9
Cyclohexanone	3-Methyl-3-ethylpyrrolidine (1.1)	34971-67-0	Benzene	4	93	86–87	1
Cyclohexanone	3,3-Diethylpyrrolidine (1.1)	34971-71-6	Toluene	0.5	88[b]	143–145	3
Cyclohexanone	2,2-Dimethylpyrrolidine (1.1)	35018-15-6	Toluene	144	62[b]	86–88	4
Cyclohexanone	2-Methylpiperidine (1.1)	109-05-7	Toluene	336	50[b]	94–96	3
Cyclohexanone	3-Azabicyclo[3.2.2]nonane (1.1)	283-24-9	Toluene	1.5	70[b]	123–125	3
Butyraldehyde	i-BuNH-n-Bu (1)		Benzene	3	36	90–94	10
Valeraldehyde	$(i\text{-Bu})_2NH$ (1.2)		Benzene	12	45	117–121	29
Isobutyraldehyde	i-BuNH-n-Bu (1.2)		None	6	70	84–86	17

[a] Moles of amine per mole of carbonyl compound in parentheses. [b] Satisfactory elementary analysis was obtained.

trogen for 4 hr. The cooled reaction mixture was diluted with water and extracted with 25 ml of benzene. The benzene phase was washed with successive portions of 2 M hydrochloric acid, water, saturated sodium bicarbonate solution, and saturated salt solution. After drying over magnesium sulfate, the filtered extract was diluted to 50 ml and analyzed by gas chromatography. Details of individual experiments are given in Tables II–IV.

***N*-Methyl-*N*-(1-cyclohexenyl)pyrrolidinium Benzenesulfonate (10).** A mixture of cyclohexanone pyrrolidine enamine (15.1 g, 0.1 mol) and methyl benzenesulfonate (17.2 g, 0.1 mol) in 85 ml of dry benzene was refluxed for 5 hr, during which time sulfonate **10** separated as a heavy oil. Benzene was removed by decantation, and the oil was triturated with ether to promote crystallization. Recrystallization of the resulting solid from 1,2-dichloroethane–ethyl acetate gave **10**: 15.7 g (49%); mp 107–108°; nmr (CF_3CO_2H, internal TMS) δ 1.74 (m, 4, nonallylic cyclohexene protons), 2.32 (m, 8, pyrrolidine β protons and allylic cyclohexene protons), 3.16 (s, 3, N-methyl), 3.7 (m, 4, pyrrolidine α protons), 6.2 (br, 1, vinyl proton), 7.5–8.2 (m, 5, aromatic protons).

Anal. Calcd for $C_{17}H_{25}NO_3S$: C, 63.45; H, 7.70; N, 4.31. Found: C, 63.26; H, 7.69; N, 4.28.

Irreversibility of N-Alkylation. A sample of quaternary salt **10** (1 g, 3 mmol) and sodium iodide (0.51 g, 3.4 mmol) in 5 ml of dry acetonitrile was refluxed under nitrogen for 7 hr. Water (5 ml) was added and the mixture was left overnight at room temperature. Dilution with water and extraction with benzene gave an organic phase containing less than 2% cyclohexanone and no 2-methylcyclohexanone, as determined by gas chromatography.

Alkylation of Enamines by Oxonium Salts. The following general procedure was used. To the oxonium salt (50 mmol) dissolved or suspended in 25 ml of solvent was added dropwise under a nitrogen atmosphere the enamine (40 mmol) with stirring and ice cooling. The reaction mixture was stirred an additional 2 hr at room temperature, then diluted with water (25 ml), and distilled to remove dichloromethane (distillation was omitted when nitromethane was the reaction solvent). From this point on, the reaction mixture was buffered, hydrolyzed, and extracted as for the alkylation with alkyl halides. Results of individual experiments are given in Table I.

Isolation and Hydrolysis of *N*-(2-Ethylcyclohexylidene)diisobutylammonium Tetrafluoroborate (9). After alkylation of the diisobutyl enamine of cyclohexanone by triethyloxonium tetrafluoroborate in dichloromethane as described above, the reaction mixture was treated with 15 ml of water and distilled to remove dichloromethane. Addition of ether (30 ml) resulted in a three-phase system. Upon standing, the middle phase solidified to a white solid which was removed by filtration, washed with cold water, and dried to give **9**: 7.05 g (69%); mp 107–130°; nmr ($CDCl_3$, internal TMS) δ 1.0 (m, 15, isobutyl and ethyl group methyls), 2.0 (m, 10, isobutyl methines, ethyl group methyl, cyclohexylidene β and γ protons), 3.0 (m, 3, cyclohexylidene α protons), 3.8 (m, 4, isobutyl methylenes). Attempts to recrystallize this material from isopropyl alcohol led only to recovery of a small quantity of solid, mp 110–142°.

A 1-g sample of **9** was refluxed for 5 hr with 5 ml of water, 0.3 ml of acetic acid, and 0.15 g of sodium acetate. The cooled mixture was extracted with benzene and the benzene phase was washed with dilute hydrochloric acid, water, saturated sodium bicarbonate solution, and saturated salt solution. After drying over magnesium sulfate, gas chromatographic analysis showed 0.47 g (96%) of 2-ethylcyclohexanone present.

Analysis and Characterization of Alkylation Products. The amount of aldehyde or ketone present in the benzene extracts of the alkylation reaction mixtures was determined by gas chromatographic comparison with a standard solution containing authentic materials at approximately the same concentration. Analysis for cyclohexanones was on a 7-ft column of 20% Apiezon L on 60–80 mesh acid-washed and silanized Chromosorb W. Aldehydes were analyzed on a 7-ft column of Dow 710 silicone oil on the same support. Areas were measured by planimeter. Except as noted below, alkylation products were further identified by preparative gas chromatography, followed by comparison of nmr and ir spectra with authentic samples. In selected cases, other procedures were used for identifying the reaction products, as follows.

2-Ethylcyclohexanone. The benzene extract from the reaction of 80 mmol of cyclohexanone diisobutyl enamine with triethyloxonium tetrafluoroborate was distilled through a spinning band column to give 6.15 g (61%) of 2-ethylcyclohexanone: bp 102–104° (54 mm). The 2,4-DNP derivative had mp 158–158.2°, alone or in admixture with the derivative of authentic ketone.

2-Ethylpentanal. After alkylation of the diisobutyl enamine of valeraldehyde (0.14 mol) with triethyloxonium tetrafluoroborate (0.15 mol), followed by buffered hydrolysis as described above, the reaction mixture was extracted with ether rather than benzene. Fractionation of the extract through a small Vigreux column gave 8.7 g (54%) of 2-ethylpentanal: bp 66–68° (61 mm) [lit.[35] bp 63–64° (50 mm)]; 2,4-DNP derivative mp 124–125° (lit.[36] mp 124–125°); semicarbazone mp 72–74° (reported[35] to be an oil).

Hydratropaldehyde. The reaction mixture (Table IV, entry 12) from phenylacetaldehyde *n*-butylisobutyl enamine (10 mmol) and methyl iodide (20 mmol) was extracted with ether rather than benzene. Removal of the ether under nitrogen, followed by short-path distillation of the residue *in vacuo* gave 1.03 g (77%) of hydratropaldehyde whose nmr spectrum was identical with that of an authentic sample.

Registry No.—9, 53516-64-6; **10,** 53516-66-8; methylamine, 74-89-5; ethylamine, 75-04-7; *n*-propylamine, 107-10-8; isobutylamine, 78-81-9; 2,2-dimethylsuccinic acid, 597-43-3; 2-ethyl-2-methylsuccinic acid, 631-31-2; 2,2-diethylsuccinic acid, 5692-97-7; 5,5-dimethyl-2-pyrrolidone, 5165-28-6; 5-methyl-2-pyrrolidinone, 108-27-0; acetaldehyde, 75-07-0; methyl benzenesulfonate, 80-18-2; 2-ethylcyclohexanone, 4423-94-3; 2-ethylcyclohexanone 2,4-dinitrophenylhydrazone, 14714-07-9; 2-ethylpentanol, 22092-54-2; 2-ethylpentanol semicarbazone, 53516-67-9; cyclohexanone, 108-94-1; butyraldehyde, 123-72-8; valeraldehyde, 110-62-3; isobutyraldehyde, 78-84-2.

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Kinetics of the Oxidation of Fluorenes to Fluorenones by Hypobromite in Aqueous Dioxane[1]

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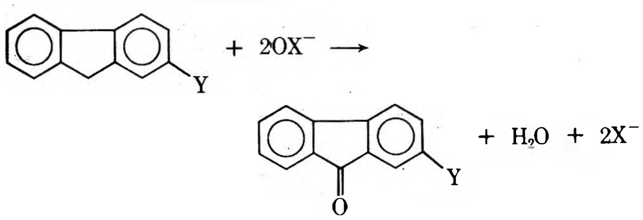
Oxidation of 2-substituted fluorenes to the fluorenones with alkaline hypobromite in aqueous dioxane has been kinetically studied by means of uv spectrophotometry and glc analysis. The rate is expressed as $v = k_1$[fluorene][NaOH] at [NaOH] < 0.4 *M*, and $v = k_2$[fluorene][OBr^-]/[Br^-] at [NaOH] > 0.6 *M*. The effect of 2 substituents on the reaction of fluorenes with a mixture of Br_2–NaOH at 25° and at [NaOH] = 0.01–0.1 *M* gives a ρ value of +4.40. The reaction of 2-bromofluorene with alkaline hypobromite at higher concentrations of NaOH (2.1 *M*) and NaBr (1.0 *M*) afforded 2,9-dibromofluorene. A mechanism is postulated, which involves a proton abstraction from the 9 position of the fluorene followed by a rapid hypobromite attack to give the 9-bromofluorene and then the fluorenone. The rate-determining step changes from proton abstraction to oxidation of 9-bromofluorene with increasing the concentration of NaOH. For the elucidation of later steps, the rate of hypobromite oxidation of 2,9-dibromofluorene to 2-bromofluorenone was measured; the observed rate expression, $v = k_3$[2,9-dibromofluorene][OBr^-]/[Br^-], suggests a mechanism involving elimination of Br^- from 9-bromofluorene followed by an attack of OBr^- to give the fluorenone.

The compounds bearing an active methylene group are oxidized by hypohalite to give dimeric olefinic derivatives in alkaline solutions[2–4] with some exceptions such as haloform reaction. For example, benzyl cyanides react with hypohalite to give α,α'-dicyanostilbenes.[2] A number of workers[2–4] have studied these reactions and suggested mechanisms involving an initial formation of carbanion, which is halogenated and then condensed to dimeric products.

$$>CH_2 \xrightarrow{RO^-} >CH^- \xrightarrow{ROX} >CHX \longrightarrow >C{=}C<$$

9-Halofluorene reacts also with alkali to give bifluorenylidene (**9**),[5] but 2-acetylfluorene is oxidized by potassium hypochlorite to fluorenone-2-carboxylic acid, but not the expected dimer.[6] We observed that fluorenes often yielded the corresponding fluorenone by the hypohalite oxidation under certain conditions.



The mechanism of these oxidations of fluorenes has not yet been studied and there is no appropriate explanation for the different oxidation behaviors between fluorenes giving fluorenones and others giving dimer.

The authors wished to clarify these phenomena and the mechanism concerning oxidation of fluorenes. The present paper reports a study on kinetics and mechanism for the hypobromite oxidation of fluorenes and 9-bromofluorene, a probable intermediate, in alkaline aqueous dioxane by following the formation of fluorenone by uv spectrophotometry or glc analysis.

Results

Products. Fluorenes were treated with alkaline hypobromite in aqueous dioxane (27% water) at 25°. Fluorenones were produced in good yields from fluorenes with electron-attracting groups and no other products were detected. Their yields were estimated by means of glc and shown in Table I. On the other hand, 2,9-dibromofluorene was obtained by the treatment of 2-bromofluorene with sodium hypobromite in the presence of excess sodium hydroxide (2.1 *M*) and sodium bromide (1.0 *M*) in aqueous dioxane (27% water) at 25°.

Table I
Products and Yields[a] of the Reaction[b] of Fluorenes with Hypobromite in Alkaline Aqueous Dioxane (27% Water) at 25° for 5 hr

Substituent of fluorene, 10^{-3} *M*	Registry No.	Products yields: Fluorenone, %	Bifluorenylidene, %
2-NO_2 (1.85)	607-57-8	100	
2-CN (2.30)	2523-48-0	100	
2-Br (1.95)	1133-80-8	96	
2-Ac (2.21)	781-73-7	99[c]	
2-MeO (2.03)	2523-46-8	15	
None (2.42)	86-73-7	5	
2,9-diBr (1.53)[d]	6633-25-6		100
2,9-diBr (0.306)		100	
2,9-diBr (1.53)		98	Trace
2,9-diBr (30.6)		87	13

[a] Yields were calculated by measurement of glc analysis of product and starting fluorene, since there is no by-product. [b] $[NaOBr]_0$ = 0.125 *M*, $[NaOH]_0$ = 0.125 *M*. [c] Fluorene-2-carboxylic acid. [d] Reaction with NaOH alone (0.125 *M*).

The reaction of 2,9-dibromofluorene with alkaline hypobromite under the same conditions as fluorenes gave 2-bromofluorenone and 2,2′-dibromobifluorenylidene but no other products detectable by glc analysis. The yield of bifluorenylidene increased with increasing the concentration of 2,9-dibromofluorene (Table I).

Kinetics. The rate of the reaction of 2-bromofluorene (2.00×10^{-5} *M*) with sodium hypobromite (0.0199–0.199 *M*) in alkaline (NaOH, 0.007–0.687 *M*) aqueous dioxane (75% water) was measured by means of uv spectrophotometry of product at 25°.

The pseudo-first-order rate constants in the rate equation of $v = k_{obsd}([\text{2-bromofluorene}]_0 - [\text{2-bromofluorenone}])$ are listed in Table II, where $[\ ]_0$ means initial concentration. The k_{obsd} value is proportional to the concentration of alkali up to 0.4–0.5 *M* sodium hydroxide, but is independent of the concentration of BrO^- and Br^-.

$$v = k_1[\text{2-bromofluorene}][OH^-] \quad (1)$$

Table II
Pseudo-First-Order Rate Constants for the Reaction of 2-Bromofluorene with NaOBr in Alkaline Aqueous Dioxane (75% Water) at 25°

Initial concn					
$[NaOBr]_0$, 10^{-2} *M*	$[NaOH]_0$,[a] 10^{-2} *M*	$[NaBr]_0$,[b] 10^{-2} *M*	$10^4 k_{obsd}$, sec^{-1}	$10^4 k_1$,[c] M^{-1} sec^{-1}	$10^4 k_2$,[d] sec^{-1}
1.99	17.7	3.99	5.39	30.5	
1.99	17.7	4.49	5.30	29.9	
1.99	17.7	4.99	5.35	30.2	
1.99	17.7	6.99	3.53		12.3
1.99	17.7	11.99	2.12		12.8
1.99	0.7	1.99	0.267	37.4	
1.99	9.2	1.99	2.60	28.3	
1.99	17.7	1.99	5.33	30.1	
1.99	26.2	1.99	7.22	27.6	
1.99	34.7	1.99	10.00	28.8	
1.99	43.2	1.99	10.7	(24.8)[e]	(10.7)[e]
1.99	51.7	1.99	12.2	(23.7)[e]	(12.2)[e]
1.99	60.2	1.99	12.2		12.2
1.99	68.7	1.99	12.3		12.3
4.99	17.7	4.99	5.33	30.1	
7.50	17.7	7.50	5.32	30.1	
9.98	17.7	9.98	5.33	30.1	
15.0	17.7	15.0	5.26	29.7	
19.9	17.7	19.9	5.32	30.1	
1.91	100	97.2	0.249		12.7
3.82	100	99.1	0.467		12.1
5.73	100	101	0.704		12.4
7.64	100	103	0.995		13.4

[a] Added concentration. [b] Total concentration. [c] $k_1 = k_{obsd}/[NaOH]_0$. [d] $k_2 = k_{obsd}[NaBr]_0/[NaOBr]_0$. [e] These values are in the break point of the plot of k_{obsd} *vs.* $[NaOH]_0$; hence the k_1 and k_2 values deviate.

However, when the concentration of alkali is over 0.6 *M*, the rate is independent of $[OH^-]$ and expressed as

$$v = k_2[\text{2-bromofluorene}][OBr^-]/[Br^-] \quad (2)$$

The rate of the oxidation of 2,9-dibromofluorene, a probable intermediate, was measured in aqueous dioxane (75% water) at 25°. The formation of bifluorenylidene was negligible at this low concentration of 2,9-dibromofluorene (2.12×10^{-5} *M*). The data are listed in Table III. The pseudo-first-order rate constant, k_{obsd}', in the equation of $v = k_{obsd}'([\text{2,9-dibromofluorene}]_0 - [\text{2-bromofluorenone}])$ is proportional to the concentration of OBr^- and inversely proportional to the concentration of Br^-. Thus the rate is expressed as

$$v = k_3[\text{2,9-dibromofluorene}][OBr^-]/[Br^-] \quad (3)$$

The rate constant k_3 is approximate to the k_2 value in eq 2.

Substituent Effect. Relative rates for the reaction of 2-nitro-, 2-cyano-, 2-acetyl-, 2-bromo-, 2-methoxy-, and unsubstituted fluorenes with sodium hypobromite were measured in alkaline aqueous dioxane (27% water, $[OH^-] = 0.0125–0.125$ *M*) at 25° by means of glc. The data are listed in Table IV, which gives a ρ value of 4.40 ($r = 0.986$) with Hammett's σ(meta).

Discussion

Initial Stage. Carbanion Formation. In our previous paper[2] on the kinetics for the oxidative coupling of benzyl cyanides with alkaline hypohalites, we suggested a mechanism which involves a rate-determining α-proton abstraction from benzyl cyanide followed by a rapid hypohalite attack to give α-halobenzyl cyanide. The analogous kinetic

Table III
Pseudo-First-Order Rate Constants for the Oxidation of 2,9-Dibromofluorene with NaOBr in Alkaline Aqueous Dioxane (75% Water) at 25°

Initial concn				
$[NaOBr]_0$, 10^{-2} *M*	$[NaOH]_0$,[a] 10^{-2} *M*	$[NaBr]_0$,[b] 10^{-2} *M*	$10^4 k_{obsd}$, sec^{-1}	$10^4 k_3$,[c] M^{-1} sec^{-1}
1.91	100	97.2	0.251	12.8
3.82	100	99.1	0.495	12.8
5.73	100	101	0.758	13.5
7.64	100	103	1.01	13.6
1.52	100	9.55	2.03	12.8
1.52	100	19.1	0.906	11.4
1.52	100	23.9	0.834	13.1
1.52	100	28.7	0.699	13.2
1.52	100	38.2	0.582	14.6
1.91	100	1.91	12.5	12.5
1.91	50.0	1.91	13.3	13.3
1.91	20.0	1.91	13.5	13.5
1.91	10.0	1.91	12.3	12.3
5.73	100	5.73	11.7	11.7

[a] Added concentration. [b] Total concentration. [c] $k_3 = k_{obsd} \cdot [NaBr]_0/[NaOBr]_0$.

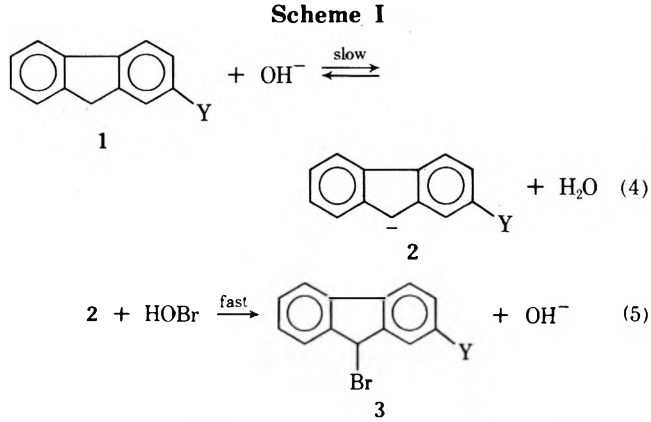
Table IV
Relative Rates for the Reaction of 2-Substituted Fluorenes with NaOBr in Alkaline Aqueous Dioxane (27% Water) at 25°

Substituent of fluorene	k_{rel}	Substituent of fluorene	k_{rel}
$2\text{-}NO_2$[a]	802	2-Ac[a,b]	83.3
2-CN[a]	141	2-OMe[b]	3.10
2-Br[a,b]	60.3	None[b]	1.00

[a] [NaOH] = 0.0125 *M*. [b] [NaOH] = 0.125 *M*.

data, *i.e.*, the rate law (eq 1) and substituent effect at [NaOH] < 0.4 *M*, are also obtained in the oxidation of fluorenes to fluorenones and these data suggest a rate-determining abstraction of the 9 proton of fluorenes 1 to give carbanion 2 at an initial stage. In other words, rate eq 1 implies that one molecule of fluorene and a base should participate in the rate-determining step. The large ρ value of 4.40 is similar to those ρ values of 3–4 for a number of reactions which involve a rate-determining deprotonation to give carbanion.[2,7]

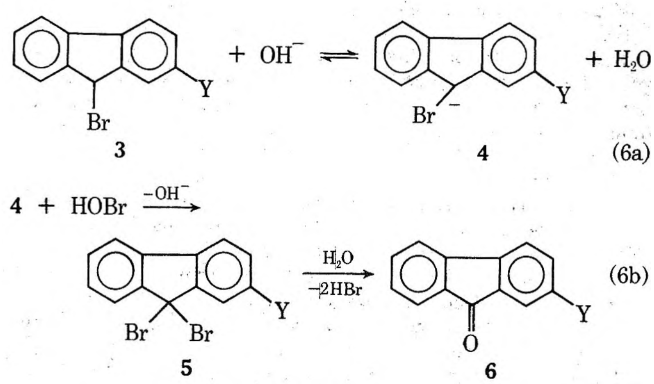
Scheme I



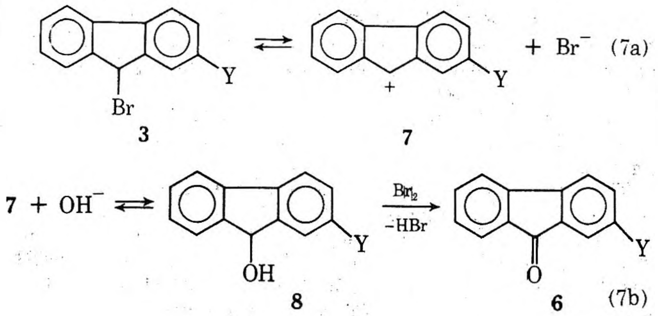
a, Y = NO_2; b, Y = CN; c, Y = Br; d, Y = Ac; e, Y = OMe; f, Y = H

In view of the analogous studies on the reaction of carbanion with hypohalites,[2,3,8] the carbanion 2 from fluorene

Scheme II



Scheme III



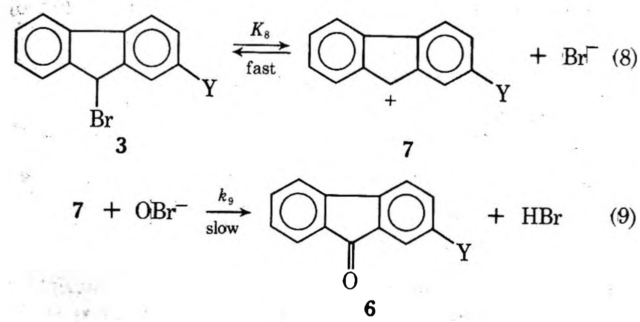
would also react rapidly with hypobromite to give 9-bromofluorene (**3**). 2,9-Dibromofluorene (**3c**) yields on treatment of hypobromite in alkaline aqueous dioxane 2-bromofluorenone together with 2,2'-dibromofluorenylidene, but no formation of fluorenylidene but fluorenone was observed at a low concentration of 2,9-dibromofluorene. The change of the rate law (eq 1 and 2) implies that the rate-determining step for 2-bromofluorene changes at 0.4–0.6 *M* NaOH; *i.e.*, at [NaOH] > 0.6 *M*, the formation of carbanion is faster than the oxidation of an intermediate, 2,9-bromofluorene, which was isolated and identified. Furthermore, the k_2 value (12.5×10^{-4} sec^{-1}) of eq 2 agrees with the k_3 value (12.9×10^{-4} sec^{-1}) for the oxidation of **3c** with alkaline hypobromite (eq 3). Hence the intermediacy of 9-bromofluorenes **3** is implied for the formation of fluorenones.

Oxidation of 2,9-Dibromofluorene (Speculation of Subsequent Steps). One of the pathways for the conversion of formed 9-bromofluorene to fluorenone may be Scheme II. 9-Bromofluorene appears to give carbanion **4** more easily than fluorene **1** because of the presence of the electron-attracting 9-bromo group. Since fluorenylidene is obtained by treatment of **3** with alkali, carbanion **4** may exist,[2-4] which may give 9,9-dibromofluorene (**5**) similarly to the conversion of **1** to **3**.[2,3,8] Then dibromide **5** may be hydrolyzed to fluorenone **6**, since α,α-dihalo compounds are hydrolyzed to carbonyl compounds as exemplified in the hydrolysis of benzophenone dichloride[9] and benzal chloride.[10] However, kinetics observed in our hands rule out this scheme, because the rate of **3c** with hypobromite is independent of the concentration of the base (eq 3).

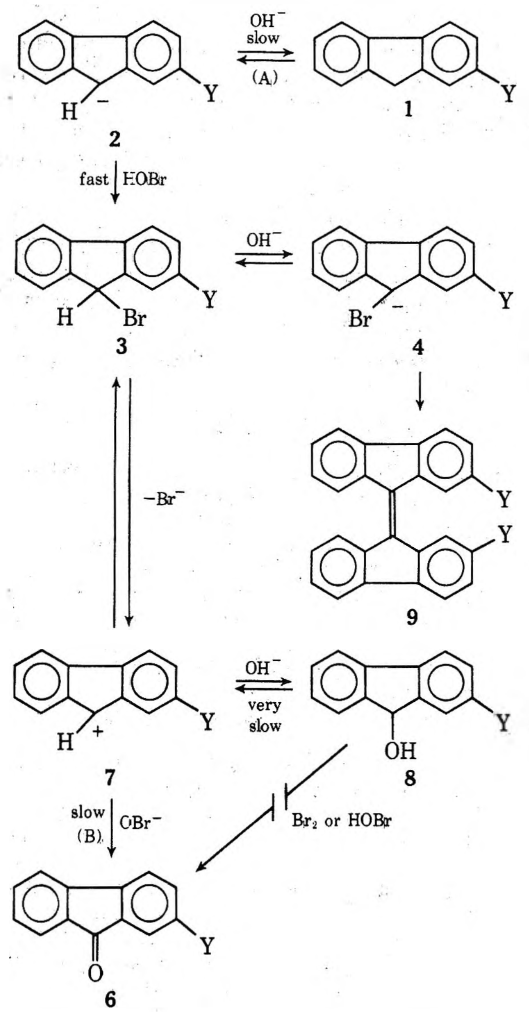
Lovins[11] observed in their study on the solvolysis of 1- and 4-carbomethoxy-9-bromofluorenes the formation of stable 9-fluorenyl cation **7** because of the planarity of **7**. Thus Scheme III is considered; *i.e.*, carbonium ion **7**, which may be formed from **3**, may give fluorenol **8** by an attack of hydroxide ion followed by its oxidation to fluorenone **6** by bromine.

However, no fluorenol **8** but bifluorenylidene **9** alone was obtained by the treatment of **3** with alkali, whereas fluorenone **6** was obtained as a main product by the treatment

Scheme IV



Scheme V



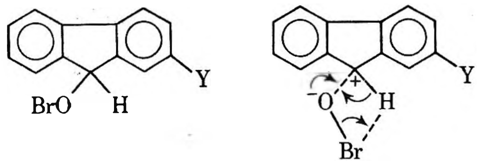
of **3** with alkaline hypobromite, so that the formation of fluorenol should be slower than the formation of bifluorenylidene and than that of fluorenone. Further, kinetic data are inconsistent with this scheme; *i.e.*, Scheme III cannot lead to the rate equation 3. Hence, the intermediacy of 9-fluorenol **8** is of doubt.

Our kinetic observations can only be explained by Scheme IV.

If eq 9 is rate-determining, the rate should be expressed as

$$v = K_8 k_9 [\mathbf{3}][\mathrm{OBr}^-]/[\mathrm{Br}^-] \qquad (10)$$

And this is the case (eq 3). The intermediacy of 9-fluorenyl hypobromite (**10**), which can give fluorenone **6**[12a] in step 9, is probable, because the nucleophilicity of OBr^- should be stronger than that of OH^-.[12b] An alternative process may be a concerted one (11); *i.e.*, fluorenone 6 is formed from 7 by an attack of OBr^- and a simultaneous elimination of HBr.



10 11

Overall Mechanism of the Oxidation of Fluorenes. In conclusion, the mechanism of the oxidation of fluorenes by a mixture of bromine and alkali may be as follows in Scheme V. The abstraction of the 9 proton from fluorenes by a base occurs initially to give carbanion 2, which then gives 9-bromofluorenes 3 by an attack of hypobromite. This scheme is similar to the initial stage of the conversion of benzyl cyanide into dicyanostilbene.[2] However, 3 should give fluorenone but no bifluorenylidene 9, because (i) carbonium ion 7 may be more stable than carbanion 4, (ii) the concentration of 3 is very low, (iii) the rate of the formation of 9 is second order in 3.[2,5d] Carbonium ion 7, which is formed from 3 by elimination of Br^-, gives directly fluorenone 6 with an attack of hypobromite OBr^- but not through fluorenol 8. The rate-determining step depends on the concentration of alkali; *i.e.*, step A determines the rate at [NaOH] < 0.4 *M* and step B determines the rate at [NaOH] > 0.6 *M*.

Experimental Section

Materials. Used fluorene was purified by recrystallization after distillation: mp 116° (lit.[13] 116°). Substituted fluorenes were prepared from fluorene according to the literature. Substituents and mp were as follows: 2-NO_2, 156° (lit.[14] 156–157°); 2-CN, 89–90° (lit.[15] 94°); 2-Br, 110–111° (lit.[16] 113°); 2-Ac, 128° (lit.[17] 128–129°); 2-OMe, 105–106° (lit.[18] 108–109°); 2,9-diBr, 124–125° (lit.[19a] 118–120°, lit.[19b] 127°). The purities of fluorenes were confirmed by glc analysis. A Hitachi K-53 gas chromatograph with a flame ionization detector was used with a 1.0 m × 3.0 mm column packed with Apiezon Grease L (3%) on Celite 545 and/or PEG 20 M (10%) on Chromosorb W at a temperature increasing at 10°/min from 150 to 250°.

Inorganic materials were of commercial guaranteed grade. Dioxane was heated to reflux over sodium and distilled (bp 101°). The solution of hypobromite (1.0 *M*) was prepared by addition of aqueous NaOH (80.0 g in *ca.* 600 ml) to Br_2 (160.0 g) with cooling in a salt–ice bath and then diluted to 1000 ml in a measuring flask. The content of hypobromite was analyzed iodometrically before use. The solution can be stored in a refrigerator for 2 months.

Products. Fluorene (50 mg) was dissolved in 50 ml of dioxane. Water (10 ml), aqueous NaOH (1 *M*, 10 ml), and aqueous NaOBr (1 *M*, 10 ml) were added to the solution which was then stirred at 25° for 5 hr. Aqueous $Na_2S_2O_3$ was poured into the mixture to remove hypobromite and extracted with benzene. Products were isolated, if necessary, with silica gel column chromatography and analyzed by glc and ir to be the expected fluorenones. Substituents, yields, and mp were as follows: 2-NO_2, 100%, 218–220° (lit.[20] 219–221°); 2-CN, 100%, 169–171° (lit.[21] 173–174°); 2-Br, 96%, 149–150° (lit.[21] 149–150°); 2-COOH, 99%, >300° (lit.[6] 310°); 2-OMe, 15%, 76–78° (lit.[21] 78–79°); unsubstituted, 5%, 83° (lit.[13] 85°).

For the preparation of 2,9-dibromofluorene, 2-bromofluorene (200 mg) was added to 200 ml of aqueous dioxane (27% water) containing NaOH (2.1 *M*), NaBr (1.0 *M*), and NaOBr (0.2 *M*) and the heterogeneous reaction mixture was stirred vigorously for 10 hr at 25°. 2,9-Dibromofluorene was obtained in a yield of 73% (by glc analysis): mp 124–125° (lit.[19b] 127°).

The NaOBr oxidation of 2,9-dibromofluorene in the same manner as fluorenes gave 2,2′-dibromobifluorenylidene (0–13%) together with 2-bromofluorenone (100–87%). On the other hand, when 2,9-dibromofluorene (50 mg) was treated with aqueous NaOH alone (10 ml of 1 *M* NaOH) in aqueous dioxane (27% water) at 25° for 5 hr, 2,2′-dibromobifluorenylidene was obtained quantitatively. 2,2′-Dibromobifluorenylidene (the mixture of cis and trans): red crystals; mp 260–280° [lit.[22] 312° (cis), lit.[23] 264° (trans)]; uv (λ_{max}) 253, 264, 282, 292 nm; ir, 810, 770, 720 cm^{-1} (no absorption of carbonyl); glc, only one peak.

Kinetics. 2-Bromofluorene was selected as the most suitable substrate, since it was oxidized at a moderate rate in aqueous dioxane. 2-Nitro- and 2-cyanofluorenes form complexes with alkali so that the rate could not be measured by means of uv spectrophotometry. Fluorene and 2-methoxyfluorene were so slowly oxidized that uv spectrophotometry could not be employed for the rate measurements. Rates of these fluorenes were measured by means of glc as described later. Typical experiments were as follows. The reactions were started by addition of aqueous hypobromite (NaOBr 5–20 × 10^{-2} *M*) to a mixture of 2-bromofluorene (2 × 10^{-5} *M*) and aqueous NaOH (0.007–0.7 *M*) in a thermostated 10 mm × 10 mm quartz cell held at constant temperature of 25°. The rate was followed by measuring the concentration of produced 2-bromofluorenone by means of uv spectrophotometry at a wavelength of 264 nm (2-bromofluorenone, λ_{max} 264 nm, ϵ 7.00 × 10^4; 2-bromofluorene, ϵ_{264} 2.00 × 10^4).

The plot of ln ([2-bromofluorene]$_0$ − [2-bromofluorenone]) against time gave a satisfactory straight line under these conditions at least up to 80% conversion, where [ ]$_0$ means initial concentration. The pseudo-first-order rate constants (k_{obsd}) were calculated from the slopes.

The rate with 2,9-dibromofluorene (ϵ_{264} 1.15 × 10^4) was measured in the same way. The formation of bifluorenylidene was negligible under these conditions.

The relative rate of fluorenes were measured by means of glc analysis of substrate and products. The typical experiments were as follows. The reaction was started by addition of a dioxane solution of fluorenes (2.5–2.0 × 10^{-3} *M*) to the solution of NaOH (0.0125 *M* or 0.125 *M*) and NaOBr (0.0125 *M* or 0.125 *M*) dipped in a thermostat at 25°. At appropriate time intervals, aliquots were taken out and extracted with benzene. The benzene extract was washed with aqueous $Na_2S_2O_3$ to eliminate hypobromite and concentrated by evaporation of benzene; then the content of fluorenes and fluorenones were measured by glc with a column packed with Apiezon Grease L (3%) as stated above. The plot of ln ([fluorene]/[fluorene]$_0$) is linear up to 60–80% conversion.

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Registry No.—Sodium hypobromite, 13824-96-9.

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Halogen Abstraction Studies. VI. Abstraction of Bromine by Phenyl Radicals from C_3–C_8 Cycloalkyl Mono- and *trans*-1,2-Dibromides[1]

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The rates of abstraction of bromine by phenyl radicals from the cyclic C_3 to C_8 monobromides and *trans*-1,2-dibromides and *meso*- and *dl*-2,3-dibromobutanes relative to the rate of chlorine abstraction from carbon tetrachloride are reported. The rates of bromine abstraction from the cycloalkyl monobromides vary with ring size in a manner similar to that observed for endothermic homolytic and carbonium ion processes which suggests that there is considerable bond breaking in the transition states leading to the cycloalkyl radical intermediates in the present study. A comparison of the monobromide:dibromide rate ratios for the different-sized rings reveals decisive variations depending upon ring size which suggests that anchimeric assistance to bromine abstraction in the dibromides is related to the ease of attainment of a trans periplanar alignment of the adjacent bromine atoms. After correcting for the slight influence of polar effects in the abstraction from 1,2-dibromoethane, it is concluded from the rate data that the 2-bromoethyl radical is stabilized by ~2 kcal/mol relative to the ethyl radical itself.

We have demonstrated in previous papers in this series that the free radical abstraction of a halogen atom is a convenient and unambiguous method of generating a specific free radical for the purpose of studying homolytic processes in organic compounds. In particular, we have elucidated a unique polar effect operative in the homolytic abstraction of a halogen atom,[2] determined the occurrence of neighboring halogen participation in such processes,[3] provided an assessment of the relative rates of formation of various bridgehead radicals,[4] investigated electronic–steric effects in ortho-substituted iodobenzenes,[5] and determined the relative ease of iodine abstraction from the isomeric iodonaphthalenes, iodopyridines, and iodothiophenes.[1a]

We presently wish to report the rates of abstraction of bromine by the phenyl radical from the cyclic C_3 to C_8 monobromides and *trans*-1,2-dibromides (with the exception of 1,2-dibromocyclobutane) relative to the rate of abstraction of chlorine from carbon tetrachloride. Ring size is known to be an important factor influencing the rate of formation of cycloalkyl cations, radicals, and anions.[6] It will be shown that the rate of homolytic bromine removal varies with ring size in a manner which parallels endothermic homolytic and carbonium ion processes. A comparison of the rate ratio for a given cycloalkyl monobromide with the corresponding cycloalkyl 1,2-dibromide reveals decisive differences with ring size which suggest that anchimeric assistance in the dibromides is related to the ease of attainment of a trans periplanar alignment of the adjacent bromine atoms. It is concluded that the 2-bromoethyl radical is stabilized by *ca.* 2 kcal/mol relative to the ethyl radical itself.

Results

The rate data reported in Table I were obtained by the competitive technique employed in our earlier studies in which phenyl radicals were allowed to react with a large excess of both alkyl bromide and carbon tetrachloride. The phenyl radicals were generated by thermal decomposition of phenylazotriphenylmethane at 60.0 ± 0.1° and the k_{Br}/k_{Cl} values were calculated from eq 3. The values for the di-

$$\text{R—Br} + \text{Ph}\cdot \xrightarrow{k_{Br}} \text{R}\cdot + \text{Ph—Br} \qquad (1)$$

$$\text{CCl}_4 + \text{Ph}\cdot \xrightarrow{k_{Cl}} \text{CCl}_3\cdot + \text{Ph—Cl} \qquad (2)$$

$$k_{Br}/k_{Cl} = [\text{PhBr}][\text{CCl}_4]/[\text{PhCl}][\text{RBr}] \qquad (3)$$

bromides were statistically corrected to give the relative rate per bromine atom. The combined yields of chlorobenzene and bromobenzene totaled 20–30% for the monobromides and 60–90% for the dibromides reflecting the enhanced reactivity of the latter; the remainder of the phenyl radicals presumably abstract hydrogen atoms to form benzene. The second bromine is eliminated from the β-bromoalkyl radical generated in the abstraction from the dibromides to give the corresponding olefin which was identified in most cases by glpc retention time with that of an authentic sample and by disappearance of olefin product upon addition of bromine to the reacted solution. The amounts of olefin produced were not determined. With phenylazotriphenylmethane as a precursor to the phenyl radicals the triphenylmethyl radical also produced presumably reaches a reasonably high steady state concentration and serves as a scavenger for the second bromine atom.

Table I
Relative Rates of Bromine Abstraction by the Phenyl Radical from Alkyl and Cycloalkyl Mono- and 1,2-Dibromides at 60°[a]

Monobromides	Registry No.	k_{Br}/k_{Cl}[b]	1,2-Dibromides	Registry No.	k_{Br}/k_{Cl}[b]	k_{di}/k_{mono}[c]
c-C_3H_5Br	4333-56-6	0.035	c-*trans*-$C_3H_4Br_2$	16837-83-5	0.31	8.9
c-C_4H_7Br	4399-47-7	0.18				
c-C_5H_9Br	137-43-9	0.26	c-*trans*-$C_5H_8Br_2$	10230-26-9	1.48	5.7
c-$C_6H_{11}Br$	108-85-0	0.16	c-*trans*-$C_6H_{10}Br_2$	7429-37-0	1.32	8.3
c-$C_7H_{13}Br$	2404-35-5	0.34	c-*trans*-$C_7H_{12}Br_2$	52021-35-9	1.52	4.5
c-$C_8H_{15}Br$	1556-09-8	0.58	c-*trans*-$C_8H_{14}Br_2$	34969-65-8	1.36	2.3
CH_3CH_2Br	74-96-4	0.076	CH_2BrCH_2Br	106-93-4	0.37	4.9
sec-C_4H_9Br	78-76-2	0.24	*meso*-$CH_3CHBrCHBrCH_3$	5780-13-2	1.49	6.2
			dl-$CH_3CHBrCHBrCH_3$	598-71-0	1.22	5.1

[a] Estimated accuracy ±5%. [b] The relative rates are corrected to a per bromine atom per molecule of CCl_4 basis. [c] Ratio of rate of bromine abstraction from dibromide relative to rate from corresponding monobromide.

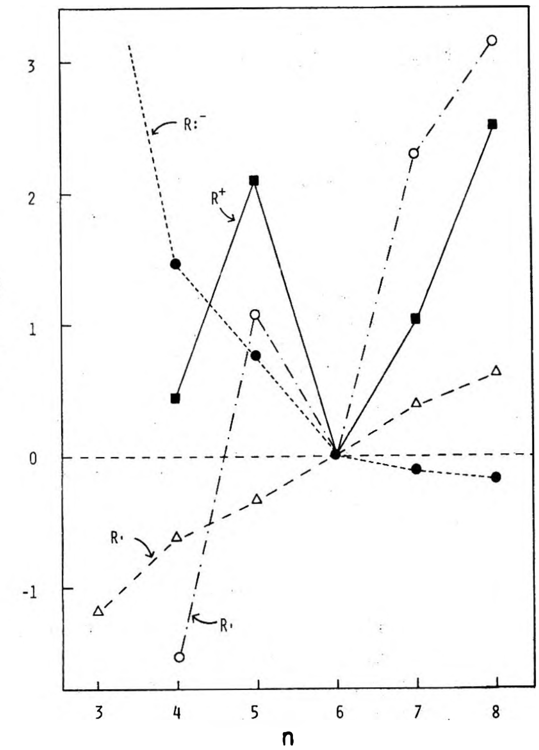


Figure 1. Dependence of ring size (n) on the rate of formation of cyclic carbonium ions, carbanions, and free radicals. (●) Rate of formation of carbanions from reaction of cycloalkanes with cesium cyclohexylamide. (■) Rate of formation of carbonium ions by solvolysis of 1-methylcycloalkyl chlorides in 80% ethanol. (△) Rate of formation of free radicals by thermal decomposition of cycloalkyl peresters. (○) Rate of formation of free radicals by thermal decomposition of cycloalkylazonitriles.

Discussion

(a) Monobromides. From the data in Table I, it is seen that the values of k_{Br}/k_{Cl} of the cycloalkyl monobromides range from 0.035 for cyclopropyl bromide to 0.58 for cyclooctyl bromide, a range of *ca.* 16-fold. However, the reactivities do not follow a regular progression depending on ring size and the rates provide an interesting correlation with data obtained from other reactions performed on the cycloalkane series. Rüchardt[6] has summarized the reaction rate data for several different types of reactions including carbonium ion, free radical, and carbanion processes. The data for the C-3 to C-8 rings are reproduced here (Figure 1).

There are at least three factors competing in the rate of reaction of cyclic compounds: hybridization differences, ring strain, and polar effects. Hybridization differences are expected to be particularly pronounced in the cyclopropyl and cyclobutyl compounds. The relatively high percentage of s character in the exocyclic bonds should facilitate carbanion and retard carbonium ion formation in these small rings. In those carbonium ion and free radical reactions in which the transition state is well along in the reaction coordinate, *i.e.*, in more endothermic reactions, the ring strain effects become more pronounced. This is because the carbon at which the reaction is taking place is going from an sp^3 to an sp^2 hybridization which relieves eclipsing effects in the cyclopentyl ring and transannular interactions in the cycloheptyl and cyclooctyl rings. In the smaller rings, especially the cyclopropyl and cyclobutyl, this rehybridization increases ring strain, thus slowing the reaction. Likewise, cyclohexyl is retarded because the almost perfectly tetrahedral arrangement is disrupted upon forming an sp^2 center. Finally, one would expect the inductive effects of added chain length in the cyclic chain to slow the rate of formation of carbanions and increase the rate of formation of carbonium ions. This effect would be the largest in going from cyclopropyl to cyclobutyl and cyclopentyl compounds and would be considerably attenuated for the larger rings. These effects are expected to be relatively small although the electronegativity differences resulting from hybridization changes can also influence polar effects.

From Figure 1 it is seen that hybridization-electronegativity effects predominate in the formation of the cyclic carbanions while ring strain effects have a pronounced effect on the formation of carbonium ions. Free radical reactions can be correlated with these effects depending upon the extent of radical character developed in the transition state. For an exothermic reaction the transition state comes early in the reaction and is structurally more similar to starting material than product according to the Hammond postulate. If polar effects are not significant an exothermic radical reaction should correlate with the carbanion reaction in Figure 1. Conversely, endothermic reactions should feel the effects of ring strain as the transition state will have considerable radical character developed and hence should correlate with the carbonium ion reactions.

In the homolytic decomposition of peresters the hybridization and polar effects appear to predominate with the rate decreasing roughly as the electronegativity of the ring carbon increases suggesting an early transition state with little radical character. However, a rigorous interpretation of these data is difficult. Two extreme mechanisms involving either one-bond or two-bond homolysis have been postulated for perester decompositions and it is possible that there is a change in the amount of radical character developed on the cycloalkyl group in the transition state depending upon ring size. The endothermic azo decomposition reaction, however, closely parallels the carbonium ion reaction, indicating a transition state late enough along the reaction coordinate to feel ring strain effects. Smith and Mead[7] have recently determined the rates of amine oxidation for a series of N-methyl nitrogen heterocycles. The results closely paralleled the decomposition of azo compounds showing the importance of ring strain effects in the transition state leading to the planar[8] aminium radical cations.

The rates of bromine abstraction from the C_3 to C_8 monobromides relative to cyclohexyl bromide are plotted in Figure 2. The values obtained are seen to correlate with the carbonium ion and azo decomposition reactions although the rate differences relative to the six-membered ring are much smaller in magnitude. According to Rüchardt's arguments, this suggests considerable bond breaking in the transition state leading to the cycloalkyl radical intermediate.

Although the abstraction of a bromine by a phenyl radical is a mildly exothermic reaction ($\Delta H = -3$ kcal/mol for abstraction from isopropyl bromide[9]) the transition state must be coming late enough along the reaction coordinate to allow ring strain effects to influence the rates of the reaction. From polar effects alone one might expect the trend to follow that of the formation of a carbanion since it has been shown that halogen abstraction reactions exhibit a positive ρ value and are accelerated by electron-withdrawing substituents.[2,3] These results also closely parallel the trend found in the abstraction of hydrogen from the cycloalkanes C_5 through C_8 by the phenyl radical reported by Bridger and Russell,[10] although the rate differences for bromine abstraction are about half again larger in magnitude relative to the six-membered ring than in the hydrogen abstraction reaction ($\Delta H = ca.\ -9.5$ kcal/mol[9]). A re-

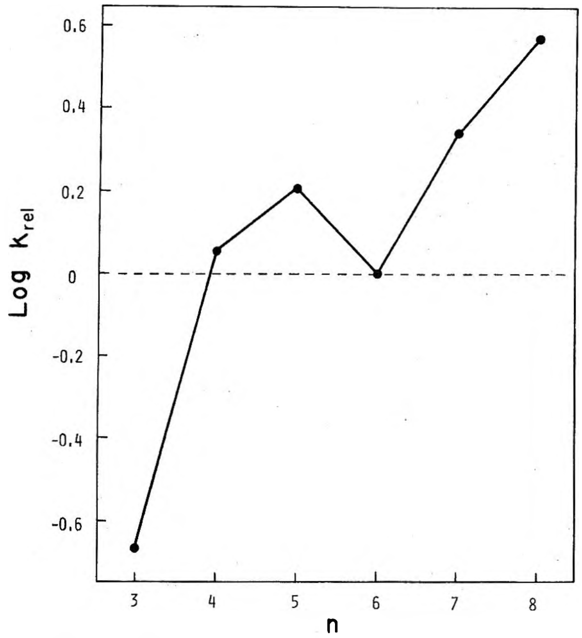


Figure 2. Dependence of ring size (n) on the rate of abstraction of bromine from cycloalkyl bromides by phenyl radicals at 60°.

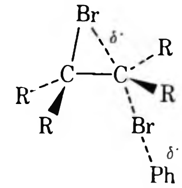
cent study by Bunce and Hadley shows similar trends.[31]

(b) 1,2-Dibromides. The rates of bromine abstraction from *trans*-1,2-dibromides reported in Table I were all considerably faster than the rates for the corresponding monobromides. We have concluded in a previous study[3] that the bromine atom in 1-iodo-2-bromoethane enhances the rate of iodine abstraction by a favorable polar effect influence as well as by anchimeric assistance. In the 1,2-dibromides of the present study the second bromine atom, like other electron-withdrawing substituents, enhances the rate of halogen abstraction because of a polar effect. From eq 4 it

$$\overset{\delta+}{R}-\overset{\delta-}{Br} + \cdot Ph \longrightarrow \left[\overset{\delta\delta\bullet+}{R}\text{-----}\overset{\delta-}{Br}\text{-----}\overset{\delta\delta\bullet+}{Ph}\right]^{\ddagger} \longrightarrow R\bullet + \overset{\delta-}{Br}-\overset{\delta+}{Ph} \quad (4)$$

can be seen that the carbon atom to which bromine is bonded in the original alkyl bromide is somewhat electron deficient at the onset of homolytic bromine removal because of the polarized C–Br bond resulting from the inductive effect of the electronegative bromine and that this carbon atom acquires an increased amount of electron density in the transition state relative to the ground state. It has been observed in both aromatic[2] and aliphatic[3] iodides that electron-withdrawing groups enhance and electron-donating groups retard the rate of iodine abstraction by phenyl radicals and that the substituent effects can be correlated reasonably well with the Hammett and Taft relationships, respectively. For 1-iodo-2-bromoethane, however, the rate of iodine abstraction was still 90% faster than that expected based only on polar effect considerations; this enhancement was attributed to anchimeric assistance to removal of the iodine by the adjacent bromine. The present results on the *meso*- and *dl*-2,3-dibromobutanes and *trans*-1,2-dibromocycloalkanes support this conclusion and lend further insight into the stereochemical aspects of neighboring bromine participation.

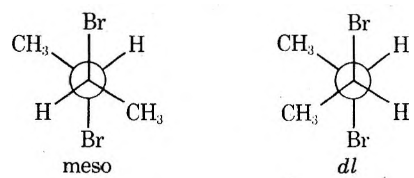
It is generally accepted that anchimeric assistance by a neighboring bromine atom occurs most readily through an antiperiplanar arrangement of atoms[11] similar to the preferred orientation for an ionic E2 elimination process. It should be noted, however, that some of the data cited as ev-



idence for homolytic anchimeric assistance has been questioned[12] and some controversy has enshrouded the topic although the most recent work of Skell and coworkers[11] and others[13] appears quite definitive and should suffice to lay this controversy to rest. In addition, there is considerable evidence from electron spin resonance studies that an adjacent chlorine,[14] bromine,[15] or iodine[15] atom (as well as sulfur, silicon, germanium, tin, phosphorus, and arsenic groups[16]) exhibits a preferred conformational orientation in which the heteroatom eclipses the p orbital of the radical center. Although the precise mode of interaction of the heteroatom with the unpaired electron is not fully understood, the results indicate that these radicals do not possess truly symmetrically bridged structures (the results for β-Br and I are not definitive in this regard) but that the interaction of orbitals is sufficient to cause hindered internal rotation about the C_α–C_β bond. This interaction must be stabilizing and the reduction in energy of the product radical should exert itself in the transition state leading to formation of the radical. It might also be pointed out that the controversy over the importance of anchimeric assistance in bromination studies stems largely from attempting to relate ratios of products possibly formed *via* several competing pathways with the rates of initial abstraction of hydrogen. Such complications are not inherent in the present study since the value of k_{Br}/k_{Cl} is a function only of the rate of abstraction of bromine from the substrate molecule.

If anchimeric assistance by a β-bromine is equally effective for all the 1,2-dibromides investigated in this study, then the ratio of rates for bromine abstraction from a dibromide relative to the rate of abstraction from the corresponding monobromide, k_{di}/k_{mono}, should be reasonably constant. The last column in Table I illustrates that this ratio varies considerably from a high of 8.9 for the cyclopropyl compounds to a low of only 2.3 for the cyclooctyl bromides. We believe that the variation in this ratio reflects the relative importance of anchimeric assistance to abstraction of bromine for each dibromide since the enhancement in rate due to a polar effect should be similar for all the dibromide–monobromide pairs. It can be shown that the ratio varies qualitatively with the relative population of that conformation for each 1,2-dibromide in which the two bromine groups are antiperiplanar to each other.

Consider the *meso*- and *dl*-2,3-dibromobutanes. The lowest energy conformation of the meso isomer is that in



which the bromines are trans to each other, whereas the conformation of the *dl* isomer which has the bromines trans requires the CH_3 groups to be gauche to each other, a somewhat higher energy conformation. This results in a faster rate of bromine abstraction for the meso isomer as compared to the *dl* compound since the β-bromine in the former compound is better aligned to contribute to lowering the activation energy barrier for abstraction. A similar mode of reasoning can account for the relatively small difference of 4.9 in the rate of abstraction of bromine from 1,2-dibromoethane as compared to ethyl bromide. A significant proportion of molecules of 1,2-dibromoethane exists in the less reactive gauche conformation in solution since the difference in energy between the trans and the gauche isomers is only 0.7 kcal/mol.[17] On the other hand, the rigidity of the three-membered ring and the relatively wide Br–C–H angles in *trans*-1,2-dibromocyclopropane (HCH angle = 115.12° in cyclopropane[18]) place the two bromine atoms in an alignment approaching the optimal trans arrangement accounting for the enhanced dibromo:monobromo ratio of 8.9. Likewise, in *trans*-1,2-dibromocyclopentane the flexibility of the five-membered ring allows for various conformations but it has been determined that the two bromines exist >90% in the diaxial form.[19] Similarly, *trans*-1,2-dibromocyclohexane is known to exist as an equilibrium mixture of diaxial and diequatorial conformers in an essentially equimolar proportion.[20] The diaxial conformation is perfectly aligned, of course, for assistance by the adjacent bromine and an enhancement in rate of 8.3 over that observed for bromocyclohexane results. From Table I it may be noted that the dibromo:monobromo ratio drops rather significantly for the cycloheptyl and, particularly, the cyclooctyl compounds. This is in accord with conformational studies on *trans*-1,2-dibromocyclooctane in which it was concluded that there is a significant population of conformations having the bromines in a "diequatorial" arrangement.[21] An inspection of molecular models suggests that transannular interactions increase as the bromines approach an anti conformation.

Although variation in k_{di}/k_{mono} ratios for the various cycloalkyl di- and monobromides can be qualitatively rationalized as reflecting the relative populations of conformations in which the two bromines in the dibromides approach a trans alignment, this reasoning should not be overextended. In particular, free radical hydrogen bromide additions to 1-bromocycloalkenes were observed to be trans-stereospecific suggesting the intermediacy of a bromine-bridged radical but alteration of the ring size made the additions monostereospecific.[22] Stereoselectivity decreased in the order $C_6 > C_5 > C_7 > C_4$ and it has been suggested[23] that the stability of the bromine-bridged radicals (probably not symmetrically bridged) relative to the classical radicals may be altered by strain. Extension of this reasoning would suggest that the cyclopropyl system would produce the most strained intermediate which is not reflected in the high k_{di}/k_{mono} value in the present study. The addition of HBr to a 1-bromocycloalkene and the abstraction of bromine from a *trans*-1,2-dibromocycloalkane differ significantly, however, and perhaps are not comparable. The former requires a bridged-bromine radical intermediate to abstract hydrogen from HBr to produce a *cis*-1,2-dibromocycloalkane whereas the present study involves removal of a bromine atom from a *trans*-1,2-dibromocycloalkane.

An alternate explanation of our data cannot be ruled out.[32] It is observed that the k_{Br}/k_{Cl} values for the 1,2-dibromides listed in Table I are reasonably constant except for the cyclopropyl and ethyl systems. If assistance by neighboring bromine is significant, it is plausible that this factor is dominant over conformational effects for all the secondary systems except cyclopropyl and the k_{di}/k_{mono} ratios thus reflect mainly on reactivity differences among the monobromides where conformational effects appear to be more important. The cyclopropyl and ethyl systems react slower in both series presumably due to C–Br bond strength considerations.

It may be noted that a crucial feature of either of the above explanations of the k_{di}/k_{mono} data is the involvement of anchimeric assistance by the neighboring bromine for the 1,2-dibromides.

In our previous work we concluded that a concerted elimination of the β-bromine was probably not responsible for the enhanced rate of iodine abstraction from 1-bromo-2-iodoethane.[3] The present results confirm this conclusion. The k_{di}/k_{mono} value of 8.9 for the cyclopropyl pair is the largest observed in the present work yet the elimination of β-bromine from the 2-bromocyclopropyl radical should be the least favored. Heat of formation data indicate an increase of 25.4 kcal/mol in ring strain in going from cyclopropane to cyclopropene whereas there is a loss of ring strain for the cyclopentyl through cyclooctyl counterparts.[24]

(c) Estimate of Stabilizing Influence of β-Bromine Substituent. It was concluded in the above section that a β-bromine substituent can stabilize a radical center although the precise mode of this stabilization is not yielded by these studies. It would seem important to be able to obtain an estimate of this stabilizing influence. Krusic and Kochi have obtained barriers to rotation in alkyl radicals of 1.2, 1.6, and 2.0 kcal/mol for the β substituents Si, Ge, and Sn, respectively.[16a] A barrier as high as 5 kcal/mol was noted for Sn in the adduct of tributylstannyl radical to butadiene.[16c] Alternatively, the stabilization energy in the 2-bromoethyl radical due to interaction of the unpaired electron with the β-bromine substituent may be defined as $D(CH_3CH_2–H) - D(BrCH_2CH_2–H)$.[25] We have observed in previous studies that the abstraction of iodine from β-bromoethyl iodide is *ca.* 90% faster than the expected rate after correcting for inductive effects.[3] From this rate enhancement an estimate of the stabilizing influence of the β-bromine can be calculated since there is an excellent correlation between the rate of abstraction of iodine from aliphatic iodides and the respective thermodynamic C–H bond dissociation energies, providing the kinetic k_I/k_{Br} values are first corrected for the slight polar effects of the groups attached to the carbon from which the iodine is abstracted.[4] Knowing the k_I/k_{Br} abstraction rate of an alkyl iodide, it is possible to obtain its D(C–H). By calculating the D(C–H) for $BrCH_2CH_2–H$ and comparing it with the known D(C–H) for $CH_3CH_2–H$, a stabilization of 2.1 kcal/mol is obtained for the 2-bromoethyl radical relative to the ethyl radical itself.

A similar analysis utilizing k_{Br}/k_{Cl} data of the sort obtained in the present study yielded a bond dissociation energy for $BrCH_2CH_2–H$ of 96.1 kcal/mol which is lower than the D(C–H) of ethane by 1.9 kcal/mol in good agreement with the estimate from the k_I/k_{Br} data. The same treatment was applied to allyl bromide as a check on the validity of this method. From the k_{Br}/k_{Cl} value of 2.43 for allyl bromide a resonance energy of *ca.* 8 kcal/mol is estimated. This compares with a value of *ca.* 10 kcal/mol determined by other workers.[25] It appears, then, that this Polanyi type of relationship is capable of yielding at least semiquantitative estimates of stabilization energies although the true values may be underestimated somewhat possibly because of the inherent assumption of a constant ΔS^* for the reactions. In this regard, Skell, *et al.*, reported a $\Delta\Delta H^* = -3.4$ kcal/mol and a $\Delta\Delta S^* = -7.2$ eu for the β-hydrogen of 1-bromobutane relative to the α hydrogen for reaction with Br atoms and interpret the differences as resulting from bromine bridging.[11a] Thus, we conclude that a β-bromine stabilizes a radical site to the extent of *ca.* 2.0 kcal/mol although this value might underestimate the stabilization somewhat.

Experimental Section

Kinetic analysis were performed as described previously.[3]

Bromocyclopropane, bromocyclobutane, bromocyclopentane, bromocyclohexane, bromoethane, 2-bromobutane, 1,2-dibromoethane, and allyl bromide were commercially available and purified by vacuum distillation if deemed necessary by glpc analysis.

Bromocycloheptane was synthesized by adding anhydrous HBr to cycloheptene following the general procedure of Mozingo and Patterson.[26] To a solution of 0.2 mol of cycloheptene in anhydrous ether in a round-bottom flask wrapped in aluminum foil was added a slight excess of dry HBr from a gas cylinder, keeping the temperature below 5°. The reaction was allowed to stir for 20 hr. As much of the unreacted cycloheptene as possible was removed by vacuum distillation. The remaining cycloheptene was brominated by saturating with Br_2, washed with 10% $NaHSO_3$ and water, and dried, and the bromocycloheptane was obtained by distillation at 26–26.5° (0.3 mm), yielding a product >99% pure by glc and containing no detectable dibromide. This compound was very sensitive to thermal decomposition, and glpc injection port temperature and distillation pot temperatures were kept below 80°. Commercially obtained bromocycloheptane was found to contain *ca.* 10% low-boiling impurities and attempted purification by spinning band distillation at reduced pressures was unsuccessful due to thermal decomposition.

Bromocyclooctane was synthesized in a similar manner from cyclooctene. Since this compound was also quite susceptible to thermal decomposition, attempts to distill the product only yielded more impurities. The major reaction impurity was cyclooctene which was removed by washing with 85% H_2SO_4 at 5 ° following the procedure of Cope, Brown, and Woo.[27] Other low-boiling components of the mixture were removed by distillation at 50° (0.3 mm), leaving bromocyclooctane that was >99% pure by glpc.

meso- and *dl*-2,3-dibromobutane were prepared from *trans-* and *cis*-2-butene, respectively, by bubbling the butene through a 0.1 mol solution of Br_2 in CCl_4. The exothermic reaction occurred quite fast and the bromine color was discharged in 15 min. The CCl_4 was removed on a rotary evaporator and the product distilled at 29–30° (5 mm). Analysis by glpc showed each isomer >99% pure, the only detectable impurity being the other diasteriomer.

trans-1,2-Dibromocyclopropane was prepared by addition of Br_2 to cyclopropene in CH_2Cl_2. The cyclopropene was generated by the method of Closs and Krantz[28] using 22 ml (0.4 mol) of allyl bromide and 16 g (0.4 mol) of sodium amide rather than allyl chloride as reported. The higher boiling allyl bromide gave better results with less allyl compound as contaminate in the product. The cyclopropene generated escaped through the condenser as it was formed and was bubbled into 5.8 g (0.4 mol) of Br_2 in CH_2Cl_2. The CH_2Cl_2 was removed by fractional distillation and the product collected by glc and identified by nmr spectroscopy.[29]

trans-1,2-Dibromocyclopentane, -cyclohexane, -cycloheptane, and -cyclooctane were prepared by the slow addition of the respective cycloalkene to a solution of bromine (*ca.* 0.3 mol) in CCl_4 until the bromine color was just discharged. The solutions were then fractionally distilled at atmospheric pressure to remove the CCl_4 and any unreacted cycloalkene, and then were vacuum distilled utilizing either a Vigreux or spinning band distillation apparatus: *trans*-1,2-dibromocyclopentane (bp 53–56° (4.5 mm)); *trans*-1,2-dibromocyclohexane (bp 55–57° (0.4 mm)); *trans*-1,2-dibromocycloheptane (bp 42–46° (0.1 mm)); *trans*-1,2-dibromocyclooctane (bp 71–73° (0.1 mm)). All products were determined to be >99% pure by glpc although all the dibromides were found to be quite sensitive to injection port temperature.[30]

Registry No.—HBr, 10035-10-6; cycloheptene, 628-92-2; cyclooctene, 931-88-4; *trans*-2-butene, 624-64-6; *cis*-2-butene, 590-18-1; bromine, 7726-95-6; cyclopropene, 2781-85-3; cyclopentene, 142-29-0; cyclohexene, 110-83-8.

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The Cyclopropenyl Free Radical. An *ab Initio* Molecular Orbital Study[1]

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Ab initio molecular orbital calculations by the STO-3G and 4-31G methods are reported for the cyclopropenyl free radical **1**. The optimum structure for the system corresponds closely to the "ethylenic" structure **1a**, with the C_1 H vector bent 47° from the C–C–C plane. Calculations by the 4-31G method indicate the latter structure is 11.1 kcal mol^{-1} more stable than the optimum planar structure of type **1a** and is 15.8 and 16.9 kcal mol^{-1} more stable than the optimum flapped and planar forms of the allylic geometry **1b**. The C_1–H bond dissociation energies of cyclopropene **2** and of cyclopropane and the barriers to planarity in the cyclopropenyl (**1**) and cyclopropyl (**4**) radicals are compared and discussed in terms of the aromaticity of **1**. The unpaired electron spin densities and total electron densities for **1a** and **1b** are discussed briefly.

Predictions by different semiempirical MO theories concerning the stabilization due to conjugation of the cyclopropenyl radical **1** are remarkably diverse. Theories (such as the simple Hückel method and Dewar's SCF π-electron method) which *neglect* overlap integrals predict that the conjugation of the unpaired electron with the double bond significantly stabilizes the system. On the other hand, theories which *include* overlap integrals predict that the conjugation is destabilizing.[2]

1 1a 1b 2 3

Given the disagreement between these theories regarding the energetic consequences of conjugation, it is difficult to predict whether the cyclopropenyl radical is planar (to maximize conjugation) or not, what order of magnitude to expect for the energy difference between planar and flapped conformations, and whether the dissociation energy of the C–H bond in cyclopropene **2** is less than, or greater than, that for cyclopropane. In some recent *ab initio* calculations, Ha and coworkers considered some of these points.[5] However, their assumptions concerning the bond lengths of the cyclopropenyl radical were rather restrictive, and may well have biased their conclusions. For this reason we have undertaken more extensive *ab initio* molecular orbital calculations for the cyclopropenyl radical **1** and for some related systems. All SCF molecular orbitals for **1** and for the cyclopropyl radical **3** were determined using Roothaan's restricted open-shell method.[6] The basis sets used were STO-3G and 4-31G expansions described by Pople and coworkers.[7] Standard molecular exponents[7] were used except in the case of the isolated hydrogen atom, the energy for which corresponds to that for optimum atomic exponents.[7] The computer program used has been described previously.[8]

Results and Discussion

By means of STO-3G calculations, the geometrical structure of the cyclopropenyl radical was optimized, subject to the following assumptions: (a) that carbon atoms 2 and 3 are equivalent, (b) that the C–H bond lengths are 1.080 Å, and (c) that each C–H bond vector bisects the corresponding C–C–C bond angle.[9] The optimum-energy structure is of the "ethylenic" type **1a**, with one C=C bond length of 1.30 Å (*i.e.*, 0.02 Å longer than that calculated by the same method for cyclopropene[10]) and two C–C bonds of length 1.47 Å (*i.e.*, 0.02 Å shorter than for cyclopropene[10]). The hydrogen atom bonded to the "methyl" carbon C_1 does *not* lie in the C–C–C plane; the angle between the C_1–H vector and this plane is 47° (compared to 56° for the methylene C–H bonds in cyclopropene[10]). Calculations of the same

Table I
Calculated Energies and Geometries for Free Radicals

System	Geometry calculated by STO-3G basis[a]	STO-3G energy, au	4-31G energy, au
Cyclopropenyl radical, ethylenic, flapped	R(C—C•) = 1.47 Å R(C=C) = 1.30 Å Flap angle = 47°	−113.7584	−115.0060
Cyclopropenyl radical, ethylenic, planar	R(C—C•) = 1.45 Å R(C=C) = 1.30 Å	−113.7319	−114.9883
Cyclopropenyl radical, allylic, flapped	R(C-̇-C) = 1.35 Å R(C—C) = 1.48 Å Flap angle = 27° (cis)	−113.7239	−114.9808
Cyclopropenyl radical, allylic, planar	[R(C-̇-C) = 1.35 Å] [R(C—C) = 1.48 Å]	−113.7172	−114.9790
Cyclopropenyl radical, equilateral, planar (S state)	R(C—C) = 1.40 Å	−113.7116	c
Cyclopropyl radical, flapped[b]	R(C—C•) = 1.48 Å [R(C—C) = 1.502 Å] Flap angle = 46°	−115.0115	−116.2359
Cyclopropyl radical, planar[b]	[R(C—C•) = 1.48 Å] [R(C—C) = 1.502 Å]	−114.9988	−116.2286

[a] All R(CH) = 1.080 Å for cyclopropenyl and R(CH) = 1.081 Å for cyclopropyl (assumed). Values in square brackets were assumed. [b] The H–C–H angles in the cyclopropyl radical were assumed to be 113.8°, *i.e.*, that deduced as optimum in cyclopropane (ref 10). [c] No energy was obtained due to convergence problems.

type for the cyclopropyl radical 3 yield an out-of-plane angle of 46° for the C_1–H vector and C–C · bond lengths of 1.48 Å (*i.e.*, 0.02 Å shorter than for cyclopropane[10]). The near equality of the flap angle for cyclopropyl and cyclopropenyl suggests strongly that the main driving force toward nonplanarity at the radical center is the same in both systems. Presumably this driving force is relief of strain, since it is known that the strain energies of three-membered rings increase as the number of planar, tricoordinated carbons increases.[11]

From the optimum STO-3G energy for cyclopropenyl (see Table I) and the values for cyclopropene[10] and hydrogen[6,7] reported by Pople and coworkers, the predicted C_1–H bond dissociation energy (bde) in cyclopropene is 92.8 kcal mol^{-1}; the corresponding value calculated for cyclopropane itself is 100.2 kcal mol^{-1}. Recalculation of the energy of the cyclopropenyl and cyclopropyl radicals at their optimum STO-3G geometries but using the extended 4-31G basis set yields a predicted C_1–H bde of 85.6 kcal mol^{-1} for cyclopropene and 93.1 kcal mol^{-1} for cyclopropane. Previous experience in the computation of bde's of hydrocarbons by Pople and coworkers[13] indicates that these values are probably too small by 5 to 15%. Nevertheless, it is clear that the C_1–H bde for cyclopropene should be significantly less (by ~7 kcal mol^{-1}) than that for cyclopropane.

In order to investigate the barrier to planarity in the cyclopropenyl radical, the optimum geometry for the planar form has been determined by STO-3G calculations. Although the C=C length remains equal to 1.30 Å as in the nonplanar form, the C–C single bonds decrease in length to 1.45 Å. The STO-3G energy of the planar form at this geometry is 16.6 kcal mol^{-1} less stable than that for the optimum flapped structure; the 4-31G basis set estimate of this energy difference is 11.1 kcal mol^{-1}. Calculation of the barrier to planarity in the cyclopropyl radical 3 yields[14] values of 8.0 and 4.6 kcal mol^{-1} by the STO-3G and 4-31G methods, respectively; thus the barrier is about 8 kcal mol^{-1} *less* in 3 than in the cyclopropenyl system **1a**.

The trends in the C_1–H bond dissociation energies and the barriers to planarity for cyclopropene and cyclopropane lead to conflicting conclusions regarding the aromaticity (or antiaromaticity) of the cyclopropenyl radical. If the lesser bde for cyclopropene is taken to be a manifestation of the stabilization of the radical by conjugation of the unpaired electron with the double bond, one would then expect a lower barrier to planarity in cyclopropenyl than in cyclopropyl since planarity further increases the conjugative interaction. As mentioned above, however, the barrier trend is in the opposite direction! Although the apparent conflict between the bde and planarity barrier trends may be due partially to steric and strain energy effects, we feel the dominant factor is a "saturation" effect to three-electron bonds. In particular, consider the orbital interaction diagram for cyclopropenyl in Figure 1. When the interaction between the π AO of C_1 and the π bonding MO of the ethylenic system is small (as in the flapped form of 1a) the stabilization $2\Delta_1$ of the bonding level outweighs the destabilization Δ_2 of the nonbonding level. As the overlap integral between the interacting orbitals increases, however, the destabilization of the singly occupied level rises more quickly than does the stabilization of the doubly-occupied level. In fact at large overlap integral values, the interaction becomes net *destabilizing*.[15] Evidently introducing planarity at the C_1 position of the cyclopropenyl radical causes the overlap with the ethylenic π MO to become too large and destroys the stabilizing interaction of ~7 kcal mol^{-1} which was present in the flapped geometry.

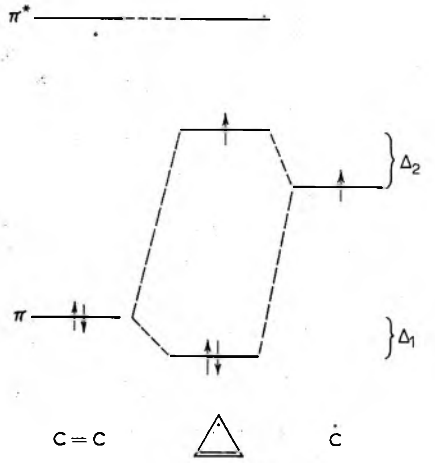

Figure 1. Interaction of the π and π^* orbitals of a C=C unit with the atomic orbital containing the unpaired electron.

Thus it can be concluded that the cyclopropenyl radical is neither aromatic as predicted by some theories, nor antiaromatic as predicted by others. Instead it is found that there exists a weak conjugative interaction between the unpaired electron and the double bond in the flapped geometry, and that this is essentially destroyed in the planar form. These results agree qualitatively with the conclusions of Shono, *et al.* (based upon electrochemical measurements on substituted cyclopropenyl radicals), that the conjugation introduces no special stability or instability in such radicals.[16] Feeble three-electron interactions have been found previously in *ab initio* calculations on the cyclopropylcarbinyl radical.[17]

In addition to the three equivalent "ethylenic" structures **1a**, there exists a second type of energy minima for the cyclopropenyl radical. These local minima correspond to structures of the "allylic" type **1b**, *i.e.*, with one long and two short, rather than two long and one short, carbon–carbon bonds. In the planar form of **1b**, the optimum allylic carbon–carbon distances R_{12} and R_{13} are 1.35 Å, and the length R_{23} of the single bond is 1.48 Å according to STO-3G calculations. Keeping these carbon–carbon distances fixed, out-of-plane distortions of the hydrogen atoms were considered. Although the C_1–H vector remains in the C–C–C plane in the allylic form, the hydrogens at the 2 and 3 positions do flap out of the plane. The optimum energy structure had these hydrogens flapped cis to each other such that the C_2–H (and C_3–H) vector makes a 27° angle with the C_3 plane. The barrier to planarity of the cis flapped structure is calculated to be 4.2 kcal mol^{-1} by STO-3G and 1.1 kcal mol^{-1} according to the 4-31G method. Curiously these results are similar to those for the $^3\pi\pi^*$ state of ethylene, for which the cis flap angle is 35° and the STO-3G and 4-31G barriers are 5.1 and 1.3 kcal mol^{-1}, respectively.[18] In contrast, however, to ethylene in which trans flapping is much less effective than is cis, the STO-3G energy for 27° trans flapped **1b** is only 0.2 kcal mol^{-1} higher than for the cis distortion.

The relative energies of some of the important geometries of the cyclopropenyl radical are illustrated in Figure 2. Both the ethylenic and allylic forms of the radical are more stable than is the planar equilateral geometry (optimum carbon–carbon length of 1.40 Å) as expected since the latter is subject to Jahn–Teller distortion[19,20] which removes the degeneracy of the antibonding π orbitals. Reducing the symmetry of the planar ring system from D_{3h} to C_{2v} by shortening the C_2–C_3 bond (relative to C_1–C_2 and C_1–C_3) stabilizes the antibonding π MO which is symmetric (S)

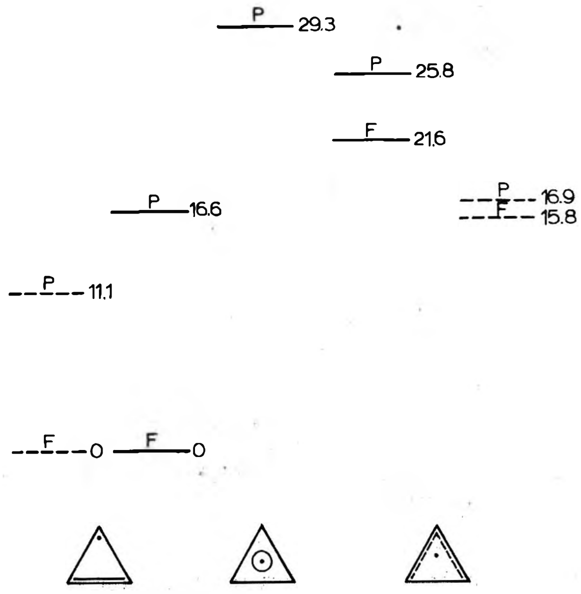

Figure 2. Energies for various conformations of the cyclopropenyl radical *via* STO-3G calculations (——) and 4-31G calculations (- - -). All values are relative to the flapped ethylenic structure, and are in kcal mol^{-1}.

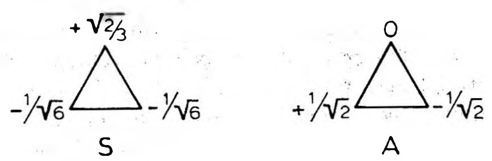

Figure 3. Hückel method coefficients for the symmetric (S) and antisymmetric (A) antibonding π orbitals of cyclopropenyl.

with respect to reflection in the plane which is perpendicular to the plane of the carbons and which bisects the C_2–C_1–C_3 angle (see Figure 3). Since the S orbital has a much larger coefficient at C_1 than at C_2 and C_3, the distribution of π electron density is not uniform. The net excess π charges (*i.e.*, deviations from neutrality) calculated for the planar species by the simple Hückel, STO-3G, and 4-31G methods are illustrated in Figure 4a. In the allylic geometry, the A orbital rather than the S is occupied and C_1 is predicted to suffer a deficiency, rather than an excess, of π electron density (see Figure 4b). In the *ab initio* calculations, the electron density associated with the two electrons of the bonding π orbital is polarized away from the carbon(s) at which the singly-occupied orbital is concentrated; thus the STO-3G and 4-31G net π charges are smaller than those predicted by the Hückel method. The carbon–carbon σ bonds also polarize so as to reduce the nonuniformity in total charge of the three carbons, as illustrated by the atomic partial charges given in Figure 5.

In purely electronic terms, the C_{2v} structures **1a** and **1b** correspond to different states of cyclopropenyl free radical, and these states do not mix since they are of different symmetry. The interaction of vibrational and electronic levels, however, will couple the two forms.[21] Since such coupling will be particularly important in the equilateral triangular forms, and since our computations do not take such interactions into account, no serious attempt to study the interconversion of **1a** and **1b** has been undertaken. In addition, convergence problems in the SCF calculations prevent us from reporting a 4-31G energy for the equilateral triangle form and from determining whether the S state or the A state of cyclopropenyl is of lowest energy at the optimum geometry for the allylic form **1b**.

The conclusion that the ethylenic structure is more stable than is the allylic agrees with the semiempirical MINDO calculations of Shanshal,[22] but is opposite to that concluded by Ha and coworkers on the basis of *ab initio* calculations.[5] We feel, however, that the *assumption* of 1.40 Å carbon–carbon distances in the latter calculation biases the calculations in favor of the allylic form. Interestingly, the C_1 out-of-plane angle of 40° found by Ha, *et al.*, for the ethylenic form agrees quite well with our value of 47°.

Finally, as a possible aid to the interpretation of the electron spin resonance spectrum of $C_3H_3\cdot$, the calculated open-shell spin densities are given in Table II. Note that the spin density is rather concentrated on the C· carbon (C_1) in both the flapped and planar conformations of the "ethylenic" form. Indeed the C_1 spin density of 0.86 e in the planar geometry is greater even than that of 0.67 e predicted from Hückel coefficients. In contrast, the spin densi-

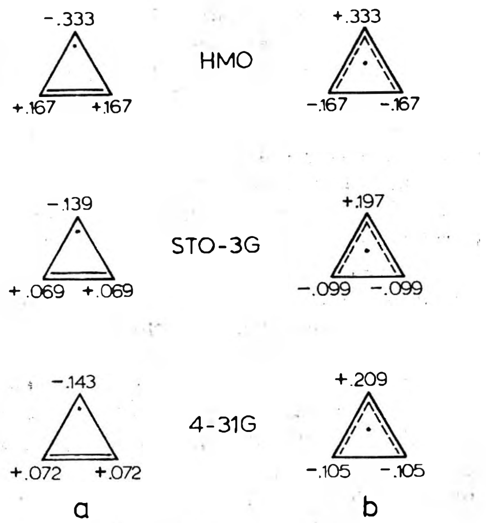

Figure 4. π excess charges (in e) for (a) the planar ethylenic cyclopropenyl radical and (b) and planar allylic cyclopropenyl radical.

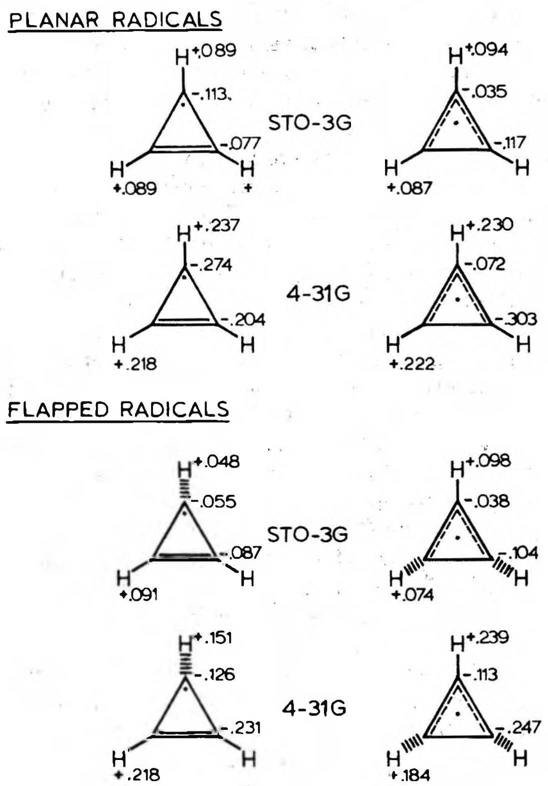

Figure 5. Partial atomic charges (in e) for "ethylenic" and "allylic" cyclopropenyl radicals by STO-3G and 4-31G methods.

Table II
Unpaired Electron Spin Densities (in e) for the Cyclopropenyl Radical

Atom	Orbital[b]	Open shell spin density STO-3G	4-31G
	Flapped Ethylenic Geometry[a]		
H_1	1s	0.030	0.025
H_2, H_3	1s	0.000	0.000
C_1	1s	0.001	0.001
	2s	0.162	0.149
	$2p_x$	0	0
	$2p_y$	0.122	0.124
	$2p_z$	0.557	0.575
C_2, C_3	1s	0.000	0.000
	2s	0.000	0.001
	$2p_x$	0.001	0.002
	$2p_y$	0.009	0.006
	$2p_z$	0.053	0.054
	Flapped Allylic Geometry[c]		
H_1	1s	0	0
H_2, H_3	1s	0.010	0.008
C_1	1s	0	0
	2s	0	0
	$2p_x$	0.008	0.006
	$2p_y$	0	0
	$2p_z$	0	0
C_2, C_3	1s	0.000	0.000
	2s	0.049	0.038
	$2p_x$	0.008	0.015
	$2p_y$	0.022	0.022
	$2p_z$	0.406	0.413

[a] For the planar ethylenic geometry form, the spin densities are nonzero only for the $2p_z$ orbitals: 0.861 (0.862) and 0.069 (0.069) for C_1 and C_2 according to the STO-3G (4-31G) method. [b] In all cases the coordinate system has the C_2–C_3 bond as the x axis and C_1 lies in the xy plane. [c] For the planar allylic geometry, the spin densities are nonzero only for the $2p_z$ orbitals of C_2 and C_3 and are 0.5 each.

ty at C_1 is zero in the allylic form, as expected from the simple wave function. Recently Cirelli and coworkers have reported an esr spectrum of the cyclopropenyl radical and conclude that the system undergoes fast exchange between three equivalent energy structures.[23]

Registry No.—1a, 19469-08-0.

References and Notes

(1) (a) Publication No. 125 of the Photochemistry Unit. (b) Research supported by the National Research Council of Canada.

(2) Calculations by Dewar's method[3] predict that the conjugation stabilizes cyclopropenyl by 21 kcal mol^{-1}, whereas the NNDO method[4] (which is similar to Dewar's procedure but which includes overlap integrals explicitly) predicts the conjugation destabilizes the system by 15 kcal mol^{-1}. The simple Hückel method predicts **1** has a π energy which is one β unit more than for ethylene plus methyl radical, whereas inclusion of overlap can yield a bonding energy which is less than that for ethylene (*vide infra*).

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(9) Approximation (c) is valid to better than 2% for the C=CH angle in cyclopropene according to the structures in ref 10.

(10) L. Radom, W. A. Lathan, W. J. Hehre, and J. A. Pople, *J. Amer. Chem. Soc.*, **93**, 5339 (1971).

(11) According to the heats of formation and group additivity values in ref 12, the strain energy increases by 14 kcal mol^{-1} in going from cyclopropane to methylenecyclopropane, and by a further 12 kcal mol^{-1} in going from the latter to cyclopropene.

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(13) W. A. Lathan, W. J. Hehre, and J. A. Pople, *J. Amer. Chem. Soc.*, **93**, 808 (1971).

(14) The C–C· length in the planar cyclopropyl radical was assumed equal to that optimum for the flapped, namely 1.48 Å.

(15) If the two interacting orbitals are initially of equal energy α and the resonance and overlap integrals between them are β and S, respectively, the resulting levels are given by the well-known expressions $(\alpha + \beta)/(1 + S)$ and $(\alpha - \beta)/(1 - S)$. The resulting stabilizations Δ_1 and Δ_2 then are $(\beta - S\alpha)/(1 + S)$ and $-(\beta - S\alpha)/(1 - S)$, respectively. Obviously the stabilization 2 Δ_1 of the electron pair outweighs the destabilization Δ_2 of the unpaired electron only when the overlap integral S is small; for $S > 0.33$ the interaction is net destabilizing. If the two original orbitals are of unequal energy, the total interaction becomes destabilizing at even smaller values of *S*. See also N. Bodor, M. J. S. Dewar, and Z. B. Maksic, *J. Amer. Chem. Soc.*, **95**, 5245 (1973).

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Radical Additions of Alcohols to Esters of Fumaric and Maleic Acids

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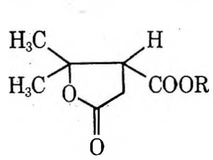
Peroxide-initiated radical additions of alcohols to esters of fumaric and maleic acids are described. By these radical additions γ-alkyl and γ-phenyl paraconic acid derivatives are produced in high yields, especially in the case of esters of maleic acid. The combination of some primary alcohols and diethyl fumarate (DEF) and diethyl maleate (DEM) yields two geometrical isomers with arbitrary isomer ratios, preferentially trans isomers from DEF and cis isomers from DEM. Relative ratios of two different attacks on DEF or DEM show straight lines in the Arrhenius plot and the compensating rule is applied for their activation parameters. A larger effect is observed in the radical additions to DEF. They are interpreted in terms of the steric effect in the transition states for the attacks of alcohol carbon radicals on DEF or DEM.

The α-hydrogen of alcohols is susceptible to abstraction, and the resulting radical is capable of reaction with olefins in a chain process.[1] The peroxide-[2] and photoinitiated[3] radical additions of alcohols to α,β-unsaturated carboxylic acids and their esters have produced a variety of γ-butyrolactone derivatives. Terebinic acid obtained by the photoinitiated addition resulted from the combination of 2-propanol and fumaric or maleic acid.[3] This investigation also provides several γ-substituted paraconic acid derivatives by the peroxide-initiated additions of several alcohols to esters of fumaric and maleic acids.

During the course of these reactions two adjacent asymmetric centers, generated in the addition step, give two geometrical isomers **a** and **b** as shown in Chart I. Accordingly, two isomers are determined by competition between two routes and the ratio of rate constants k_a/k_b may be determined directly by measuring the isomer ratio **a/b.** Then we may expect the systematic change of the various isomer ratios from the different geometries of their transition states, which would probably be caused by combining several alcohols ($R_1 \neq R_2$) with DEF or DEM. On the basis of this consideration, to obtain any information on the behavior of the addition step was the second subject of this investigation.

Results and Discussion

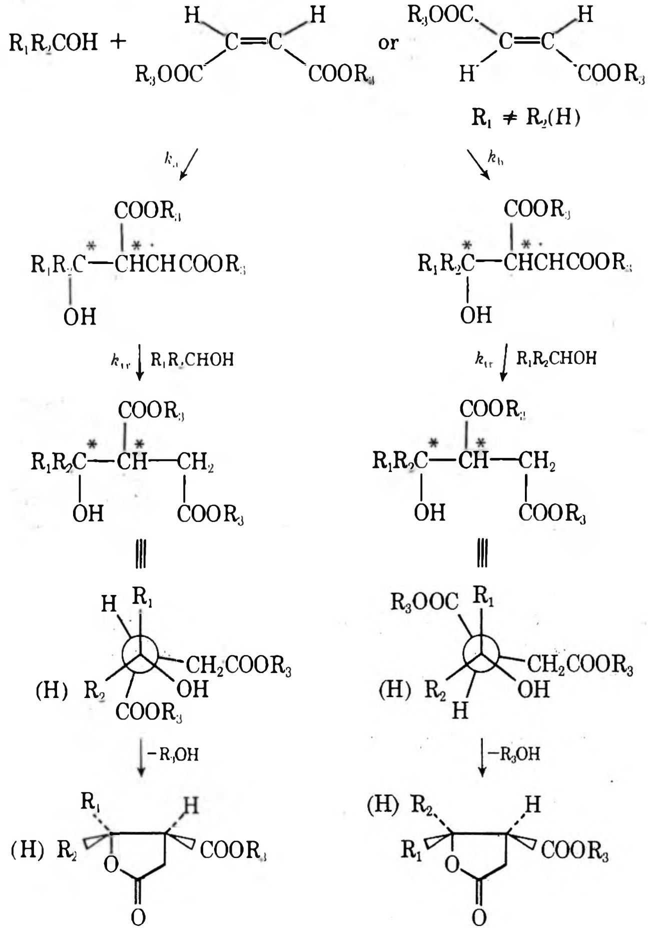
The present reactions were accomplished by heating a reaction mixture in a sealed tube at an arbitrary temperature (70–150°). Upon continued heating a mixture of 2-propanol, maleic anhydride, and di-*tert*-butyl peroxide (DTBP), terebinic acid 1 and its ester 2 were obtained in 21



1, R = H
2, R = $CH(CH_3)_2$

and 34% yields, respectively. In this reaction the 1:1 adduct of alcohol and maleic anhydride was not formed, because maleic anhydride in alcohol is esterified rapidly and quantitatively.[4] Furthermore, the reactions in monoisopropyl maleate, in diisopropyl fumarate, and in diisopropyl maleate yielded 2 in 49, 48, and 75% yields, respectively. In the case of the reaction in monoisopropyl maleate, 1 was also obtained in 37% yield in addition to **2.** It is obvious that **1,** derived from monoisopropyl maleate, is formed by an attack on the carbon adjacent to the carboxylic acid group, while 2 is formed by an attack on the carbon adjacent to the alkoxycarbonyl group.

Chart I
Formation Routes of Two Isomers by Radical Addition to DEM or DEF

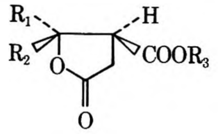


trans **a** cis **b**

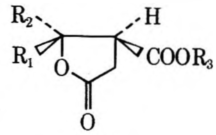
Similarly, reactions in a variety of alcohols and diesters of fumaric and maleic acids gave the various γ-substituted derivatives of paraconic acid. The survey of these products is shown in Tables I and II.

A good yield of a 1:1 adduct should be obtained by highly effective hydrogen abstraction before propagation. As is suggested by Mayo's equation,[5] a low molecular weight polymer or telomer containing a 1:1 adduct should be obtained under conditions of lower monomer concentration. The results for **7a** and **7b** listed in Table I apparently show the tendency expected from Mayo's equation. Generally, the chain transfer constant C ($= k_{tr}/k_p$) increases with temperature because of higher activation energy for trans-

Table I
Products and Yields of γ-Substituted Paraconic Acid Derivatives



a



b

Product[a]	R_1	R_2	R_3	Mole ratio of alcohol to monomer	Temp, °C	Yield, %[b], for monomer used: Fumarate	Maleate
2	CH_3	CH_3	$CH(CH_3)_2$	20	130		75
3	CH_3	CH_3	CH_3	20	130		96
4	H	H	CH_3	20	130		20
5	$(CH_2)_5$		CH_3	20	130		50
6a,b	CH_2CH_3	CH_3	CH_3	20	130		64
7a,b	CH_3	H	CH_2CH_3	20	150	34	83
				20	130	27	73
				20	70	6	20
				5	130	12	46
				40	130	28	86
8a,b	CH_2CH_3	H	CH_2CH_3	20	150	31	52
				20	130	24	49
9a,b	$CH_2CH_2CH_3$	H	CH_2CH_3	20	130		35
10a,b	$C(CH_3)_3$	H	CH_2CH_3	20	130		30
11a,b	C_6H_5	H	CH_2CH_3	20	130		50

[a] Satisfactory elemental analyses for C, H (±0.35%) were obtained. [b] Yields were calculated, based on monomer employed and given as the sum of two isomers for the compounds 6–11 ([monomer]/[alcohol] = 0.05 mole ratio).

Table II
Indices of Refraction and Ir and Nmr Spectra

Product	Nmr, δ: R_1	R_2	R_3	α-CH_2 and β-CH	n^{20}_D	Ir, $\nu_{C=O}$, cm^{-1}	
2[a]	1.56 (s)	1.28 (s)	4.8–5.2 (m), 1.27 (d)	2.4–3.4 (m)	1.4500	1735	1785
3[a]	1.61 (s)	1.31 (s)	3.68 (s)	2.4–3.4 (m)	1.4502	1746	1785
4[a]	4.39 (d)	4.31 (d)	3.69 (s)	2.4–3.6 (m)	1.4618	1745	1792
5[a]	1.0–1.9 (m)		3.72 (s)	2.4–3.4 (m)	c	1748	1787
6a[b]	1.83 (q), 0.97 (t)	1.20 (s)	3.69 (s)	2.4–3.4 (m)		1748	1794
6b[b]	1.49 (q), 0.72 (t)	1.48 (s)	3.69 (s)	2.4–3.4 (m)			
7a	1.49 (d)	4.65 (m)	4.17 (q), 1.27 (t)	2.5–3.2 (m)	1.4443	1744	1793
7b	1.27 (d)	4.85 (m)	4.21 (q), 1.28 (t)	2.4–3.6 (m)	1.4462	1743	1794
8a	1.81 (m), 1.05 (t)	4.50 (m)	4.24 (q), 1.30 (t)	2.5–3.3 (m)	1.4539	1725	1780
8b	1.50 (m), 1.07 (t)	4.57 (m)	4.27 (q), 1.32 (t)	2.4–3.6 (m)	1.4547	1734	1792
9a	1.5–1.9 (m), 0.98 (t)	4.0–4.7 (m)	4.18 (q), 1.28 (t)	2.4–3.2 (m)	1.4480	1740	1780
9b	1.1–1.9 (m), 0.98 (t)	4.2–4.8 (m)	4.19 (q), 1.30 (t)	2.4–3.6 (m)	1.4514	1740	1780
10a	0.99 (s)	4.11 (d)	4.24 (q), 1.27 (t)	2.4–3.3 (m)	1.4498	1739	1786
10b	1.00 (s)	4.18 (d)	4.17 (q), 1.30 (t)	2.4–3.4 (m)	1.4568	1738	1791
11a[b]	7.33 (s)	5.52 (d)	4.16 (q), 1.21 (t)	2.2–2.9 (m)		1725	1770
11b[b]	7.26 (s)	5.65 (d)	3.63 (q), 0.77 (t)	2.6–3.8 (m)			

[a] R_1 and R_2 groups of 2, 3, 4, and 5 are situated in the trans and cis positions to the alkoxycarbonyl group, respectively, *i.e.*, in the configuration of **a**. [b] Separation of two isomers was unsuccessful. [c] Mp 67–69°.

fer reaction than for propagation. Furthermore, the chain transfer constant for DEM becomes inevitably larger, compared with that for DEF, because the rate of propagation of DEM is considerably smaller. Reactions of DEM at higher temperatures may therefore give lactones in higher yields.

Reactions of DEF and DEM with some primary alcohols (except methanol) produced the respective sets of two geometrical isomers (**7a** and **7b**; **11a** and **11b**) with arbitrary ratios as evidenced by elemental analyses and nmr and ir spectra.

Evidence for the configurational assignment of two isomers was obtained by the comparison of nmr spectra between γ-substituted paraconic acid derivative(s) and the corresponding itaconic acid derivative(s),[6] which is derived by the treatment of γ-substituted paraconic acid derivative(s) with potassium *tert*-butoxide.[7] It was concluded in our earlier results that the resonance of the cis methyl protons (1.53 and 1.31 ppm) to the carboxyl group of **1** and to the alkoxycarbonyl group of **3** is shifted to a higher field than that of the trans methyl protons (1.73 and 1.61 ppm) as identified from the results of nmr spectra for terebinic acid **1** and its ester **3** reported by Savostianoff, *et al.*[8] Similar results for the assignment of **7a** and **7b** were also obtained between any signals for a cis hydrogen atom (4.65 ppm) and cis methyl protons (1.27 ppm) to the alkoxycarbonyl group and those for the corresponding trans protons (4.85 and 1.49 ppm). Also, in the case of γ-phenyl paraconic

Table III
Isomer Ratios and Activation Parameters for the Additions to DEF and DEM

Product	Isomer ratios a/b(k_a/k_b)[a] at temp, °C 150	130	110	70	Activation parameters $\Delta H_a^* - \Delta H_b^*$, kcal/mol	$\Delta S_a^* - \Delta S_b^*$, cal/deg
			DEF			
7a,b	1.16	1.23	1.21	1.30	−0.6	−1.1
8a,b	1.13	1.26	1.40	1.59	−1.3	−2.7
9a,b	1.52	1.96	2.68	4.24	−3.8	−8.1
10a,b	1.43	1.93	2.74	6.30	−5.6	−12.4
11a,b	1.32	1.77	1.98	2.89	−2.8	−6.1
			DEM			
7a,b	0.92	0.84	0.80	0.74	0.9	2.0
8a,b	0.91	0.88	0.82	0.79	0.5	1.3
9a,b	0.87	0.83	0.75	0.72	0.9	1.9
10a,b	(0.85)[b]	(1.12)	(1.59)	(2.04)		
11a,b	(1.16)[b]	(1.67)				

[a] The k_a/k_b ratios were determined by extrapolating the isomer ratios to infinite dilution. [b] The reversible addition to DEM ([DEM]/[alcohol] = 0.05 mole ratio) is designated in parentheses.

acid esters (**11a,b**), cis alkoxy protons (3.63 and 0.77 ppm) to the phenyl group resonate upfield, compared with trans alkoxy protons (4.16 and 1.21 ppm). In conclusion, the results presented in Table II show that the resonances of cis methyl protons, a cis hydrogen atom, and even cis phenyl protons are shifted to the higher field by 0.3–0.2, 0.2–0.1, and 0.07 ppm, respectively, when they are in the cis position to the alkoxycarbonyl group. Also cis alkoxy protons to the phenyl group resonate upfield by *ca.* 0.5 ppm. These upfield shifts can be attributed to the diamagnetic anisotropy and the long-range shielding effects in the carbonyl and phenyl groups.

Further evidence for the isomer assignment was indirectly obtained by predicting the predominant isomer **7b** or **11b** on the basis of Cram's rule[9] from the reaction of the ethyl ester of acetylsuccinic acid or benzoylsuccinic acid with sodium borohydride. This selective reduction, in which a new asymmetric center is created on a carbon adjacent to the asymmetric center already present in a molecule, gave two isomers **7a** and **7b** or **11a** and **11b**. Cram's model predicts that the threo isomer should predominate over the erythro isomer because of the order of decreasing effective size of three groups on the adjacent carbon to the carbonyl group: COOR > CH_3 = CH_2COOR[10] > H. The spectral data for **7a** and **7b** or **11a** and **11b** obtained by this reduction were completely identical with those for the corresponding products in Table II.

Consequently, the faster eluting component (Apiezon Grease L) of two isomers is confirmed to be a trans isomer, *i.e.*, the **a** type, and its refractive index shows a slightly smaller value.

The two geometrical isomers formed in the addition of the alcohol carbon radicals in the presence of DEF or DEM are governed by the competing reactions. Accepting the premise that the rate-determining step of this process is the addition step, the isomer ratio should give the ratio of the rate constants, k_a/k_b, directly. Although it has been said that the reversible radical addition of the carbon radical species under usual experimental conditions does not occur,[11] the cis–trans isomerization of DEM in the cases of neopentanol and phenylmethanol was observed to occur frequently. However, such a reversible reaction of DEM in each solution of ethanol, 1-propanol, and 1-butanol was negligibly small, as well as that of DEF in any alcohol solution. All of our data in some five alcohols and the two monomers DEF and DEM are shown in Table III. *A trans isomer* **a** *from DEF and a cis isomer* **b** *from DEM are predominantly produced, respectively, and furthermore, the isomer ratios from both monomers become closer to unity with an increase in temperature.*

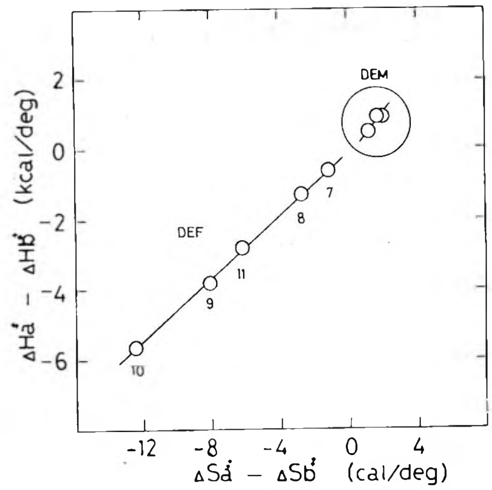


Figure 1. Isokinetic relationship in the effect of alcohols (RCH_2OH) on a/b ratios in the radical additions of alcohols to DEF and DEM. R: 7, CH_3; 8, CH_3CH_2; 9, $CH_3CH_2CH_2$; 10, $(CH_3)_3C$; 11, C_6H_5.

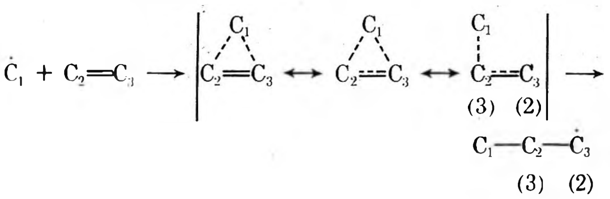
From the transition state theory, we express the rate constant in terms of the corresponding free energy of activation. As all the required data are given as the ratios of rate constants, this expression is given as the difference of the corresponding energies. From the isomer ratios, the activation parameters may be calculated in the usual manner by plotting log k_a/k_b *vs.* $1/T$. The results for the differences in the enthalpy and entropy of activation are given on the right side of Table III. The interchange of DEF and DEM is effective in reversing reactivity and, also, a variety of alcohols are efficient in altering reactivity, especially in the reactions of DEF.

Such an effect caused by a change in alcohol resembles seemingly very closely the solvent effects in many radical reactions. Changes in the reaction rates caused by solvents have been discussed as the effects of solvents on the transition states involved and the compensating law applies to the changes in enthalpy and entropy of activation.[12] This research provides also an example of such a compensating trend as can be seen from Table III or by examination of the isokinetic plot (Figure 1), introduced by Leffer.[13] This excellent linear relationship in a negative region suggests a certain steric influence of a substituent in alcohol in the order of methyl, ethyl, phenyl, propyl, and *tert*-butyl. This is about the order expected on the basis of the steric effect, which appears to be that of increasing effective size of the substituent.[14] The small clump of encircled points includes the reactions of DEM in ethanol, 1-propanol, and 1-butanol, implying an undiscernible dependence of such an effect on the substituent.

The two different types of the effect permit us to conclude that both additions to DEF and DEM proceed through the respective different transition states and give trans and cis isomers with arbitrary ratios. The difference in the reactivity between DEF and DEM means that the transition state is rigid in respect to the central C–C bond. The contribution of a considerable resonance energy to the transition state is reflected in the higher reactivity of DEF, which is approximately planar, and manifested by the lower activation energy of the addition reaction to DEF.[15]

Since the transition state is rigid and no internal rotation takes place along the C–C bond, the configuration of the transition state should resemble somewhat that of the starting material, especially in the case of DEF.[15,16]

Next we turn our attention to an important problem, namely, how to account for the dependence of the isomer ratios on monomers used. Since the radical addition reactions are of the three-center type, *via* the transition states such as shown in eq 1,[17] where C_1 and $C_2{=}C_3$ are R$\dot{C}$HOH



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and DEF or DEM, respectively, we can speculate on selectivity in the formation of trans and cis isomers from the tentative models of the transition states.

An attack of C-1 on C-2 of DEM leads to a trans isomer and the other attack of C-1 on C-3 gives a cis isomer, as expected from the geometry of transition state models (see Chart II). Since the bridging model of the C=C double bond presents exactly a common geometry to the formation of trans and cis isomers, the effect of a substituent R on both routes does not appear. However, when the energy localized on the C=C double bond migrates onto the C—C single bond (quasi-single C_1—C_2 and C_1—C_3 bonds), the difference in the potential energies between two routes first develops. As it can be assumed that models of these two states resemble approximately the final states (C_1—C_2—$\dot{C}_3$ and C_1—C_3—$\dot{C}_2$ radicals), the radical species leading to a

Chart II

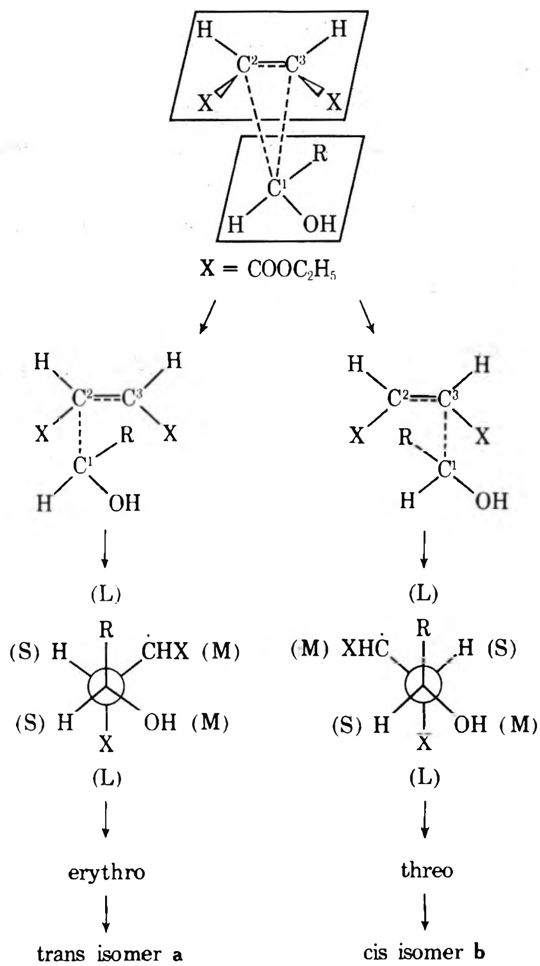
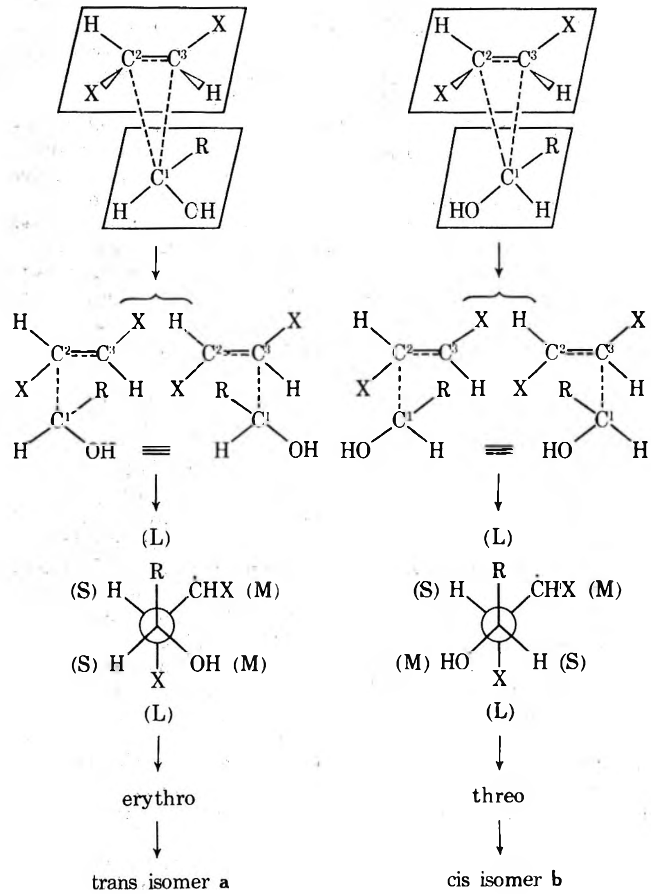


Chart III



threo isomer proves to be more stable, judged from the effective size of substituents around two carbons (C_1—C_2 and C_1—C_3) in Newman's projection diagram of the resulting radicals. This means that the addition reaction with alcohol and DEM demonstrates the predominance of a cis isomer **b**.

On the other hand, in the case of DEF, models of the respective transition states between two routes are geometrically different from each other (see Chart III). A bridging model gives a trans isomer by an attack of C-1 on either C-2 or C-3, and also a cis isomer is obtained by a similar attack on another bridging model. From the steric grounds between both models the former is apparently more operative, because nonbonded repulsion between the attacking radical and DEF is more significant in the latter model, while the model having a quasi-single bond (C_1---C_2=C_3 and C_1---C_3=C_2) is operative for the cis isomer in a case similar to DEM. However, since the transition state of the addition to DEF resembles the structure of the starting material very closely, the state of the bridging model may be considered to function more largely. The conclusion is, therefore, obvious: the trans isomer is obtained by the addition to DEF in preference to the cis isomer.

Experimental Section

All alcohols, dimethyl maleate, DEM, DEF, and di-*tert*-butyl peroxide (DTBP), are of commercial origin and these reagents were purified by fractional distillation. Maleic anhydride and benzoyl peroxide (BPO) were recrystallized from benzene and carbon tetrachloride, respectively. Diisopropyl maleate was prepared from maleic anhydride and 2-propanol and diisopropyl fumarate was formed from the inversion of the maleate.[18]

Nmr spectra were obtained on a Japan Electron Optics Laboratory 4H 100 spectrometer and taken in a CCl_4 solution. Chemical shifts are reported as δ (parts per million) relative to tetramethylsilane as standard. According to our requirements, the spin decoupling procedure was used. Infrared spectra were obtained with a Japan Spectroscopic Co. DS-402G spectrometer and taken in a CCl_4 solution. Glc analyses were performed with a Yanagimoto MFG Co. GCG-550T gas chromatograph with a 3 mm × 2.5 m 10% Apiezon GL column on 60–80 mesh Neopack 1A.

Reactions of 2-Propanol with Maleic Anhydride and Its Esters. A solution of 2-propanol (120.2 g, 2.00 mol), maleic anhydride (9.81 g, 0.10 mol), and DTBP (1.46 g, 0.01 mol) was sealed under nitrogen in a glass tube and heated for 10 hr at 130°. Unreacted 2-propanol was evaporated. The residue was gas chromatographed and yields of terebinic acid **1** and its isopropyl ester **2** were determined to be 21 and 34%, respectively. On standing or cooling **1** was isolated from the residue: mp 172–173° (lit.[3] 174–175°); ir (KBr) 1740; nmr (CCl_4) 1.73 (s, CH_3), 1.53 (s, CH_3) (lit.[8] 1.75 and 1.56, respectively), 2.8–3.9 (m, α-CH_2 and β-CH). *Anal.* Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.98; H, 6.37.

Also the preparative glpc or the vacuum distillation of the residue gave **2**, bp 115–116° (5 mm). Physical data for **2** are shown in Table II.

A similar procedure for the reaction of 2-propanol with monoisopropyl maleate (half ester) yielded **1** and **2** in 37 and 49% yields, respectively. Also, the similar reactions of diisopropyl maleate and diisopropyl fumarate gave **2** in 75 and 48% yields, respectively.

Reactions of Alcohols with Esters of Fumaric and Maleic Acids. A solution of DTBP or BPO (10 mol % of monomer used), the diester of fumaric or maleic acid (0.05–0.40 equiv), and each of several alcohols (2.0 equiv) was packed into a glass tube under nitrogen and heated at an arbitrary temperature for 5 (DTBP, 130 and 150°) or 10 (DTBP, 110°, and BPO 70°) hr. After evaporation of unreacted materials, the residue was gas chromatographed to determine the yields and the isomer ratio, and thereafter distilled *in vacuo*. Subsequently, two geometrical isomers were separated by preparative glpc. The faster eluting component of isomers was assigned as an **a** type lactone (trans isomer), as a result of this work. The isomer ratios of **6a** and **6b** and **11a** and **11b** were determined by the intensity ratios on nmr spectra because of the unsuccessful separation by means of glpc. Experimental results and physical and spectral data for the products are summarized in Tables I, II, and III.

Reaction of Diethyl Ester of Acetylsuccinic Acid[19] with Sodium Borohydride. A cold aqueous solution (4 ml) of sodium borohydride (0.95 g, 0.025 mol) was added dropwise while stirring a cold solution of the ethyl ester (10.8 g, 0.05 mol) dissolved in alcohol (35 ml). The mixture was stirred for 1 hour at room temperature, hydrolyzed with aqueous ammonia, and then extracted with ether. The ether solution was washed with diluted hydrochloric acid and with a saturated sodium chloride solution, then dried with sodium sulfate, and finally evaporated. Glpc analysis of the crude product mixture yielded two compounds and the ratio of the faster eluting component to the second was calculated to be 1:4.3. Glpc and nmr analyses of the respective components showed identical results with those of **7a** and **7b**: nmr (CCl_4) for the faster eluting component 1.47 (d, γ-CH_3), 4.57 (m, γ-H), 2.5–3.2 (m, α-CH_2 and β-CH), 4.17 (q, $COOCH_2CH_3$), 1.27 (t, $COOCH_2CH_3$), $J_{\beta,\gamma\text{-H}}$ = 5.6 Hz; for the second component 1.27 (d, γ-CH_3), 4.79 (m, γ-H), 2.4–3.6 (m, α-CH_2 and β-CH), 4.21 (q, $COOCH_2CH_3$), 1.28 (t, $COOCH_2CH_3$), $J_{\beta,\gamma\text{-H}}$ = 7.0 Hz.

Reaction of Diethyl Ester of Benzoylsuccinic Acid[20] with Sodium Borohydride. The ester was reduced in a manner similar to that described above. Nmr analysis of the crude product mixture yielded two products **11a** and **11b** with a ratio of 1:2.5: nmr (CCl_4) for **11a** 7.28 (s, 5 aromatic H), 5.49 (d, γ-CH), 2.2–2.9 (m, α-CH_2 and β-CH), 4.14 (q, $COOCH_2CH_3$), 1.21 (t, $COOCH_2CH_3$), $J_{\beta,\gamma\text{-H}}$ = 7.4 Hz; for **11b** 7.21 (s, 5 aromatic H), 5.61 (d, γ-H), 2.6–3.8 (m, α-CH_2 and β-CH), 3.61 (q, $COOCH_2CH_3$), 0.77 (t, $COOCH_2CH_3$), $J_{\beta,\gamma\text{-H}}$ = 7.5 Hz.

Registry No.—**1**, 79-91-4; **2**, 34341-66-7; **3**, 6934-77-6; **4**, 5204-91-1; **5**, 18363-04-7; **6a**, 53684-24-5; **6b**, 53684-25-6; **7a**, 34310-48-0; **7b**, 34310-47-9; **8a**, 34310-49-1; **8b**, 34310-50-4; **9a**, 53684-26-7; **9b**, 53684-27-8; **10a**, 53684-28-9; **10b**, 53684-29-0; **11a**, 53684-30-3; **11b**, 53684-31-4; DEF, 623-91-6; DEM, 141-05-9; 2-propanol, 67-63-0; methanol, 67-56-1; ethanol, 64-17-5; maleic anhydride, 108-31-6; monoisopropyl maleate, 924-83-4; diisopropyl maleate, 10099-70-4; diisopropyl fumarate, 7283-70-7; diethyl acetylsuccinate, 1115-30-6; sodium borohydride, 16940-66-2; diethyl benzoylsuccinate, 10539-50-1.

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The Triple Bond as a Potential Double Donor in Solvolytic Participation

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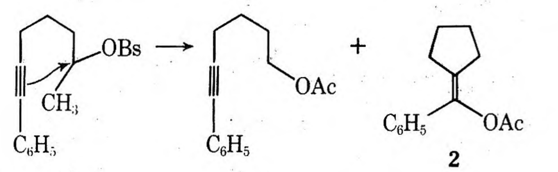
The acetylenic functionality in 6-dodecyne-2,11-diyl ditosylate (4) is potentially capable of providing stepwise assistance in the ionization of two leaving groups to form doubly ring-closed products. The ditosylate solvolyzes in acetic and trifluoroacetic acids with participation by the triple bond to form cyclized products (>85%). The nearly identical and entirely monocyclic product distributions in both solvents demonstrate that the triple bond in 4 provides only one site of unsaturation capable of nucleophilic π participation.

Participation of a remote triple bond in the departure of the leaving group in solvolysis reactions has been established by the observation of substantial amounts of cyclized material. Thus 6-phenyl-5-hexyn-1-yl brosylate (1) acetolyzes to form 64% noncyclized and 36% cyclized (2) material (eq 1).[2] Similarly, 6-octyn-2-yl tosylate (3) produces 82% cyclized material on formolysis and 100% on trifluoroacetolysis.[3] Less cyclization is observed in formic acid



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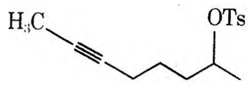

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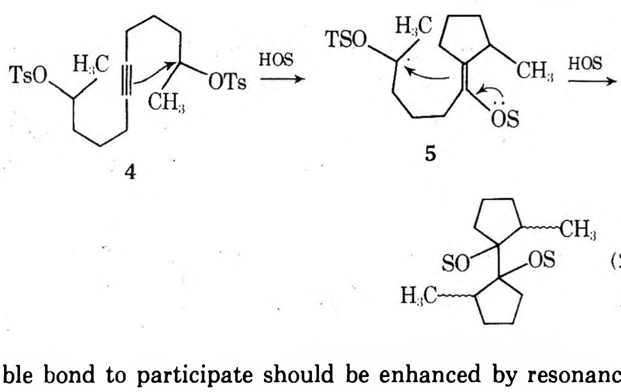
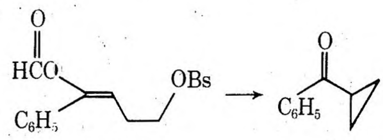
because this more nucleophilic and less ionizing solvent is better able to compete with the triple bond in nucleophilic attack. Rate enhancements are not generally observed with cyclization because of the inductive effect of the triple bond that arises from the dipole of the bond between the sp and sp^3 carbon atoms.

The double bond in the cyclized enol ester, *e.g.*, **2**, can conceivably provide assistance to the departure of a second leaving group in an appropriately constructed molecule. In an acetylenic molecule containing two available leaving groups, the triple bond could thus effectively serve as a double π donor. 6-Dodecyne-2,11-diyl ditosylate (4) contains the requisite structural features for double cyclization. The product of the first cyclization, an enol ester tosylate (5), serves as the substrate for the second cyclization, in which the enolic double bond assists in the ionization of the remaining tosylate group (eq 2). The ability of the dou-



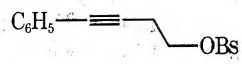
4 5 (2)

ble bond to participate should be enhanced by resonance electron donation from the ester substituent. Cyclization of the enol formate 6 to give 7 has in fact been found to occur



6 7

more rapidly than reaction of the corresponding acetylenic brosylate (8).[4] Depending on whether cyclization of 4 favors five- or six-membered rings, the end products could be



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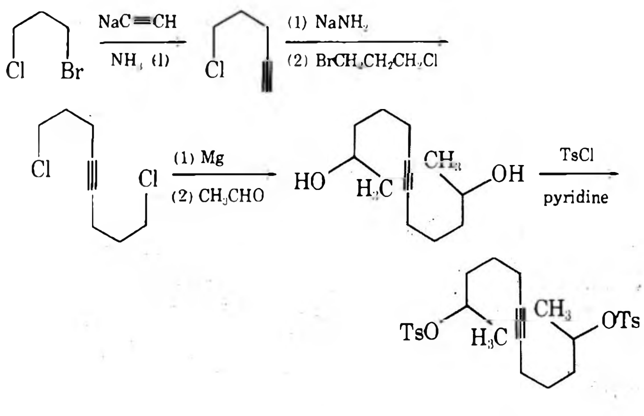
vors five- or six-membered rings, the end products could be bicyclopentanes (eq 2), spiro[4.5]decanes, or decalins.[5] We have therefore prepared 6-dodecyne-2,11-diyl ditosylate (4) in order to test the triple bond as a potential double π donor in solvolytic reactions.

Results

6-Dodecyne-2,11-diyl ditosylate (4) was synthesized by the procedure outlined in Scheme I.[6] Condensation of 2

Scheme I



mol of 1-bromo-3-chloropropane with acetylene in two steps afforded 1,8-dichloro-4-octyne. Fairly dilute concentrations of base (<0.25 *M*) were necessary to avoid elimination. For the same reason, a one-step condensation with disodium acetylide proved impossible. Reaction of the di-Grignard reagent of the dichloride resulted in a complex mixture of products. 6-Dodecyne-2,11-diol was isolated in low yield by distillation, purified by column chromatography, and converted to the ditosylate.

Titrimetric rate constants were obtained at two temperatures for the formolysis of the ditosylate 4 in the presence of 2.2 equiv of sodium formate. Rates were determined by titration of aliquots withdrawn sequentially from the solvolytic mixture. Because the rate constant was observed to drop off with time (30–50% after 2–3 half-lives), the figures

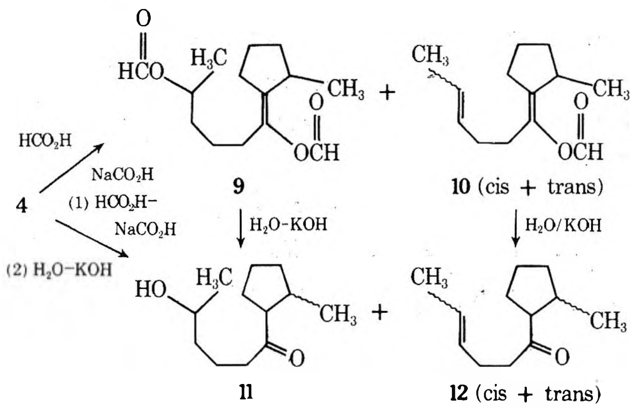
Table I
Rate Constants for the Formolysis of 6-Dodecyne-2,11-diyl Ditosylate (4)

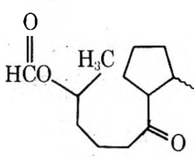
Temp, °C	$k \times 10^5$, sec^{-1}	Temp, °C	$k \times 10^5$, sec^{-1}
25.0	5.3	40.0	33
25.0	5.5	40.0	35

given in Table I result from extrapolation to zero time. This behavior is symptomatic of formation of a more slowly reacting intermediate, such as **5**. Similar observations were obtained previously in a solvolytic study of another ditosylate, *exo-cis*-2,3-norbornyl ditosylate.[7] Solvolysis of **4** for 1 half-life and column chromatography of the product mixture yielded a formate tosylate with spectral properties consonant with **5**, as well as unreacted ditosylate and formate products identical to those formed after 5 half-lives (*vide infra*). Formolysis followed by hydrolysis of the intermediate formate tosylate produced the same "final" materials found after 5 half-lives. Calculations from the data in Table I gave $\Delta H^{\ddagger} = 22.2$ kcal/mol and $\Delta S = -3.5$ gibbs.

The ditosylate was solvolyzed for 5 half-lives at 40° and quenched for product studies by dilution with ether. After removal of the formic acid by extraction with bicarbonate, two major products were isolated by preparative vapor phase chromatography. The products were assigned the structures **9** (73%) and **10** (12%) (Scheme II) on the basis of their nmr, ir, and mass spectra (Experimental Section).[8,9] The monocyclic nature of the products was confirmed by examination of the products on saponification of the crude ether extracts. The two major products under these conditions were found to be an hydroxy ketone (**11**, 69%) and an unsaturated ketone (**12**, 12%) (Scheme II).[5,8,9] Pure samples of **9** and **10** gave **11** and **12**, respectively, on independent saponification. Partial hydrolysis of the ether-soluble formolysis products resulted in the isolation of a material whose spectra were consistent with the structure **13**, the half-hydrolyzed ester ketone.[5] The retention time of uncyclized material corresponding in structure to the starting material fell in the midst of several very small, unidentifiable product peaks.[9] An upper limit of 3% can be placed on the double-k_s product.

Scheme II



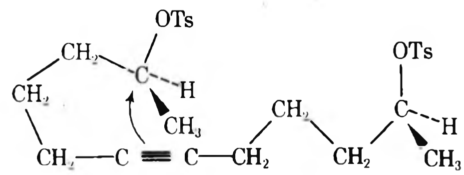


13

The ditosylate **4** was also solvolyzed for 5 half-lives at 25° in trifluoroacetic acid containing 1% by weight trifluoroacetic anhydride and 2.2 equiv of sodium trifluoroacetate. The two major ether-soluble products were found to be the trifluoroacetates corresponding to **9** (75%) and **10** (14%).[5,8,9] Hydrolysis of these materials or trifluoroacetolysis followed directly by hydrolysis of the crude mixture resulted in materials identical to those obtained in the formolysis, **11** (73%) and **12** (11%).[5,8,9] Thus the products of formolysis and trifluoroacetolysis of the ditosylate **4** are essentially identical. Moreover, neither solvent induces the triple bond to participate in the ionization of both leaving groups to form doubly cyclized products.

Discussion

More than 80% of the products of formolysis of 6-dodecyne-2,11-diyl ditosylate (**4**) derive from a single ring closure (**9, 10**). This result is comparable to that of 6-octyn-2-yl tosylate (**3**), which forms 82% cyclized materials on formolysis.[3] Little or no completely uncyclized 6-dodecyl-2,11-diyl diformate was observed. The rate of formolysis of **4** at 25° (5.4×10^{-5} sec^{-1}) is similar to those for 6-octyn-2-yl tosylate (9.85×10^{-5}) and 6-heptyn-2-yl tosylate (2.66×10^{-5}).[3] Thus triple-bond participation competes quite favorably with solvent displacement during the loss of the first leaving group. One can therefore conclude that the first stage of cyclization, from ditosylate **4** to formate tosylate **5** (eq 2), occurs readily. The reactive conformation (**14**)



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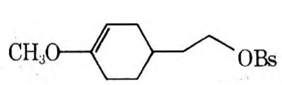
is devoid of nonbonded interactions between chains, and there are no methyl–methyl interactions. The *dl* and meso diastereomeric modifications[6] should have nearly identical reactivities in this step. Moreover, the chain length is quite favorable for five-membered ring formation, but not sufficient for facile six-membered ring formation.[5]

Because trifluoroacetolysis was observed to increase the amount of cyclization in **3** from 82 to 100%, it was expected that this solvent would have a similar influence on the alkynic ditosylate **4**. It was observed, however, that the decrease in solvent nucleophilicity provided by trifluoroacetic acid brought about no further cyclization. The second stage of the reaction in both formic and trifluoroacetic acids therefore is a simple k_s substitution–elimination process that leads to the observed monocyclic products **9** and **10**. The failure to observe doubly cyclized material must result from the inability of the enol ester double bond in **5** to compete with solvent in nucleophilic displacement, even when the solvent nucleophilicity is quite low. Thus k_Δ (triple bond) > k_s > k_Δ (enol ester) for this system.

This result is surprising because substitution of an acyloxy or an alkoxy group on a double bond, as in **5**, is known to increase its nucleophilic properties by electron donation through resonance. Thus the enol formate **6** ionizes an order of magnitude more rapidly than the acetylenic analog **8**,[4] and the enol ether **15** reacts a 100 times more rapidly than the alkenic substrate **16**.[10] The failure to observe increased cyclization in trifluoroacetic acid can be explained



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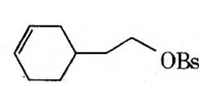

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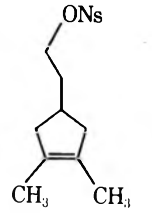
as a counterbalancing of two effects. The decrease in solvent nucleophilicity is offset by a decrease in the nucleophilicity of the double bond in **5** as the result of changing from OCHO to $OCOCF_3$. The electron-withdrawing nature of the trifluoromethyl group reduces resonance electron donation to the enol trifluoroacetate double bond. What special properties of the enol formate then are responsible for the apparently reduced nucleophilic properties of its double bond? Although the double bond in **5** is both tetrasubstituted and exocyclic, neither of these characteristics should inhibit participation in light of previous observations on **17** and **18**.[11,12] The nucleophilic properties of a



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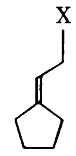

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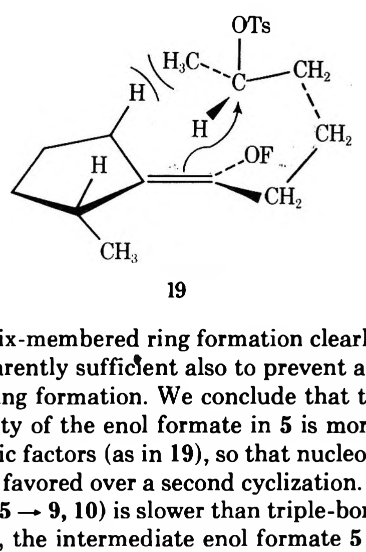
double or triple bond are maximized when the π electrons are symmetrically disposed and backside to the leaving group. The flexibility of the two chains in the ditosylate **4** apparently permits a very effective orientation between the triple bond and the leaving group (**14**). Once the first ring is formed, however, specific steric interactions between the ring and the remaining side-chain atoms in **5**, particularly those of the methyl group, must be sufficient to prevent the critical orientation of orbitals necessary for solvolytic participation and a second cyclization (**19**). Although methyl–methyl interactions can be avoided in the reactive conformation of either diastereomer[6] by placement of the methyl groups on opposite faces of the ring, there are severe interactions between the methyl group on the extended chain and the cis-2 or -5 proton on the ring (**19**). These interac-



19

tions make six-membered ring formation clearly impossible and are apparently sufficient also to prevent a second five-membered ring formation. We conclude that the increased nucleophilicity of the enol formate in **5** is more than overcome by steric factors (as in **19**), so that nucleophilic attack by solvent is favored over a second cyclization. Because solvent attack (**5** → **9, 10**) is slower than triple-bond participation (**4** → **5**), the intermediate enol formate **5** builds up in concentration and depresses the overall rate of *p*-toluenesulfonic acid formation.

Experimental Section

Nmr spectra were taken on Varian Associates Model T-60 and A-60 spectrometers. Infrared spectra were recorded on a Beckman IR-5 spectrophotometer. Mass spectra were obtained by Dr. Leo Raphaelian of the Department of Chemistry's Analytical Services Laboratory on a Consolidated Electrodynamics Corporation Model 21-104 instrument. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Analytical vapor phase chromatography was performed on a Varian Aerograph series 1520B instrument utilizing 10% silicone gum rubber (SE-30) or 10% Carbowax 20M on Chromosorb W in ⅛-in. × 6-ft copper columns. Preparative vapor phase chromatography was performed on a Hewlett-Packard (F & M) Model 700 instrument utilizing 0.25-in. columns of the same materials and length. Kinetic measurements were made with a Haake Model NB-22 constant temperature bath and a Metrohm Herisau type E-415 automatic titrator.

5-Chloro-1-pentyne.[13,14] Sodium acetylide was prepared by bubbling acetylene through 2 l. of liquid NH_3 and slowly adding 24.75 g (1.1 mol) of sodium metal. The acetylene was passed initially through a cold (−78°) trap and bubbled through concentrated H_2SO_4. Safety traps and a mercury bubbler escape valve were included. The acetylene flow was continued for 15 min after addition of sodium was completed. 1-Bromo-3-chloropropane (157.5 g, 1.0 mol) was then added, and the solution was stirred for 2 hr. Ammonium hydroxide (100 ml) and water (100 ml) were added, and the NH_3 was allowed to evaporate overnight. The product, which separated as the top layer, was taken up in ether. The above procedure was performed three times. The combined organic layers were washed with dilute HCl, water, and brine, and dried over $CaSO_4$. The product was isolated by distillation and purified by a second distillation: 189 g (63%): bp 115–119°; nmr (neat) δ 1.7 (m, 3), 2.0 (m, 2), 3.3 (t, 2).

1,8-Dichloro-4-octyne.[13,14] Sodium amide was prepared by adding 25 g (1.1 mol) of sodium metal to 2 l. of liquid ammonia containing 1 g of ferric nitrate. The solution was stirred until the dark blue color was replaced by gray (1–3 hr). 5-Chloro-1-pentyne (95 g, 0.95 mol) was added over a period of about 30 min, followed by 157 g (1.0 mol) of 1-bromo-3-chloropropane. The solution was stirred for 2 hr, 150 ml of anhydrous ether and a solution of 25 ml absolute ethanol in 50 ml anhydrous ether were added, and the NH_3 was allowed to evaporate overnight. Another 95 g of 5-chloro-1-pentyne was treated in a similar manner. The combined reaction mixtures were filtered, and the organic layer was washed with dilute HCl, water, and brine, and dried over anhydrous $MgSO_4$. The product was isolated by distillation and purified by a second distillation: 96 g (25%); bp 67–68° (0.1 mm); nmr (neat) δ 1.7 (m, 4), 2.0 (m, 4), 3.3 (t, 4).

6-Dodecyne-2,11-diol. Magnesium metal (25 g, 1.1 mol) and a crystal of iodine were placed in a 3-l., three-necked, round-bottomed flask and stirred under nitrogen overnight. 1,8-Dichloro-4-octyne (89.5 g, 0.5 mol), dissolved in 2 l. of ether (freshly distilled from lithium aluminum hydride), was added over 6 hr. Stirring was continued for 4 days. Freshly distilled acetaldehyde (85 ml, 1.5 mol) was dissolved in cold ether and added slowly at 0°. Stirring was continued for 2 hr. Water was added dropwise until the solids coagulated. The ether was decanted, the solids were washed with ether, and the ethereal solutions were dried over anhydrous $MgSO_4$. The product was isolated by distillation (140–65°, 0.5 mm), purified by column chromatography (15 g of crude diol applied to a column consisting of 2 lb of alumina in 25% ether–hexane). Pure diol (10 g) was isolated by slowly increasing the ether concentration), and redistilled: 8 g (16%); bp 130–132° (0.3 mm); nmr ($CHCl_3$) δ 0.8 (d, 6), 1.1 (m, 8), 1.7 (m, 4), 3.3 (m, 2), 4.1 (s, 2). *Anal.* Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18; O, 16.14. Found: C, 72.66; H, 11.09.

6-Dodecyne-2,11-diyl Ditosylate (4). 6-Dodecyne-2,11-diol (2 g, 0.01 mol) was dissolved in 15 ml of cold pyridine (distilled from BaO). *p*-Toluenesulfonyl chloride (4.3 g, 0.022 mol) was added, and the mixture was kept in the freezer (−15°) for 3 days. The reaction mixture was poured onto 50 ml of ice and water. The resulting milky emulsion was washed with ether, and the organics were washed with dilute HCl, cold water, and brine, and dried over anhydrous $MgSO_4$. The solution was concentrated and added slowly to 50 ml of pentane (distilled from calcium hydride). An oil was isolated by cooling the solution to −78° and decanting the pentane. The remaining pentane was removed on a vacuum line. The oil crystallized slowly: 4.1 g (60%); mp ~40°; nmr ($CHCl_3$) δ 0.8 (d, 6), 1.1 (m, 8), 1.7 (m, 4), 2.1 (s, 6), 4.3 (m, 2), 7.2 (m, 10). *Anal.* Calcd for $C_{26}H_{34}O_6S_2$: C, 61.63; H, 6.76; O, 18.95; S, 12.66. Found: C, 61.73; H, 6.86.[6]

Kinetic Studies. Rates of formolysis were determined by a titrimetric technique. A 0.05 *M* solution of ditosylate (4) in 10 ml of formic acid (freshly distilled from boric anhydride) buffered with 2.2 equiv of sodium formate was placed in a constant temperature bath. Aliquots (1 ml) were withdrawn and titrated for formate content (hence *p*-toluenesulfonic acid content) with a standard solution of perchloric acid in acetic acid (1% anhydride) to the Bromphenol Blue end point (yellow to clear). Rates were obtained from the slope of the least-squares fit of a plot of logarithm of concentration *vs.* time. The values reported in Table I are the averages of two or three runs.

Formolysis Product Studies. Ditosylate 4 (1.013 g, 0.002 mol) was added to a solution of 0.272 g (0.004 mol) of sodium formate in 40 ml of formic acid (freshly distilled from boric anhydride) equilibrated at 40°. After 4.5 hr (5 half-lives) the mixture was cooled to room temperature and diluted with 150 ml of ether. Formic acid was removed by extraction with $NaHCO_3$. The ether extract was dried over anhydrous $MgSO_4$ and concentrated by distillation. Two components were isolated by preparative vapor phase chromatography (SE-30, 150°, 60 ml/min). The major component was assigned structure **9**: nmr ($CDCl_3$) δ 0.9 (d, 3), 1.1 (d, 3), 1.5 (m, 8), 2.0 (m, 5), 4.9 (m, 1), 7.9 (s, 2); ir (neat) 1725 cm^{-1} (ester C=O).[8] The minor component was assigned structure **10**: nmr ($CDCl_3$) δ 0.9 (d, 3), 1.5 (m, 7), 2.0 (m, 7), 5.3 (s, 2), 7.9 (s, 1); ir (neat) 1730 cm^{-1} (ester C=O).[6] Product composition was determined by analytical vapor phase chromatography. Thermal conductivity factors were assumed to be identical for each component, and the amount of each product was determined as the percentage of the total area under the trace. Structures **9** and **10** were confirmed by characterization of the products of formolysis followed by saponification with 50 ml of 0.5 *M* NaOH. Two components were isolated by preparative vapor phase chromatography (Carbowax, 120°, 60 ml/min). The major component was assigned structure **11**: nmr ($CDCl_3$) δ 0.8 (d, 3), 1.0 (d, 3), 1.5 (m, 11), 2.1 (m, 3), 3.8 (m, 1), 4.4 (br s, 1); ir (neat) 3500 (O-H), 1710 cm^{-1} (C=O); mass spectrum (10 eV) *m/e* 198 (small), 180, 165, 147, 139, 125, 112, 97, 83, 69, 67.[8] *Anal.* Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18; O, 16.14. Found: C, 71.51; H, 10.21.[15] The minor component was assigned structure **12**: nmr ($CDCl_3$) δ 0.9 (d, 3), 1.5 (m, 10), 2.2 (m, 5), 5.3 (br s, 2); ir (neat) 1710 cm^{-1} (C=O); mass spectrum (10 eV) *m/e* 180, 165, 139, 125, 112, 97, 83, 70.[8] *Anal.* Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18; O, 8.88. Found: C, 78.77; H, 11.09.[15] Pure samples of **9** and **10** were hydrolyzed independently to products having identical retention times (by peak enhancement) to those of **11** and **12**, respectively.

The reaction was also stopped after 1 half-life and the resulting mixture was diluted with ether. Formic acid was removed by extraction with $NaHCO_3$. The organics were concentrated by rotary evaporation, and the residue was chromatographed on a silica gel column. Elution was begun with 2% THF-hexane. The products **9** and **10** came off with 10% THF–hexane. One or more mixed formate tosylates came off with 15% THF, and unreacted ditosylate with 20–50% THF. The mixed formate–tosylate fractions were allowed to react with wet formic acid, and the resulting products were **9** and **10**.

Trifluoroacetolysis Product Studies. Ditosylate 4 (1.012 g, 0.002 mol) was added to a solution of 0.475 g (0.004 mol) of sodium trifluoroacetate in 40 ml of trifluoroacetic acid (1% anhydride) at 25°. After 5 half-lives (determined by changes in the aromatic methyl resonances) the solvolysis was worked up in the manner described for formolysis. Two components were isolated from the ether extract by preparative vapor phase chromatography (SE-30, 130°, 60 ml/min). The major component was assigned a structure analogous to **9**: nmr ($CDCl_3$) δ 0.9 (d, 3), 1.1 (d, 3), 1.5 (m, 8), 2.0 (m, 5), 4.9 (m, 1); ir (neat) 1780 cm^{-1} (ester C=O).[8] The minor component was assigned a structure analogous to **10**: nmr ($CDCl_3$) δ 0.9 (d, 3), 1.5 (m, 7), 2.1 (m, 7), 5.3 (s, 2); ir (neat) 1800 cm^{-1} (ester C=O).[8] Pure samples of these products were hydrolyzed to materials with vapor phase chromatographic retention times identical (by peak enhancement) to those of **11** and **12**, respectively. Trifluoroacetolysis followed by saponification resulted in materials having nmr and ir spectra identical with those of **11** and **12** produced by formolysis.

Registry No.—**4**, 53013-73-3; **9**, 53783-61-2; **9** (trifluoroacetyl analog), 53783-62-3; **10**, 53783-63-4; **10** (trifluoroacetyl analog), 53783-64-5; **11**, 53783-65-6; **12**, 53783-66-7; 5-chloro-1-pentyne, 14267-92-6; acetylene, 74-86-2; 1-bromo-3-chloropropane, 109-70-6; 1,8-dichloro-4-octyne, 53783-67-8; 6-dodecyne-2,11-diol, 53783-68-9; *p*-toluenesulfonyl chloride, 98-59-9; sodium trifluoroacetate, 2923-18-4.

References and Notes

(1) (a) This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by the National Science Foundation (Grant GP-35868X); (b) National Science Foundation Trainee, 1969–1970; NDEA Fellow, 1970–1973.
(2) W. D. Closson and S. A. Roman, *Tetrahedron Lett.*, 6015 (1966).
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(5) Secondary tosylates have been found to favor five-membered ring formation.[2,3] Although the products are therefore depicted throughout this paper as five-membered rings, we do not exclude the concomitant presence of some six-membered ring products.
(6) The ditosylate 4 can exist in *dl* and meso diastereomeric modifications. We are presuming that the isolated product is isomerically pure, but this presumption does not alter our conclusions (see Discussion). We have no way of knowing which diastereomer is present in our study.
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(8) The nmr and ir spectra are reproduced in J. J. Papay, Ph.D. Dissertation, Northwestern University, 1973.
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(15) Twice-collected samples still exhibited some impurities by vpc. The poor elemental analyses must result from these impurities, which had little or no affect on the nmr, ir, and mass spectra.

Field Desorption Mass Spectrometry of Phosphonium Halides

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Field desorption mass spectra are reported for six mono- (1–6) and four bisphosphonium halides (7–10) derived from triphenylphosphine. All of the former show base peaks corresponding to the phosphonium cation and several show other peaks of structural significance. Base peaks for the latter are influenced by structural factors, in particular, the stability of a complex of the dication with one halide. Fragmentation and the general behavior of these compounds under field desorption conditions are discussed in terms of the utility of this technique for confirmation of structure of these important synthetic intermediates.

Organic "onium" salts, and phosphonium salts in particular, are increasingly important intermediates for organic synthesis.[2] The increased acidity conferred on protons adjacent to the positive center allows their easy removal and the ylides so formed react in a variety of useful ways, depending largely on the nature of the heteroatom involved.[3]

While the preparation of such salts is usually straightforward, difficulties can arise. For instance, rearrangement during quaternization of phosphines with allylic halides[4] can lead to unexpected products or mixtures of products. The use of dihaloalkanes can lead to mixtures of mono- and bisphosphonium salts,[5] and salts derived from addition of triphenylphosphine hydrobromide to polyenes or alcohols[4b,6] can lead to products with ambiguous structures.

During a continuing investigation of the preparation and synthetic application of vinylphosphonium salts,[7] such problems were encountered and in particular we required a rapid and reliable method for the determination of molecular weights of the products of quaternization of triphenylphosphine. Since electron-impact mass spectrometry is not suitable for such nonvolatile compounds, we turned to the recently developed field desorption technique which has already been applied to ammonium salts.[8] We report here the results obtained from a number of related mono- and bisphosphonium salts of established structure which clearly indicate the utility of field desorption mass spectrometry (FDMS) in structure determination of these compounds.

Numerous reviews outlining the principles upon which FDMS depends have appeared since Beckey first demonstrated the technique in 1969, including a recent brief and lucid account of FDMS in the context of field ionization from which it is derived.[9] The key facts are that a nonvolatile sample can be deposited on an anode which is subsequently inserted into the mass spectrometer source. Upon application of a high positive voltage (and usually some heat) to the anode, electrons are removed from sample molecules and the resulting low-energy molecular ions are focused and detected in the usual way.

Results and Discussion

Phosphonium halides 1–10 (Chart I) yield FD spectra which are highly characteristic of their structure at minimum anode temperatures, along with fragmentation which increases as anode temperature is increased.

Chart I

$Ph_3\overset{+}{P}CH_2Ph$ Cl^- (353) (35, 37) **1**

$Ph_3\overset{+}{P}CH_2CH_3$ Br^- (291) (79, 81) **2**

$Ph_3\overset{+}{P}CH_2CH{=}CH_2$ Br^- (303) (79, 81) **3**

$Ph_3\overset{+}{P}CH{=}CH_2$ Br^- (289) (79, 81) **4**

$Ph_3\overset{+}{P}CH{=}C(CH_3)_2$ Cl^- (317) (35, 37) **5**

$Ph_3\overset{+}{P}CH_2CH{=}CHCH_3$ Cl^- (317) (35, 37) **6**

$Ph_3\overset{+}{P}(CH_2)_2\overset{+}{P}Ph_3$ $2Br^-$ (552) (79, 81) **7**

$Ph_3\overset{+}{P}(CH_2)_3\overset{+}{P}Ph_3$ $2Br^-$ (566) (79, 81) **8**

$Ph_3\overset{+}{P}(CH_2)_4\overset{+}{P}Ph_3$ $2Br^-$ (580) (79, 81) **9**

$Ph_3\overset{+}{P}CH_2CH{=}CHCH_2\overset{+}{P}Ph_3$ (trans) $2Cl^-$ (578) (35, 37) **10**

The presence of two isotopes for each of the halogens (^{35}Cl = 75.4%, ^{37}Cl = 24.6%; ^{79}Br = 50.6%, ^{81}Br = 49.4%) aids in the identification of peaks to which they contribute and in addition a comparison of observed and calculated isotope peak intensities provides an opportunity to check on the reproducibility of minor peaks. The results for monophosphonium halides 1–6 are presented in Table I.

The phosphonium cation gave rise to the base peak in each of these spectra. From the point of view of determination of an unknown structure, the fact that there are frequently several peaks of higher *m/e* may be a nuisance, but the family of ions representing the original cation is so much more intense than any others that a correct assignment should be relatively straightforward. Similar identification of the halide would be possible only for 1, where the

Table I
Field Desorption Mass Spectra of $Ph_3\overset{+}{P}$–R X^-[a]

1, R = CH_2Ph; X = Cl; anode current = 16 mA
m/e 744 (2.6%), 743 (6.3), 742 (7.9), 741 (14), 674 (5.0), 649 (5.8), 571 (7.1), 495 (10.5), 479 (5.0), 477 (5.5), 443 (6.5), 429 (15), 399 (7.6), 390 (5.5), 389 (12), 388 (14), 387 (34), 355 (7.9), 354 (50), 353 (100, base), 299 (8.1), 298 (9.2), 297 (24), 277 (3.1), 262 (3.4)

2, R = CH_2CH_3; X = Br; anode current = 13 mA
m/e 664 (5.5%), 663 (13), 662 (6.2), 661 (11), 369 (2.9), 367 (5.6), 343 (4.7), 341 (4.4), 292 (37), 291 (100, base)

3, R = $CH_2CH{=}CH_2$; X = Br; anode current = 13 mA
m/e 688 (3.3%), 687 (5.8), 686 (3.2), 685 (5.6), 381 (2.2), 343 (3.6), 305 (4.0), 304 (31.5), 303 (100, base), 277 (3.1)

4, R = $CH{=}CH_2$; X = Br; anode current = 15 mA
m/e 660 (5.1%), 659 (8.3), 658 (4.3), 657 (7.5), 290 (21.7), 289 (100, base)

5, R = $CH{=}C(CH_3)_2$; X = Cl; anode current = 10.5 mA
m/e 319 (8%), 318 (30), 317 (100, base)[b]

6, R = $CH_2CH{=}CHCH_3$ (trans); X = Cl; anode current = 10 mA
m/e 319 (5%), 318 (48), 317 (100, base)[c]

[a] All ions of relative abundance greater than 5% and others of particular interest are reported. [b] Cluster ions near 669, 671 are too small to be measured accurately. [c] Cluster ions at 669, 671 are below threshold. One scan at high gain yields 669 = 2.0%, 671 = 0.8%.

peak at 387 corresponding to the major isotope of chlorine associated with the cation less one H has a relative intensity of 34%. All of these compounds show some evidence for a singly charged cluster ion composed of two cations and one anion (+−+), although 5 and 6 would present some difficulty in anion identification as unknowns.

Reference has been made to the fact that the base peak in these spectra occurs as part of a family, and in the case of 1, the peaks assigned to the neutral salt less an electron appear to have a hydrogen missing. This observation of hydrogen gain and loss is very common in FDMS and represents a limitation of this method for structural studies. However, in the present work where molecules are composed mainly of atoms of high mass number (P, Cl, Br) combined with stable groups (C_6H_5), hydrogen transfer presents no particular difficulty. It should be noted that molecules containing 20 or more carbons have substantial ^{13}C isotope peaks (20 × 1.1 = 22%), and after subtraction of this contribution, the amount of M + H and M + 2 H is not very large. However, assignment of fragmentation peaks requires that one or occasionally two hydrogens be treated as disposables to be added or subtracted. This arbitrary procedure may take on some mechanistic meaning as larger numbers of FD spectra on various classes of compounds become available.

Benzyltriphenylphosphonium chloride (1) gives a particularly rich FD spectrum, a fact which may be related to the low ionization potential of the benzyl group. In addition to the base peak (*m/e* 353) and peaks arising from the intact phosphonium halide (*m/e* 387–390), there are several assignments that are straightforward. Triphenylphosphine (*m/e* 262), which could arise from benzyl loss from the base peak, and the elements of methyltriphenylphosphonium cation (*m/e* 277) are peaks found in most of our compounds. The peaks at *m/e* 297, 299 correspond to Ph_3PCl^+ and show the appropriate isotope ratio. Most of the other peaks can be tentatively assigned by manipulation of the major structural units, although at this stage the manner in which these sometimes thoroughly rearranged fragments actually arise is not clear. The peaks at 649, 571, and 495 correspond to loss of $PhCH_3$, $PhCH_3 + C_6H_6$, and $PhCH_3$

Table II
Intensity of Cluster Ions in $Ph_3P^+–R\ X^-$

Compound	Cluster *m/e*	Intensity,[a] %	^{13}C and + H[b]
1, R = CH_2Ph; X = Cl	741, 743	14, 6.3	7.9, 2.6
2, R = CH_2CH_3; X = Br	661, 663	11, 13	6.2, 5.5
3, R = $CH_2CH{=}CH_2$; X = Br	685, 687	5.6, 5.8	3.2, 3.3
4, R = $CH{=}CH_2$; X = Br	657, 659	7.5, 8.3	4.3, 5.1

[a] Relative to base peak = 100. [b] Intensities for peaks 1 amu above those quoted (*e.g.*, 742, 744 for 1).

+ C_6H_4 from the major isotope peak of the cluster ion at *m/e* 741. There are two ions that may be related to additions to the base peak, *i.e.*, *m/e* 429 (353 + C_6H_4) and *m/e* 443 (353 + PhCH). Addition of Cl to the latter would give *m/e* 478, 480, a process which may be represented by the peaks actually found one unit lower. Whether this exercise in provisional assignment has any merit or not, study of this compound does emphasize that under some conditions FD produces a good deal more than molecular ions.

The remaining compounds in Table I give much simpler spectra. There is evidence in 2 for Ph_3PBr^+ (341, 343) as well as small peaks which may represent the phosphonium halide − 3 H (*m/e* 367, 369). For compound 3, the peaks at 343 and 381 may represent the addition of allyl (actually C_3H_4) and benzene to the base peak by analogy with the 429 and 443 peaks in 1. However, at this level the absence of isotope peaks may be accidental, and it is therefore possible that these peaks are bromine containing.

Attention has already been drawn[8] to the existence of ion clusters in FDMS. Our results confirm this behavior, and the presence of isotopes for each of our anions allow these assignments to be made with some confidence. In Table II we present the ions corresponding to two phosphonium cations combined with one halide anion for compounds 1–4.

The intensities of the cluster ions reflect fairly accurately the isotopic composition of chlorine (1) and bromine (2–4). Although the contribution of extra hydrogens to these peaks could in principle distort the observed ratios, a quick calculation shows that the "^{13}C and +H" peaks are in fact predominantly composed of ^{13}C, a result of the high carbon number (40–50) of these cluster ions. Thus, these data show that FD ion peaks of 5–15% relative intensity contain sufficient ions that they reproduce fairly faithfully the expected isotope ratios. In fact, our experience has been that reasonable ion statistics and reproducibility are maintained at even lower intensity levels when measurement of peak intensities is not complicated by noise.

The observed FD spectra for bisphosphonium salts 7–10 are presented in Table III. Unlike the monophosphonium salts, these compounds have base peaks which appear to be related to their specific geometry. Thus, 8 and 9 have (+−+) ions as base peaks, *m/e* 645, 647 for the former, and 659, 661 for the latter. Compound 7 has corresponding peaks (631, 633) of low intensity and 10 has peaks one unit higher (614, 616) which we attribute to (+−+) + H. It is difficult to escape the conclusion that the unusually prominent cluster ions in 8 and 9 reflect their ability to form a ring-like structure with the halide held between the two phosphorus atoms. Whether the failure of 7 to show this enhanced cluster peak is related to ring-size problems or to competition from favorable fragmentations (both methy-

Table III
Field Desorption Mass Spectra of $(Ph_3P)_2R^+\ X^-$[a]

7, R = $(CH_2)_2$; X = Br; anode current = 16 mA
m/e 659 (5%), 657 (4), 633 (7), 631 (6), 291 (6), 290 (35), 289 (100, base)

8, R = $(CH_2)_3$; X = Br; anode current = 18 mA
m/e 649 (22%), 648 (29), 647 (81), 646 (49), 645 (100, base), 303 (22)

9, R = $(CH_2)_4$; X = Br; anode current = 17.5 mA
m/e 663 (9%), 662 (44), 661 (100, base), 660 (43), 659 (89), 291 (1), 290.5 (4), 290 (8)[b]

10, R = $CH_2CH{=}CHCH_2$;[c] X = Cl; anode current = 15 mA
m/e 661 (4%), 660 (11), 659 (6), 658 (12), 617 (4) 616 (5), 615 (7), 614 (15), 339 (13), 316 (6), 292 (8), 291 (29), 290.5 (24), 290 (100, base), 276 (7)

[a] All ions of relative abundance greater than 5% and others of special interest are reported. [b] At high gain, small peaks are present at 341, 343 (Ph_3PBr, <1% of base) and at 397, 399 ($Ph_3P(CH_2)_4Br$, 2% of base). [c] This compound is predominantly trans.

lenes are activated by adjacent P^+) is not clear. In any event, the base peak in 7 corresponds to $Ph_3PCH{=}CH_2^+$, whereas the base peak in 10 is *m/e* 290 which we assign at least in part to a doubly charged bisphosphonium ion. This latter assignment requires that the dication pick up two hydrogens. It is doubtful that this is a sufficient assignment because it demands a 580^{2+} ion containing 40 carbons and should be accompanied by a 581^{2+} ion of 44% intensity representing the ^{13}C isotope. The peak at 290.5 has an intensity just over half of this which suggests that about half of the *m/e* 290 peak may in fact be a singly charged ion of that mass. The peak at 291 is a good deal larger than would be demanded for the ^{13}C isotope corresponding to the latter, which in turn suggests that it may in part represent 582^{2+}. Increased anode temperature results in a reduction of the 290/290.5 ratio before they both disappear. That fact, and the emergence of new base peaks, is consistent with our assignment of both a singly and doubly charged ion to the *m/e* 290 peak at lower temperatures.

Compound 9 also shows evidence of doubly charged ions. In this case the ion at *m/e* 290 corresponds to $Ph_3P(CH_2)_4PPh_3^{2+}$, and the calculated ^{13}C isotope peak at 290.5 ($40 \times 1.1 \times 8 = 3.5\%$) agrees very well with the observed intensity. Compound 8 shows only one important fragment ion at *m/e* 303 which we assign to $Ph_3PC_3H_5^+$ (loss of Ph_3P and H). The two high *m/e* peaks in 7 appear to contain one Br and we assign them to the cluster ion plus C_2H_2 (631, 633 + 26 = 657, 659), implying that the elements of acetylene are transferred, perhaps from a species related to the base peak (*m/e* 289, $Ph_3PCH{=}CH_2^+$). The minor ion at 276 in 10 no doubt represents $Ph_3PCH_2^+$, but the ions at 658–661 in this compound are not readily assigned. The ion at 339 we attribute to Ph_4P^+ and *m/e* 316 may be a doubly charged ion, since it is flanked by ions at 315.5 and 316.5 which are clearly distinguished at scans taken at high gain, although in no case do they exceed threshold (5%).

The bisphosphonium halides may be desorbed from the emitter at a variety of temperatures. Some interesting and potentially useful information is obtained in this way, but a good deal more work will be necessary before the trends are understood in detail. The behavior of 8 at anode temperatures above 18 mA may be summarized as an example. Upon heating to 19–21 mA, the base peak for this compound shifts from *m/e* 645, 647 to *m/e* 303. At still higher temperatures m/e 645, 647 disappears and the base peak shifts to m/e 277 ($Ph_3PCH_3^+$), an ion not present in the original 18-mA spectrum. Fragments of m/e 262 (Ph_3P^+) and m/e 289 ($Ph_3PCH{=}CH_2^+$) also appear above 23 mA.

In summary, we conclude that field desorption mass spectrometry provides a means of characterizing mono- and bisphosphonium halides formed in synthetic sequences and may have some application in the identification of these and similar salts when they are presented as unknowns. In general, the lowest anode current at which the sample is desorbed is most likely to provide ions related to unfragmented species. However, where additional current can be applied without causing instant desorption, valuable supplementary information may be obtained. This series of related salts has also provided some further background on the behavior of molecules under field desorption conditions, information which is essential if this technique is to have wide applicability as a supplement to electron impact mass spectrometry in structure determination.

Experimental Section

All compounds used in this work were prepared and characterized by published procedures.[2] The mass spectrometer was a Varian MAT Model CH5 DF with combined FD–FI–EI source. The samples were prepared as chloroform solutions (about 1 mg in 100 μl) and transferred to a conditioned anode by dipping.[10] The anodes are 10-μ tungsten wires spot-welded on supporting posts and conditioned in a Varian apparatus in a manner similar to that described by Beckey.[11] After excess solvent had evaporated, the anode carrying the sample was introduced into the cool source (generally 80°) through a vacuum lock. When vacuum better than 10^{-6} Torr was restored, the high voltage was applied (+3 kV to anode and −7 kV to cathode) and the focusing elements adjusted using the signals from a field ion beam produced by a mixture of acetone, toluene, and 6-undecanone introduced through the reference inlet. Anode heating was increased until a steady ion beam was obtained on the total ion beam monitor and the magnet scan was then commenced. Signals were obtained from an electron multiplier set at 1.75–2 kV (gain of 10^5–10^6) and spectra were recorded at nominal resolution of 1500 on an oscillographic recorder. The mass scale was calibrated with a Varian mass marker calibrated against perfluorokerosene (EI mode) every 20 amu (±0.4 amu). After each sample, the anode current was gradually increased to its maximum value (50 mA) to clean the wire before a new sample was run.

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Registry No.—**1**, 1100-88-5; **2**, 1530-32-1; **3**, 1560-54-9; **4**, 5044-52-0; **5**, 42855-48-1; **6**, 7354-47-4; **7**, 1519-45-5; **8**, 7333-67-7; **9**, 15546-42-6; **10**, 53643-43-9.

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5-Thio-D-fructofuranose[1,2]

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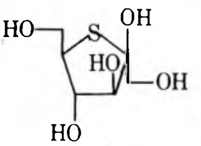
Three routes of synthesis for 5-thio-D-fructofuranose (1) are examined. Treatment of methyl 4-*O*-acetyl-1,3-*O*-benzylidene-5-*O*-tosyl-α-L-sorbopyranoside (5) with potassium thioacetate in DMF gives methyl 4-*O*-acetyl-5-*S*-acetyl-1,3-*O*-benzylidene-5-thio-β-D-fructopyranose (13). After three hydrolysis steps 1 is obtained. Alternately, 5 can be hydrolyzed to 4-*O*-acetyl-5-*O*-tosyl-α-L-sorbopyranoside (22). This, after acetylation with acetic acid, acetic anhydride, and sulfuric acid is treated with potassium thioacetate in DMF solution to give 1,2,3,4-tetra-*O*-acetyl-5-*S*-acetyl-5-thio-β-D-fructopyranose (24). Deacetylation of 24 leads to 1. 1 is also obtained from 1,3-*O*-isopropylidene-α-L-sorbose (25) by selective tosylation and treatment with potassium thioacetate to give the 5-*S*-acetyl compound which is then hydrolyzed with aqueous trifluoroacetic acid and deacetylated.

The interesting chemical and biochemical properties of thiosugars containing sulfur as the ring heteroatom have led in recent years to several examples of their preparation.[4] Such monosaccharides as 5-thio-D-glucopyranose,[4a] methyl 4-thio-D-arabinoside,[4b] 4-thio-D- and -L-ribose,[4c] and methyl 5-thio-D-xyloside[4d] have been synthesized. To provide analogs of D-fructose for metabolic examination we have prepared 6-thio-D-fructose[4e] and now 5-thio-D-fructose (1).

Recently Murphy[5] has found that treatment of methyl 1,3-*O*-benzylidene-4,5-di-*O*-mesyl-α-L-sorbopyranoside (3) with an excess of sodium benzoate or sodium azide in boiling *N,N*-dimethylformamide leads to displacement at the C-5 position to give the D-fructo sugars **9** and **10**, respectively. Treatment of 1,2-*O*-isopropylidene-3,4,5-tri-*O*-mesyl-α-L-sorbose (11) with sodium azide in hexamethylphosphoric triamide results in ready displacement of the mesyl group at C-5 only, to give the sugar 12 with the D-fructo configuration.[6] Armenakian, Mahmood, and Murphy[7] have found that 2 when treated with an equimolar amount of tosyl chloride in pyridine gives a good yield of the 5-substituted derivative 4 only.[8] These results suggested the synthesis of 5-thio-D-fructose (1) from an L-sorbose derivative.

Compound **5**, prepared according to Murphy's procedure,[5,7] when heated at 100° in *N,N*-dimethylformamide in



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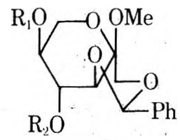
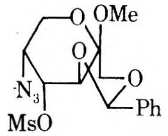
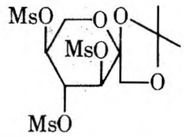


2. $R_1 = R_2 = H$
3. $R_1 = R_2 = Ms$
4. $R_1 = Ts$; $R_2 = H$
5. $R_1 = Ts$; $R_2 = Ac$
6. $R_1 = R_2 = Ts$
7. $R_1 = H$; $R_2 = Ts$
8. $R_1 = Ac$; $R_2 = Ts$



9, $R_3 = OBz$
10, $R_3 = N_3$



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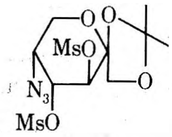

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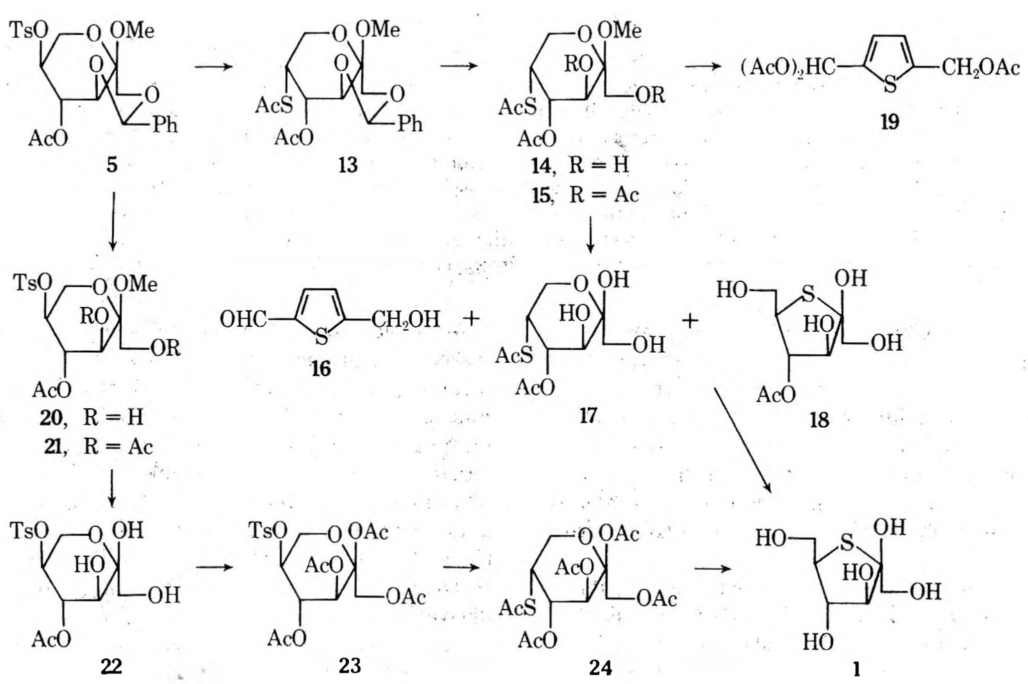
the presence of an excess of potassium thioacetate yielded methyl 4-*O*-acetyl-5-*S*-acetyl-1,3-*O*-benzylidene-5-thio-β-D-fructopyranoside (**13**). The nmr spectrum (*cf.* Experimental Section) of **13** shows signals characteristic for acetyl, thioacetyl, methoxyl, and benzylidene groups. H-3 signal at δ 4.03 is in the form of a doublet ($J_{3,4}$ = 10.9 Hz) whereas H-4 at δ 5.86 is a pair of doublets ($J_{3,4}$ = 10.9 and $J_{4,5}$ = 4.6 Hz). These data verify the β-D-fructose configuration of **13**.

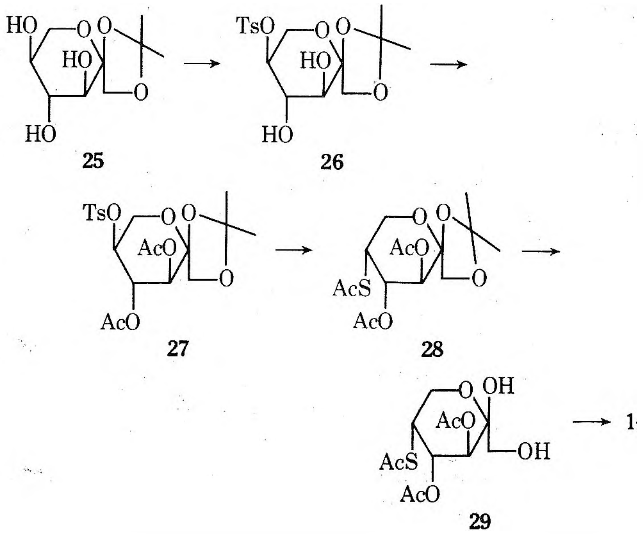
Hydrolysis of **13** with 50% aqueous acetic acid proceeds smoothly and affords the methyl 4-*O*-acetyl-5-*S*-acetyl-5-thio-β-D-fructopyranoside of **14**. Acid hydrolysis of **14** did not give a satisfactory yield of **17** or **18**. Numerous experiments using diluted acids such as sulfuric acid, hydrochloric acid, acetic acid, and ionic exchange resin IR120 (H^+) were unsuccessful. Compound **14** easily undergoes transformation into the thiophene derivative **16**. Likewise the acetolysis of **14** with acetic acid and acetic anhydride in the presence of a catalytic amount of sulfuric acid gives a mixture of several products. The major component was isolated chromatographically and identified as the triacetate **19**. Mineral acids induce formation of furan compounds from mono- and polysaccharides[9] and ketoses decompose more readily than aldoses.[10] The possibility of obtaining the more stable thiophene, higher energy of resonance than furan, makes the degradation of derivatives of 5-thio-D-fructose into **16** and **19** very easy. Treatment of **14** with trifluoroacetic acid at 25°, however, gave a mixture of three compounds which could be separated chromatographically. From their nmr spectra, the less polar (tlc) compound is the thiophene derivative **16** and the others are 4-*O*-acetyl-5-*S*-acetyl-5-thio-β-D-fructopyranose (**17**) and 4-*O*-acetyl-5-thio-β-D-fructofuranose (**18**). The nmr spectrum of **17** shows two singlets at δ 2.08 and 2.60, corresponding to *O*-acetyl and *S*-acetyl groups, and does not show an absorption due to an *O*-methyl group. The doublet of H-3 at δ 3.99 with $J_{3,4}$ = 10.4 Hz and the pair of doublets of H-4 at δ 5.48 ($J_{3,4}$ = 10.4 and $J_{4,5}$ = 4.7 Hz) indicates a fructo configuration and a pyranose ring in **17**. The nmr spectrum of **16** indicated the absence of *S*-acetyl and *O*-methyl groups. A three-proton singlet at δ 2.24 for *O*-acetyl, a doublet for H-3 at δ 4.31 ($J_{3,4}$ = 9.8 Hz), and a pair of doublets at δ 5.53 ($J_{3,4}$ = 9.8 and $J_{4,5}$ = 7.6 Hz) support a furanose ring structure for **18**. Deacetylation of **18** with sodium methoxide in methanol led to the free sugar **1**.

An alternate method was examined for the synthesis of **1** so as to avoid the necessity of hydrolyzing **14** with acid. Compound **5** can be hydrolyzed with aqueous trifluoroacetic acid to give **20**. After removing benzaldehyde, **20** was again hydrolyzed with trifluoroacetic acid. The crude product **22**, when acetylated at 0° with acetic acid and acetic anhydride in the presence of a catalytic amount of sulfuric acid, gave 1,2,3,4-tetra-*O*-acetyl-5-*O*-tosyl-α-L-sorbose **23** only. The structure of **23** was readily deduced from its nmr spectrum (*cf.* Experimental Section). Treatment of **23** with potassium thioacetate in *N,N*-dimethylformamide at 70° produces the pentaacetate **24**, which after deacetylation gives **1**.

Because the overall yield in these reactions was not satisfactory a shorter and more efficient route was worked out. 1,2-*O*-Isopropylidene-α-L-sorbose (**25**) was the starting material.

Compound **25** is readily tosylated with an equimolar amount of tosyl chloride at 0° to produce the 5-*O*-tosyl derivative **26** in 40% yield. The structure of **26** was deduced from its nmr spectrum and from the spectrum of its diacetate **27**. The nmr spectrum of **26** shows signals characteristic of isopropylidene and tosyl groups. The pair of triplets for H-5 ($J_{4,5} \simeq J_{5,6a} \simeq 9$ and $J_{5,6e} \simeq 7$ Hz) at δ 5.06 testifys that only the hydroxyl group at C-5 was substituted. Heating **27** at 80° in *N,N*-dimethylformamide in the presence of

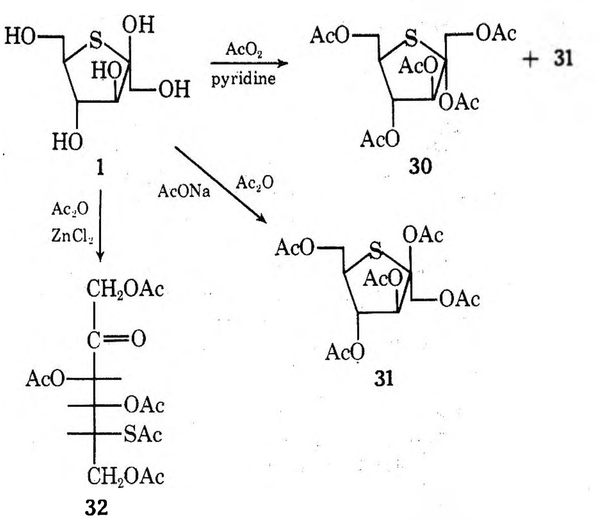




an excess of potassium thioacetate gives 3,4-di-*O*-acetyl-5-*S*-acetyl-1,2-*O*-isopropylidene-5-thio-*β*-D-fructopyranose (**28**) in good yield. The structure of **28** is deduced from its nmr spectrum (*cf.* Experimental Section). Triacetate **28** is easily hydrolyzed with aqueous trifluoroacetic acid and yields **29**. Deacetylation of **29** gives the free sugar **1**.

5-Thio-D-fructofuranose (**1**) is a colorless syrup, stable at 25°, and does not oxidize at a perceptable rate. The specific optical rotation in methanol is +1.4°.

Acetylation of **1** with acetic anhydride and pyridine leads to a mixture of two pentaacetates, **30** (highest R_f on tlc) and **31**, whereas acetylation in boiling acetic anhydride and sodium acetate gives **31** only. Pentaacetates **30** and **31** can



be separated chromatographically. That **30** and **31** are the anomers of 1,2,3,4,6-penta-*O*-acetyl-5-thio-D-fructofuranose is easily deduced from their ir and nmr spectra. The ir spectra of **30** and **31** show acetyl–carbonyl absorption but do not show any absorption attributable to SAc, OH, and SH groups. The nmr spectra of both compounds integrated for five OAc groups, and the coupling constants $J_{3,4}$ and $J_{4,5}$ are 6.8 and 6.7 Hz for **30**, whereas they are 7.9 and 5.8 Hz for **31**, respectively. Due to the opposition of the anomeric *O*-acetyl group it was expected that in nmr spectra the signals of H-3 and H-5 in the *α*-D-anomer would be shifted downfield and H-4 would be shifted upfield when compared with *β*-D-anomer. In the spectrum of **30** H-3 was observed at δ 6.06, H-4 at δ 5.56, and H-5 at δ 3.90, whereas the corresponding data for **31** are H-3 at δ 5.80, H-4 at δ 5.65, and H-5 at δ 3.66. Consequently we characterize **30** as *α*-D-anomer and **31** as *β*-D-anomer of 1,2,3,4,6-penta-*O*-acetyl-5-thio-D-fructofuranose. The specific optical rotation of **30** is +153.8° and that of **31** is −91.3°. These rotations are fully consistent with proposed structures.[11] Acetylation of **1** with acetic anhydride in the presence of zinc chloride leads to a mixture of three isomeric pentaacetates. The major component **32** readily crystallizes from the mixture in 25% yield. On the basis of the nmr spectra and the specific optical rotation it is recognized as 1,3,4,6-tetra-*O*-acetyl-5-*S*-acetyl-5-thioketo-D-fructose (**32**) and the two remaining compounds as **30** and **31**.

Acetylation of 5-thio-D-fructose (**1**) differs from that of natural D-fructose. D-Fructose, however, exists in the crystalline form as *β*-D-fructopyranose only, while in solution it occurs in an equilibrium of pyranose and furanose forms.[11,12] Our thio analog remains in the furanose form.

The acetylation of D-fructose has been the subject of numerous investigations.[11–18] Acetylation using boiling acetic anhydride and sodium acetate leads to an unidentified mixture of acetates.[13] The only crystalline product isolated after acetylating D-fructose in pyridine solution is keto-D-fructose pentaacetate in 5% yield.[14] Treatment of D-fructose with acetic anhydride and zinc chloride at 50° leads to the open chain pentaacetate,[15] whereas at 0–5° 1,3,4,5-tetra-*O*-acetyl-*β*-D-fructopyranose is obtained.[14] Sulfuric acid as a catalyst at 0–5° gives this same tetraacetate.[16] Perchloric acid in an acetylating mixture at 70° gives 1,2,3,4,5-penta-*O*-acetyl-*β*-D-fructopyranose.[17] No crystalline acetate of D-fructofuranose has been prepared. D-Fructofuranose pentaacetate (a liquid) was first synthesized using perchloric acid as the catalyst.[17,18]

5-Thio-D-fructose (**1**) is sufficiently stable in the presence of the basic catalysts such as pyridine or sodium acetate to produce the pentaacetates of the furanose form only. Production of the mixture of **30** and **31** in pyridine proves that in this solvent **1** exists as an equilibrium of *α*- and *β*-D-anomers of the furanose form. The observed specific optical rotation of **1** of −7.7° in water and +13.5° after 4 hr in pyridine strongly supports this view. In aqueous solution, **1** exists predominantly as *β*-D-furanose, which can be deduced from the nmr spectrum of **18** in D_2O. This shows H-3 and H-4 signals for one anomer only. There is no reason to expect that the $\alpha \rightleftarrows \beta$ equilibrium of **1** is different than that for **18**. In addition, the optical rotation of **1** is close to the value expected for *β*-D-fructofuranose ($[\alpha]^{25}$D −4.58°).[19] The opening of the thioacetal ring is possible in the presence of a Lewis acid catalyst ($ZnCl_2$). The main product **32** is probably the most stable pentaacetate. The formation of pentaacetate or tetraacetate with the pyranose ring, as obtained with D-fructose, was not observed under any conditions with our thio analog. The lower stability of **1**, however, in the presence of strong acids precludes using perchloric acid or sulfuric acid as a catalyst.

Experimental Section

General Methods. Purity of products was determined by thin-layer chromatography (tlc) on silica gel G (E. Merck, Darmstadt, Germany). Components were located by spraying with 5% sulfuric acid in ethanol and heating. Column chromatography was performed on silica gel, powder 60–200 mesh (J. T. Baker Chemical Co.). Melting points were determined with a Fisher-Johns apparatus and were corrected. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Nuclear magnetic resonance spectra were obtained in chloroform-*d* and pyridine-d_5 solution (TMS as internal standard) or deuterium oxide (*tert*-butanyl alcohol as internal standard) with a Varian T-60A spectrometer. Ir spectra were recorded with a Perkin-Elmer Model 337 infrared spectrometer.

Methyl 4-*O*-acetyl-1,3-*O*-benzylidene-5-*O*-tosyl-*α*-L-sorbopyranoside (**5**) was prepared according to Murphy's procedure.[5,7] 1,2-*O*-Isopropylidene-*α*-L-sorbose (**25**) was obtained according to the literature procedure.[20]

A sample of the crude **4**[5] was chromatographed using 9.9:0.1

benzene–acetone mixture as eluent. In addition to **4**, the small amounts of the less polar (tlc) methyl 1,3-*O*-benzylidene-4,5-di-*O*-tosyl-α-L-sorbopyranoside (**6**) and the more polar methyl 1,3-*O*-benzylidene-4-*O*-tosyl-α-L-sorbopyranoside (**7**) were isolated.

6: mp 121–122° dec; $[\alpha]^{25}\mathrm{D}$ −71.3° (*c* 1.54, $CHCl_3$); nmr ($CDCl_3$) δ 2.31, 2.54 (2 s, 6, CH_3 of tosyl), 3.43 (s, 3, OCH_3), 3.59 (d, 1, $J_{1,1}$ = −12.8 Hz, H-1), 3.66 (d, 1, $J_{3,4}$ = 10.1 Hz, H-3), 3.87 (t, 1, $J_{5,6a}$ = 11.0, $J_{6a,6e}$ = −11.3 Hz, H-6a), 4.32 (pd, 1, $J_{5,6e}$ = 6.2 Hz, H-6e), 4.45 (d, 1, H-1′), 4.72 (pt, 1, $J_{4,5}$ = 9.0 Hz, H-5), 5.39 (pd, 1, H-4), 5.50 (s, 1, CH of benzylidene), 7.08–8.23 (m, 13, aromatic).

Anal. Calcd for $C_{28}H_{30}S_2O_{10}$: C, 56.9; H, 5.1; S, 10.9. Found: C, 57.2; H, 5.2; S, 10.7.

7: mp 124–125° dec; $[\alpha]^{25}\mathrm{D}$ −76.6° (*c* 1.24, $CHCl_3$); nmr ($CDCl_3$) δ 2.39 (s, 3, CH_3 of tosyl), 3.41 (s, 3, OCH_3), 3.60 (d, 1, $J_{1,1'}$ = −12.7 Hz, H-1), 3.6–4.4 (m, 3, H-5, H-6a, H-6e), 3.73 (d, 1, $J_{3,4}$ = 10.1 Hz, H-3), 4.45 (d, 1, H-1′), 5.06 (pd, 1, $J_{4,5}$ = 7.5 Hz, H-4), 5.58 (s, 1, CH of benzylidene), 7.2–8.0 (m, 9, aromatic).

Anal. Calcd for $C_{21}H_{24}SO_8$: C, 57.8; H, 5.6; S, 7.3. Found: C, 58.0; H, 5.8; S, 7.4.

Acetylation of **7** with acetic anhydride and pyridine gave **8**: mp 128–129° dec; $[\alpha]^{25}\mathrm{D}$ −88.4° (*c* 0.98, $CHCl_3$); nmr ($CDCl_3$) δ 2.13 (s, 3, OAc), 2.37 (s, 3, CH_3 of tosyl), 3.46 (s, 3, OCH_3), 3.63 (d, 1, $J_{1,1'}$ = −12.7 Hz, H-1), ~3.7 (pd, 1, $J_{5,6a}$ = 9.2, $J_{6a,6e}$ = −11.0 Hz, H-6a), 3.76 (d, 1, $J_{3,4}$ ≃ 9.2 Hz, H-3), 4.05 (pd, 1, $J_{5,6e}$ = 6.1 Hz, H-6e), 4.47 (d, 1, H-1′), 5.23 (pt, 1, $J_{4,5}$ ≃ 9.2 Hz, H-5), 5.50 (t, 1, H-4), 5.60 (s, 1, CH of benzylidene), 7.2–8.0 (m, 9, aromatic).

Anal. Calcd for $C_{23}H_{26}SO_9$: C, 58.0; H, 5.1; S, 6.7. Found: C, 58.1; H, 5.3; S, 6.6.

Methyl 4-*O*-Acetyl-5-*S*-acetyl-1,3-*O*-benzylidene-5-thio-β-D-fructopyranoside (13). A mixture of **5** (2.0 g) and potassium thioacetate (3.0 g) in *N,N*-dimethylformamide (40 ml) was stirred and heated at 100° in a current of nitrogen for 6 hr. The reaction mixture was then poured into water (500 ml). The precipitate was filtered, washed with water, and dried. Recrystallization from isopropyl alcohol gave colorless crystals (1.2 g): mp 123–124°; $[\alpha]^{25}\mathrm{D}$ −117.8° (*c* 1.35, $CHCl_3$); yield 75%; ν_{max} (Nujol) 1740 (*O*-acetyl) and 1680 cm^{-1} (*S*-acetyl); nmr ($CDCl_3$) δ 2.04 (s, 3, OAc), 2.45 (s, 3, SAc), 3.46 (s, 3, OCH_3), 3.71 (d, 1, $J_{1,1'}$ = −12.4 Hz, H-1), 3.80 (pd, 1, $J_{5,6e}$ = 2.0, $J_{6a,6e}$ = −13.3 Hz, H-6e), 4.03 (d, 1, $J_{3,4}$ = 10.9 Hz, H-3), ~4.4 (m, 3, H-1′, H-5, H-6a), 5.86 (pd, 1, $J_{4,5}$ = 4.6 Hz, H-4), 5.80 (s, 1, CH of benzylidene), 7.66 (m, 5, aromatic).

Anal. Calcd for $C_{18}H_{22}SO_7$: C, 56.5; H, 5.8; S, 8.4. Found: C, 56.7; H, 5.9; S, 8.2.

Methyl 4-*O*-Acetyl-5-*S*-acetyl-5-thio-β-D-fructopyranoside (14). A stirred solution of **13** (0.50 g) in 50% aqueous acetic acid (10 ml) was heated at 75° under nitrogen for 30 min. The solvents were then carefully removed under vacuum. The oily residue was crystallized from an ethyl acetate–hexane mixture and 0.23 g (60%) of **14** was obtained: mp 127–128°; $[\alpha]^{25}\mathrm{D}$ −190.7° (*c* 1.02, $CHCl_3$); nmr ($CDCl_3$) δ 2.06 (s, 3, OAc), 2.44 (s, 3, SAc), 3.46 (s, 3, OCH_3), 3.80 (pd, 1, $J_{5,6e}$ = 2.1, $J_{6e,6a}$ = −12.3 Hz, H-6e), 3.88 (s, 2, H-1, H-1′), 4.20 (pd, 1, $J_{5,6a}$ = 4.7 Hz, H-6a), 4.26 (d, 1, $J_{3,4}$ = 10.4 Hz, H-3), ~4.3 (m, 1, H-5), 5.50 (pd, 1, $J_{4,5}$ = 4.5 Hz, H-4).

Anal. Calcd for $C_{11}H_{18}SO_7$: C, 44.9; H, 6.2; S, 10.9. Found: C, 45.1; H, 6.2; S, 11.4.

Acetate **15**: oil; $[\alpha]^{25}\mathrm{D}$ −108.9° (*c* 1.12, $CHCl_3$); nmr ($CDCl_3$) δ 1.99, 2.12, 2.17 (3 s, 9, 3 OAc), 2.45 (s, 3, SAc), 3.44 (s, 3, OCH_3), 3.86 (pd, 1, $J_{5,6e}$ = 2.1, $J_{6e,6a}$ = −13.0, H-6e), 4.26 (s, 2, H-1, H-1′), ~4.3 (m, 2, H-5, H-6a), 5.48 (d, 1, $J_{3,4}$ = 10.7 Hz, H-3), 5.64 (pd, 1, $J_{4,5}$ = 3.6 Hz, H-4).

Anal. Calcd for $C_{15}H_{22}SO_9$: C, 47.6; H, 5.9; S, 8.5. Found: C, 48.1; H, 6.1; S, 8.1.

2-Diacetoxymethyl-5-acetoxymethylthiophene (19). To a cold mixture of acetic acid (12 ml), acetic anhydride (12 ml), and sulfuric acid (0.5 ml), 0.5 g of **14** was added. The mixture was refrigerated for 48 hr. Then 2 g of sodium acetate was added, and the solvents were carefully evaporated under pressure. To the residue 50 ml of ice and water was added, and the mixture was extracted with chloroform. The extract was washed, dried, and evaporated to dryness. The oil was chromatographed with hexane–ethyl acetate (9.5:0.5) mixture. The less polar **19** (0.1 g) was obtained: colorless oil; nmr ($CDCl_3$) δ 2.16 (s, 9, 3 OAc), 5.40 (s, 2, CH_2), 7.20 (d, 1, *J* = 4 Hz, H-4), 7.35 (d, 1, H-3), 8.11 (s, 1, CH).

Hydrolysis of 14. Compound **14** (7.50 g) was dissolved in 50% aqueous trifluoroacetic acid (60 ml) and kept under nitrogen for 30 hr at room temperature. The mixture was then neutralized with Amberlite IR-45. The aqueous solution was evaporated to dryness and chromatographed with chloroform–methanol (9.8:0.2, v/v) as eluent. Three fractions were isolated, the first containing 0.80 g of a mixture of **14** and **16**, the second 0.18 g of **17**, and the third 1.44 g of **18**. The first fraction was chromatographed using hexane–ethyl acetate (9:1, v/v) as eluent; 0.50 g of **14** and 0.17 g of **16** were obtained.

16: colorless oil; nmr ($CDCl_3$) δ 5.01 (s, 2, CH_2), 7.30 (d, 1, *J* = 3.9 Hz, H-4), 7.93 (d, 1, H-3), 10.12 (s, 1, OHC); ν_{max}^{film} 3400 (OH), 1650 cm^{-1} (C=O).

17: colorless syrup; $[\alpha]^{25}\mathrm{D}$ −67.6° (*c* 0.52, MeOH); nmr (D_2O) δ 2.08 (s, 3, OAc), 2.60 (s, 3, SAc), 3.62 (d, 1, $J_{1,1'}$ = ~12.0 Hz, H-1), 3.80 (d, 1, H-1′), ~3.8 (m, 1, H-6a), 3.99 (d, 1, $J_{3,4}$ = 10.4 Hz, H-3), ~4.4 (m, 1, H-5), 4.54 (pd, 1, $J_{5,6e}$ = 2.1, $J_{6e,6a}$ = −12.8 Hz, H-6e), 5.48 (pd, 1, $J_{4,5}$ = 4.7 Hz, H-4).

Anal. Calcd for $C_{10}H_{16}SO_7$: C, 42.9; H, 5.8; S, 11.4. Found: C, 43.0; H, 5.8; S, 11.3.

18: colorless syrup; $[\alpha]^{25}\mathrm{D}$ −11.6° (*c* 0.92, MeOH); nmr (D_2O) δ 2.24 (s, 3, OAc), 3.1–4.1 (m, 5, H-1, H-1′, H-5, H-6, H-6′), 4.31 (d, 1, $J_{3,4}$ = 9.8 Hz, H-3), 5.53 (pd, 1, $J_{4,5}$ = 7.6 Hz, H-4).

Anal. Calcd for $C_8H_{14}SO_6$: C, 40.3; H, 5.9; S, 13.4. Found: C, 39.6; H, 5.8; S, 13.1.

Deacetylation of **17** and **18** with sodium methoxide in methanol gave **1** as a colorless syrup; $[\alpha]^{25}\mathrm{D}$ +1.4° (*c* 0.92, MeOH).

Anal. Calcd for $C_6H_{12}SO_5$: C, 36.7; H, 6.1; S, 16.3. Found: C, 37.0; H, 6.1; S, 16.1.

Methyl 4-*O*-Acetyl-5-*O*-tosyl-α-L-sorbopyranoside (20). A solution of **5** (40.0 g) in 90% aqueous trifluoroacetic acid (40.0 ml) was stirred at room temperature for 30 min. The solution was then diluted with 200 ml of water and then the solvents were carefully removed under vacuum. Crude **20** was crystallized from a hexane–ethyl acetate mixture: yield 95% (31.0 g); mp 129–130°; $[\alpha]^{25}\mathrm{D}$ −72.9° (*c* 0.94, $CHCl_3$); nmr ($CDCl_3$) δ 1.89 (s, 3, OAc), 2.53 (s, 3, CH_3 of tosyl), 3.43 (s, 3, OCH_3), 3.66 (t, 1, $J_{6a,6e}$ = −11.0, $J_{6a,5}$ = 10.6 Hz, H-6a), 3.76 (d, 1, $J_{3,4}$ = 9.5 Hz, H-3), 3.84 (s, 2, H-1, H-1′), 4.03 (pd, 1, $J_{5,6e}$ = 5.6 Hz, H-6e), 4.64 (m, 1, H-5), 5.41 (t, 1, $J_{4,5}$ = ~9.5 Hz, H-4), 7.5–8.1 (m, 4, aromatic).

Anal. Calcd for $C_{16}H_{22}SO_9$: C, 49.2; H, 5.7; S, 8.2. Found: C, 49.3; H, 5.7; S, 8.3.

Acetate **21**: colorless oil; $[\alpha]^{25}\mathrm{D}$ −24.2° (*c* 1.05, $CHCl_3$); nmr ($CDCl_3$) δ 1.78, 2.06, 2.12 (3 s, 9, 3 OAc), 2.53 (s, 3, CH_3 of tosyl), 3.43 (s, 3, OCH_3), 3.71 (t, 1, $J_{5,6a}$ = 11.6, $J_{6a,6e}$ = −11.6 Hz, H-6a), 4.10 (pd, 1, $J_{5,6e}$ = 6.2 Hz, H-6e), 4.29 (d, 1, $J_{1,1'}$ = −11.6 Hz, H-1), 4.40 (d, 1, H-1′), 4.72 (m, 1, H-5), 5.08 (d, 1, $J_{3,4}$ = 10.6 Hz, H-3), 5.64 (pd, 1, $J_{4,5}$ = 8.6 Hz, H-4), 7.5–8.2 (m, 4, aromatic).

Anal. Calcd for $C_{20}H_{26}SO_{11}$: C, 50.6; H, 5.5; S, 6.8. Found: C, 50.7; H, 5.4; S, 6.9.

1,2,3,4-Tetra-*O*-acetyl-5-*O*-tosyl-α-L-sorbopyranose (23). Compound **20** (30.0 g) was dissolved in 70% aqueous trifluoroacetic acid (50 ml) and heated at 80° for 3 hr. The solvents were then carefully removed and the oily residue (**22**) was treated with a cold solution of acetic acid (40 ml), acetic anhydride (40 ml), and sulfuric acid (2.4 ml). The mixture was then refrigerated for 24 hr. Sulfuric acid was then neutralized with sodium acetate (10.0 g). The mixture was poured over ice and extracted with chloroform. The extract was washed with sodium bicarbonate, dried, and evaporated to dryness. The crude syrup was purified chromatographically: yield 39.0% (15.0 g); colorless syrup; $[\alpha]^{25}\mathrm{D}$ −35.2° (*c* 1.01, $CHCl_3$); nmr ($CDCl_3$) δ 1.83, 2.07, 2.11, 2.24 (4 s, 12, 4 OAc), 2.53 (s, 3, CH_3 of tosyl), 3.76 (t, 1, $J_{5,6a}$ = 11.6, $J_{6a,6e}$ = −11.6 Hz, H-6a), 4.16 (pd, 1, $J_{5,6e}$ = 6.1 Hz, H-6e), 4.65 (d, 1, $J_{1,1'}$ = −12.2, H-1), ~4.7 (m, 1, H-5), 7.81 (d, 1, H-1′), 5.30 (d, 1, $J_{3,4}$ = 10.0 Hz, H-3), 5.61 (pd, 1, $J_{4,5}$ = 8.5 Hz, H-4), 7.5–8.1 (m, 4, aromatic).

Anal. Calcd for $C_{21}H_{26}SO_{12}$: C, 50.2; H, 5.2; S, 6.4. Found: C, 50.4; H, 5.5; S, 6.6.

1,2,3,4-Tetra-*O*-acetyl-5-*S*-acetyl-5-thio-β-D-fructopyranose (24). A solution of **23** (2.9 g) and potassium thioacetate (2.9 g) in *N,N*-dimethylformamide (30 ml) was stirred and heated at 70° in a current of nitrogen for 30 hr. The reaction mixture was then poured into 500 ml of water and then extracted with ether. The extract was washed, dried, and evaporated to dryness. The crude oil was purified chromatographically using (9.5:0.5, v/v) benzene–ethyl acetate as eluent: yield 52% (1.2 g); mp 104–105° (hexane–ethyl acetate); $[\alpha]^{25}\mathrm{D}$ −116.7° (*c* 0.87, $CHCl_3$); nmr ($CDCl_3$) δ 2.01, 2.11, 2.18, 2.24 (4 s, 12, 4 OAc), 2.47 (s, 3, SAc), 4.01 (pd, 1, $J_{5,6e}$ = 1.5, $J_{6e,6a}$ = −13.3 Hz, H-6e), ~4.4 (m, 2, H-5, H-6a), 4.64 (d, 1, $J_{1,1'}$ = −12.0 Hz, H-1), 4.82 (d, 1, H-1′), 5.53 (d, 1, $J_{3,4}$ = 10.3 Hz, H-3), 5.65 (pd, 1, $J_{4,5}$ = 3.8 Hz, H-4).

Anal. Calcd for $C_{16}H_{22}SO_{10}$: C, 47.3; H, 5.5; S, 7.9. Found: C, 47.4; H, 5.5; S, 8.0.

Deacetylation of **24** with sodium methoxide in methanol gave **1**.

1,2-*O*-Isopropylidene-5-*O*-tosyl-α-L-sorbose (26). Compound **25** (30.0 g) and tosyl chloride (27.0 g) were added to dry pyridine (200 ml), and the solution was kept at 0° for 2 days. The reaction mixture was then poured into cold water and extracted with chloroform. The extract was dried and evaporated to dryness. The residue crystallized immediately and this mass was then cooled and stirred in absolute ether (50 ml). After further cooling, the crystalline product was removed by filtration: yield 20.0 g (39%); mp 130–131° dec (ethanol); $[\alpha]^{25}D$ −52.1° (c 1.11, $CHCl_3$); nmr (pyridine-d_5) δ 1.61 (s, 6, isopropylidene), 2.29 (s, 3, CH_3 of tosyl), 3.9–4.8 (m, 6, H-1, H-1′, H-3, H-4, H-6a, H-6e), 5.06 (pt, 1, $J_{4,5} \simeq J_{5,6a} \simeq 9$, $J_{5,6e} \simeq 7$ Hz, H-5), 7.5–8.4 (m, 4, aromatic).

Anal. Calcd for $C_{16}H_{22}SO_8$: C, 51.3; H, 5.9; S, 8.6. Found: C, 51.5; H, 5.9; S, 8.6.

Acetylation of **26** with acetic anhydride and pyridine give **27**: mp 109–110° dec (hexane–ethyl acetate); $[\alpha]^{25}D$ −27.5° (c 1.12, $CHCl_3$); nmr ($CDCl_3$) δ 1.44, 1.50 (2 s, 6, isopropylidene), 1.83, 2.10 (2 s, 6, 2 OAc), 2.53 (s, 3, CH_3 of tosyl), 4.62 (m, 4, H-1, H-1′, H-6a, H-6e), 4.73 (pt, 1, $J_{4,5} = J_{5,6a} = 9.1$, $J_{5,6e} = 7.3$ Hz, H-5), 5.10 (d, 1, $J_{3,4} = 10.1$ Hz, H-3), 5.60 (pd, 1, H-4), 7.5–8.1 (m, 4, aromatic).

Anal. Calcd for $C_{20}H_{26}SO_{10}$: C, 52.4; H, 5.7; S, 7.0. Found: C, 52.7; H, 5.8; S, 7.1.

3,4-Di-*O*-acetyl-5-*S*-acetyl-1,2-*O*-isopropylidene-5-thio-β-D-fructopyranose (28). To a solution of **27** (10.0 g) in dry *N,N*-dimethylformamide (200 ml), potassium thioacetate (10.0 g) was added, and the mixture stirred and heated at 75° for 70 hr in a current of nitrogen. The reaction mixture was then poured into cold water and the solid filtered off. Recrystallization from hexane–ethyl acetate gave 6.5 g (82%) of **28**: mp 74–75°; $[\alpha]^{25}D$ −86.7° (c 0.56, $CHCl_3$); nmr ($CDCl_3$) δ 1.45, 1.52 (2 s, 6), isopropylidene, 2.02, 2.15 (2 s, 6, 2 OAc), 2.45 (s, 3, SAc), 3.85 (m, 1, H-6a), 4.06 (s, 2, H-1, H-1′), 4.4 (m, 1, H-5), 4.55 (pd, 1, $J_{5,6e} = 2.1$, $J_{6a,6e} = -11.5$ Hz, H-6e), 5.32 (d, 1, $J_{3,4} = 10.8$ Hz, H-3), 5.70 (pd, 1, $J_{4,5} = 4.2$ Hz, H-4).

Anal. Calcd for $C_{15}H_{22}SO_8$: C, 49.7; H, 6.1; S, 8.9. Found: C, 49.9; H, 6.2; S, 9.1.

3,4-Di-*O*-acetyl-5-*S*-acetyl-5-thio-β-D-fructopyranose (29). A solution of **28** (6.0 g) in 90% aqueous trifluoroacetic acid (40 ml) was kept under nitrogen for 3 hr at room temperature. The solvents were then carefully removed under vacuum to give the crude product, 5.0 g (24%). After recrystallization from ethyl acetate–ethyl ether, pure **29** was obtained: mp 118–120°; $[\alpha]^{25}D$ −68.9° (c 0.75 $CHCl_3$).

Anal. Calcd for $C_{12}H_{18}SO_8$: C, 44.7; H, 5.6; S, 10.0. Found: C, 44.6; H, 5.8; S, 9.9.

Deacetylation of crude **29** gave **1**.

1,2,3,4,6-Penta-*O*-acetyl-5-thio-α-D-fructofuranose (30) and 1,2,3,4,6-Penta-*O*-acetyl-5-thio-β-D-fructofuranose (31). Compound **1** (0.30 g) was acetylated with acetic anhydride and pyridine. Following evaporation of the solvents, the crude mixture of pentaacetates was separated chromatographically using hexane–ethyl acetate (9:1, v/v) as eluent. 0.13 g of **30** and 0.08 g of **31** were obtained.

30: mp 107–108°; $[\alpha]^{25}D$ +153.8° (c 0.67, $CHCl_3$); nmr ($CDCl_3$) δ 2.15 (s, 15, 5 OAc), 3.90 (q, 1, $J_{4,5} = 6.4$, $J_{5,6} = 6.9$, $J_{5,6'} = 6.6$ Hz, H-5), 4.21 (pd, 1, $J_{6,6'} = -11.5$ Hz, H-6), 4.53 (pd, 1, H-6′), 4.61 (d, 1, $J_{1,1'} = -12.2$ Hz, H-1), 4.84 (d, 1, H-1′), 5.56 (t, 1, $J_{3,4} = 6.4$ Hz, H-4), 6.06 (d, 1, H-3).

Anal. Calcd for $C_{16}H_{22}SO_{10}$: C, 47.3; H, 5.5; S, 7.9. Found: C, 47.5; H, 5.7; S, 7.8.

31: mp 70–73°; $[\alpha]^{25}D$ −91.3° (c 0.87, $CHCl_3$); nmr ($CDCl_3$) δ 2.15 (s, 15, 5 OAc), 3.66 (q, 1, $J_{4,5} = 6.0$, $J_{5,6} = 7.0$, $J_{5,6'} = 6.6$ Hz, H-5), 4.20 (pd, 1, $J_{6,6'} = -11.0$ Hz, H-6), 4.46 (pd, 1, H-6′), 4.64 (d, 1, $J_{1,1'} = -12.1$ Hz, H-1), 4.77 (d, 1, H-1′), 5.65 (pd, 1, $J_{3,4} = 7.5$ Hz, H-4), 5.80 (d, 1, H-3).

Anal. Calcd for $C_{16}H_{22}SO_{10}$: C, 47.3; H, 5.5; S, 7.9. Found: C, 47.5; H, 5.7; S, 8.2.

1,2,3,4,6-Penta-*O*-acetyl-5-thio-β-D-fructofuranose (31). Compound **1** (0.60 g) was heated with acetic anhydride (7 ml) and sodium acetate (0.5 g) for 2 hr. The mixture was then poured into ice and water and extracted with ether. The extract was dried and evaporated. The crude product was purified chromatographically; yield 20% (0.25 g).

1,3,4,6-Tetra-*O*-acetyl-5-*S*-acetyl-5-thioketo-D-fructose (32). Compound **1** (0.50 g) was stirred under nitrogen at room temperature for 24 hr with acetic anhydride (5 ml) containing zinc chloride (0.05 g). The solution was then poured into ice and water and extracted with ether. The extract was dried, and evaporated to dryness. Upon treatment with ethanol (1 ml), **32** crystallizes after several hours in a 25% yield (0.20 g): mp 91–92°; $[\alpha]^{25}D$ +14.1° (c 0.501, $CHCl_3$); nmr ($CDCl_3$) δ 2.13, 2.16, 2.25, 2.31 (4 s, 12, 4 OAc), 2.45 (s, 3, SAc), 4.0–4.7 (m, 3, H-5, H-6, H-6′), 4.83 (d, 1, $J_{1,1'} = -18.0$ Hz, H-1), 5.11 (d, 1, H-1′), 5.83 (m, 2, H-3, H-4).

Anal. Calcd for $C_{16}H_{22}SO_{10}$: C, 47.3; H, 5.5; S, 7.9. Found: C, 47.5; H, 5.6; S, 8.0.

Registry No.—**1**, 53821-50-4; **4**, 35013-06-0; **5**, 35013-04-8; **6**, 53821-51-5; **7**, 53821-52-6; **8**, 53821-53-7; **13**, 53821-54-8; **14**, 53821-55-9; **15**, 53821-56-0; **16**, 53821-57-1; **17**, 53821-58-2; **18**, 53821-59-3; **19**, 53821-60-6; **20**, 53821-61-7; **21**, 53821-62-8; **23**, 53821-63-9; **24**, 53821-64-0; **25**, 18604-34-7; **26**, 53821-65-1; **27**, 53821-66-2; **28**, 53821-67-3; **29**, 53821-68-4; **30**, 53821-69-5; **31**, 53821-70-8; **32**, 53821-71-9; potassium thioacetate, 10387-40-3.

References and Notes

(1) Journal Paper No. 5609, Purdue Agricultural Experiment Station, Lafayette, Ind.
(2) Presented before the Great Lakes Regional Meeting of the American Chemical Society, West Lafayette, Ind., June 1974.
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13β-Hydroxystylopine. Structure and Synthesis

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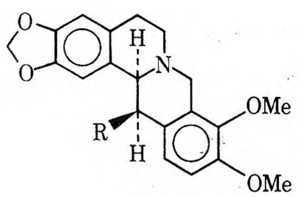
The isolation of 13β-hydroxystylopine (**2**, R = OH) is described and the elucidation of its structure by spectral methods is confirmed by a synthesis of the alkaloid.

Despite the large number of alkaloids belonging to the protoberberine group, most of which differ from each other in the number and placement of various oxygen functions on the two aromatic rings, ophiocarpine (**1**, R = OH) is the only alkaloid of this group containing a 13-hydroxyl group that has been reported.[2] Since 13-oxygenated protoberberines are established as the biosynthetic precursors of the phthalide–isoquinoline alkaloids[3] and are potential intermediates in the formation of other alkaloid families, such as the rhoeadines,[4] it is somewhat surprising to find that 13-hydroxylated protoberberines are not of more widespread occurrence.

In connection with a study of the biosynthesis of ophiocarpine, we have reinvestigated the alkaloids of *Corydalis ophiocarpa,* one of the two plants in which this alkaloid is reported to occur.[5]

Chromatography of the crude alkaloid fraction over alumina in benzene–ethyl acetate gave (−)-tetrahydroberberine (**1**, R = H), (−)-stylopine (**2**, R = H), and a fraction



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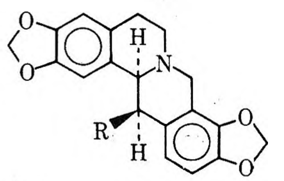

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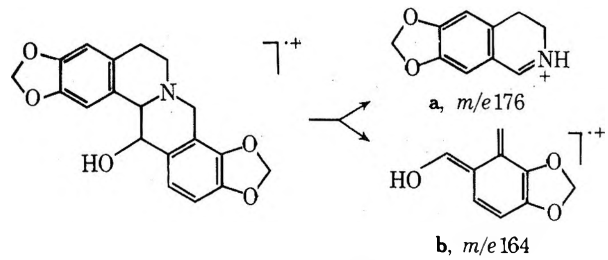
eluted with benzene–ethyl acetate and ethyl acetate:ethyl acetate–methanol (9:1) which contained a mixture of three components. Preparative layer chromatography of the mixture on silica gel impregnated with 5% K_2CO_3 afforded (−)-13β-hydroxystylopine (**2**, R = OH), which crystallized as colorless prisms from ethanol, mp 214°, $[\alpha]_{589}$ −259°. The molecular formula $C_{19}H_{17}NO_5$ for this base was derived initially by high-resolution mass spectral analysis and was subsequently supported by the results of combustion analysis. Classification of the new alkaloid as a member of the protoberberine series was readily apparent from examination of its ^1H nmr and mass spectral features and elucidation of its structure relied on many parallel comparisons which could be made with its companion alkaloid, ophiocarpine.

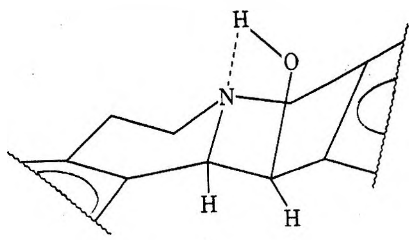
The 100-MHz ^1H nmr spectrum (Figure 1) contained four proton signals in the aromatic region as two singlets at δ 6.80 and 6.02 and a pair of doublets at 6.95 and 6.79 (J = 8.0 Hz) and established the substitution pattern on rings A and D. These signals are accompanied by a two-proton singlet at δ 6.00 and a two-proton "quartet" at δ 5.94 which we assigned to two methylenedioxy groups in which the hydrogens of one of these groups exhibit chemical-shift nonequivalence. These observations and the general appearance of the spectrum suggested that the alkaloid was a protoberberine base related to stylopine. Further evidence in support of this contention was the occurrence of the C-8 methylene group as an AB system at δ 4.07 and 3.53 (J = 16 Hz). This significant difference in chemical shift is indicative of a 9,10-substituted protoberberine in which the presence of a 9-oxygen function enhances the nonequivalence of the C-8 methylene hydrogens by selective deshielding of the more proximate quasiequatorial C-8 β hydrogen.[6]

Placement of the fifth oxygen function as a hydroxyl group at the C-13 position was suggested by the occurrence of a broadened singlet at δ 4.80 ($W_{1/2}$ = 8.0 Hz) in the nmr spectrum of the alkaloid which sharpened upon addition of D_2O ($W_{1/2}$ = 4.0 Hz). Support for this assignment was provided by the mass spectrum which displayed prominent ions at *m/e* 176 (**a**) and *m/e* 164 (**b**) resulting from separate cleavage pathways leading to the characteristic retro-Diels–Alder fragmentation of ring C of the protoberberine system. Confirmation of the presence of a hydroxyl group in



the alkaloid was provided by the formation of an *O*-acetyl derivative ($\nu_{C=O}$ 1730 cm^{-1}).

The infrared spectrum of the alkaloid exhibited a broad hydroxyl absorption at 3500 cm^{-1} which proved to be concentration independent in $CHCl_3$ solution over the range 10^{-3}–10^{-4} *M* and was thus in keeping with an intramolecular OH–H hydrogen bond.[7] The infrared spectrum also showed multiple absorption bands (Bohlmann bands) in the region 2700–2800 cm^{-1} and indicated the predominant conformation of the alkaloid was represented by a *trans*-quinolizidine structure.[8] On the basis of a *trans*-quinolizidine structure, the existence of an intramolecular hydrogen-bonded hydroxyl implies that the 13-hydroxyl is trans to H-14 as indicated in the partial structure **3**. The opposite stereochemistry at C-13 cannot lead to an intramolecular hydrogen bond between a hydroxyl at this position and the nitrogen. The dihedral angle between H-13 and H-14 in the partial structure **3** is *ca.* 60° and it is known in related systems to give rise to $J_{13,14}$ = 2–4 Hz.[9] While the broad singlet of the H-13 resonance observed in the spectrum of the alkaloid is in conformity with this stereochemical assignment, the spectrum (Figure 2) of its *O*-acetyl derivative



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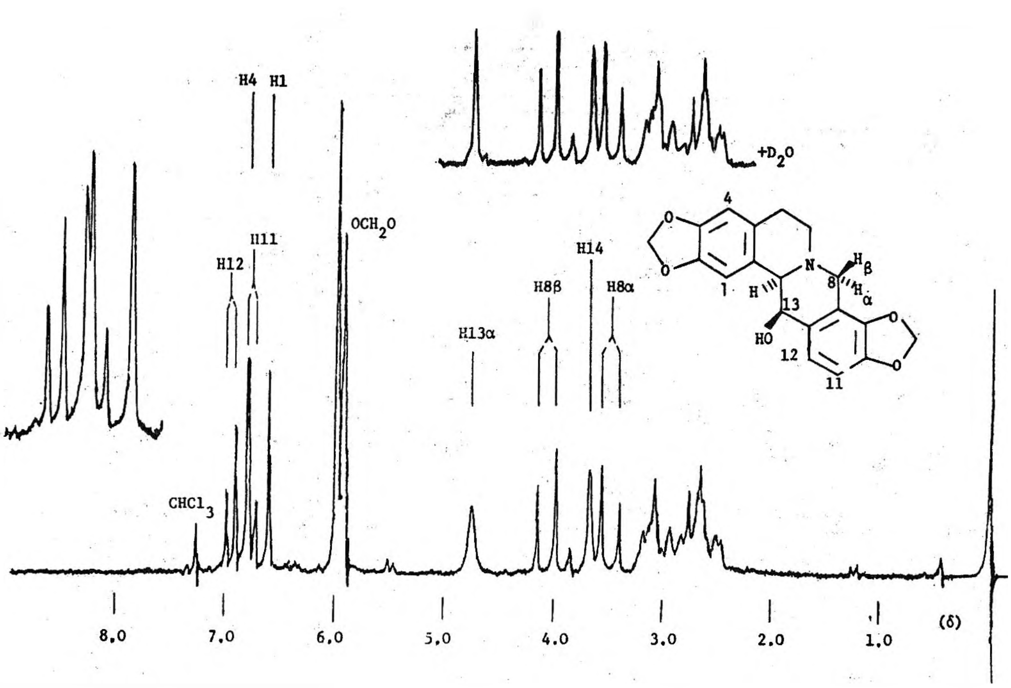

Figure 1. ^1H nmr spectrum of 13β-hydroxystylopine.

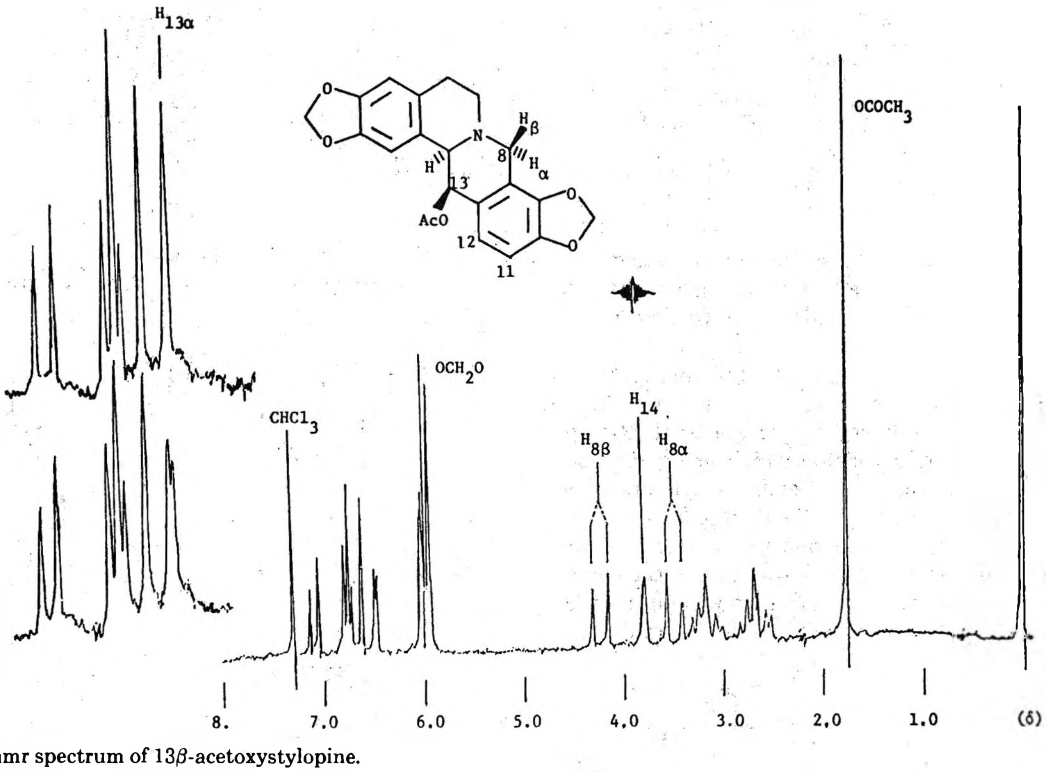

Figure 2. ^1H nmr spectrum of 13β-acetoxystylopine.

2 (R = OAc) reveals this more clearly in that the H-13 signal appears as a doublet at δ 6.46 (J = 3.0 Hz). Confirmation of the assignment of the latter signal was obtained by a spin-decoupling experiment in which irradiation of the H-14 signal at δ 3.78 resulted in collapse of the H-13 resonance to a singlet (Figure 2). A somewhat distinctive feature of the spectrum of the O-acetyl compound was the occurrence of the acetate methyl resonance at abnormally high field (δ 1.76). A similar situation is observed in the spectrum of O-acetylophiocarpine in which the acetate methyl shift is at δ 1.78 whereas the acetate methyl shift in O-acetyl-13-epiophiocarpine appears at a more typical value of δ 2.23. It has been pointed out by Ohta and coworkers[10] that the acetyl group in O-acetylophiocarpine is shielded by ring D and a similar situation obviously obtains in the analogous 13β-acetoxystylopine.

With the foregoing spectral evidence supporting the structure of the alkaloid as 13β-hydroxystylopine it remained to establish its absolute configuration. Tetrahydroberberines belonging to the 14R series exhibit a negative ORD spectrum from 600 to 240 nm.[11] Before applying this method to 13β-hydroxystylopine it was necessary to establish what effect the introduction of a 13β-hydroxyl group in this ring system would have on the ORD spectrum. Examination of the ORD spectrum of (−)-ophiocarpine showed a plain negative dispersion curve from 600 to 250 nm and indicated that when the new chiral center at C-13 is a β-hydroxyl the sign of curve is not affected. Consequently the

1

EXPERIMENTAL

General Methods

Melting points were determined on a Thomas-Hoover Mel-Temp apparatus and are uncorrected. Infrared spectra were determined on Perkin-Elmer models 237 and 621 recording spectrophotometers. Nuclear magnetic resonance spectra were determined at 60 MHz on Varian A-60 and T-60 instruments, at 90 MHz on the Bruker HFX-10, and at 100 MHz on the JEOL MH-100 spectrometer. Chemical shifts are reported in δ-units relative to internal TMS. Ultraviolet spectra were recorded on Beckman DB-G and Cary Model 14 recording spectrophotometers. The ORD spectra were obtained on a Durrum-Jasco ORD-UV/5.

Low resolution mass spectra were recorded on a DuPont 21-490 and an AEI MS 902 instruments. High resolution spectra were obtained on the MS-902 at the Research Triangle Institute Center for Mass Spectrometry.

Elemental analyses were performed by MHW Laboratories, Garden City, Michigan.

Chromatography was routinely performed on neutral Woelm Aluminum Oxide, grade III, or W. R. Grace silica gel unless otherwise indicated. Thin layer (0.25 mm) and preparative layer (1 mm) chromatography using aluminum oxide, silica gel or silica gel-5% potassium carbonate was used. Various solvent systems and multi-development techniques are noted. Visualization was achieved by ultraviolet light and by spraying with iodoplatinic acid or ceric ammonium sulfate in sulfuric acid.

All solvents were routinely redistilled prior to use.

Isolation of the Alkaloids from Corydalis Ophiocarpa plants.

Corydalis ophiocarpa plants were grown in the Duke University Phytotron from seeds obtained from the Ipswich Seed Co., Great Britain. Top growth from the plants was periodically trimmed and dried. The dried material *ca*. 9 Kg was thoroughly ground in a Waring blender with 95% ethanol and filtered. The filter cake was extracted with ethanol in a Soxhlet. The combined extracts were concentrated *in vacuo*, diluted with a large volume of hot water, and acidified with concentrated hydrochloric acid to a Congo Red endpoint. The acidic extract was allowed to stand at room temperature for 2 days and

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filtered through Celite. The filtrate was washed twice with ether and basified with concentrated ammonium hydroxide producing a flocculent precipitate. This aqueous portion was extracted several times with chloroform and emulsified material was readily separated by vacuum filtration through a layer of Celite. The combined organic extracts were washed twice with water, dried over magnesium sulfate, and solvent removed *in vacuo* to give 21.4 gm (0.23%) of crude alkaloids as a dark brown foam.

Purification by Column and Preparative Layer Chromatography

The crude alkaloids (12 g) in chloroform were evaporated over alumina (100 g) and thoroughly dried under high vacuum. The alkaloid containing alumina was then placed on a wet-packed column of alumina (1.5 kg) in benzene and eluted successively with the linear gradients: benzene - EtOAc (4 1), EtOAc-EtOAc/MeOH (9:1, 2 1) EtOAc/MeOH (9:1)-EtOAc/MeOH (4:1, 2 1). A total of 450 fractions of 20 ml were collected and every tenth fraction was examined by tlc and pooled according to the results as follows: Fr. 1-50 (trace), Fr. 51-89 unknown base (115 mg), Fr. 90-114 (trace), Fr. 115-120, (-)-stylopine (233 mg), Fr. 121-134, mixture of (-)-stylopine and (-)-tetrahydroberberine (1.185 g), Fr. 135-239, mixture of (-)-ophiocarpine, protopine and (-)-13β-hydroxystylopine (7.0 g), Fr. 240-450, unknown alkaloids (1.02 g). Preparative layer chromatography (plc) of Fr. 121-134 on silica using a $CHCl_3$-EtOAc (9:1) and triple development gave 300 mg pure (-)-stylopine mp 195-197 (lit.[20] mp 202°) and 1.19 g (-)-tetrahydroberberine, mp 131-132° (lit.[21] mp 135°). Full characterization by nmr, ms, and ir supported the identification of these alkaloids.

A 300 mg sample of the mixture of alkaloids contained in Fr. 135-239 was separated by plc on SiO_2-5% K_2CO_3 by triple development with benzene - EtOAc (4:1) giving 125 mg (-)-ophiocarpine, mp 187-188 (lit.[5] mp 188°), 81 mg protopine, mp 202-204 (lit.[14] 207-208°), both of which were fully characterized by their nmr, ms and ir spectral properties, and 73 mg of a new base, (-)-13β-hydroxystylopine (2, R=OH), mp 213-215°C, $[\alpha]_D$ - 259° (c 0.1, $CHCl_3$); R_f 0.72; ir λ_{max} ($CHCl_3$) 3500 cm^{-1} (w, OH) (concentration independent over the range 10^{-3} to 10^{-4}M), 2800-2700 cm^{-1} (Bohlmann bands, *trans*-quinolizidine); mass spectrum m/e (rel intensity) 339 (9), 176 (100), 164 (22); Calcd for $C_{19}H_{17}NO_5$, 339.1106; Found: 339.1113; nmr (100 MHz) ($CDCl_3$) δ 6.95 (d, 1, J=8 Hz), (C-12 H), 6.80 (s, 1, C-4 H), 6.79 (d, 1, J=8 Hz, C=11 H), 6.62 (s, 1, C-1 H), 6.00 (s, 2, OCH_2O), 5.94 (m, 2, OCH_2O), 4.76 (bs, 1, $W_{1/2}$=8 Hz, C-13H), addition of D_2O

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sharpened this to a singlet with $W_{1/2}$=4 Hz, 4.07 (d, 1, J-16 Hz, C-8βH, 3.72 (s, 1, C-14H, unaffected by D_2O), 3.53 (d, 1, J-16 Hz, C-8αH); ORD (c 0.1 95% EtOH) $[\alpha]_{350}$ - 1380°, $[\alpha]_{300}$ - 2400° (trough), $[\alpha]_{292}$ - 2340° (peak), $[\alpha]_{260}$ - 6100°, $[\alpha]_{240}$ - 12,100° (trough), $[\alpha]_{233}$ - 11,500° (peak), $[\alpha]_{226}$ - 13, 300°.

Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.04; N, 4.12. Found: C, 67.23; H, 5.04; N, 3.84.

(-)-13-Hydroxystylopine Acetate (2, R=OAc). 70.0 mg (0.2 mmole) of the base was dissolved in dry pyridine (1 ml) under nitrogen and freshly distilled acetic anhydride (2 ml) was added in one portion. A solid slowly formed and after 4 hours it was removed by filtration, washed with cold water, and air dried to give 41.0 mg. The filtrate was diluted with water (10 ml) and basified with satd. Na_2CO_3 until CO_2 evolution had ceased. This was washed with $CHCl_3$ (2 x 20 ml), the combined organic layers were washed with H_2O (2 x 50 ml), satd. NaCl (1 x 50 ml), dried (Na_2SO_4), and solvent removed *in vacuo* to give a yellow oil containing pyridine. The tlc (SiO_2, $CHCl_3$-EtOAc 9:1, 2x) indicated that the above solid and yellow oil were indentical, R_f 0.75. The yellow oil was dissolved in $CHCl_3$ and passed through a short column of alumina. The acetate was immediately eluted and this was combined with the above solid to give 69.0 mg (88%) of the acetate. Recrystallization from CH_2Cl_2-pet. ether gave fine needles; mp 237-239°C (sealed tube); ir λ_{max} ($CHCl_3$) 1730 cm^{-1} (C=O), 1200 cm^{-1} (COC); nmr (100 MHz) ($CDCl_3$) δ 7.09 (d, 1, J=8 Hz, C-11H), 6.76 (d, 1, J=8 Hz, C-12H), 6.74 (s, 1, C-4H), 6.60 (s, 1, C-1H), 6.46 (d, 1, J=3 Hz, C-13H) irradiation at 3.78 collapsed this to a singlet, 6.00 (q, 2, J=1.5 Hz, OCH_2O), 5.92 (s, 2, OCH_2O), 4.24 (d, 1, J=16 Hz, C-8βH), 3.78 (bs, 1, C-14H), 3.52 (d, 1, J=16 Hz, C-8αH), *ca*. 3.20 (m, 2, C-5H or C-6H), 2.68 (m, 2, C-5H or C-6H), 1.76 (s, 3, acetate CH_3).

Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.14; H, 5.02; N, 3.67. Found: C, 66.19; H, 4.95; N, 3.45.

Dihydrocoptisine-N-metho chloride (9). The following is a modification of the method of Haworth and Perkin.[16] Protopine (2.83 mmole) was refluxed for 20 min under a dry N_2 atmosphere in freshly distilled phosphoryl chloride (5 ml). Solvent was removed *in vacuo* and the residue recrystallized from water to give a yellow solid. This was filtered, washed with a small amount of 10% HCl, and air dried. Recrystallization from MeOH-EtOAc gave 660 mg (63%) of dihydrocoptisine -N-methochloride (9) as yellow crystals: mp 193-195°C (lit.[16] 215°C); uv λ_{max}

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(95% EtOH) 373 nm (ε 21,000), 356 (ε 23,500), 343 sh (ε 18,000), 305 (ε 6950), 255 (ε 6840); (lit.[20] 375 (ε 21,400), 357 (ε 24,000), 343 sh (ε 18,299), 306 (ε 7590), 255 (ε 6910).

Dihydrocoptisine (7). 111.3 mg, (0.3 mmole) prepared from protopine was placed in a sublimation apparatus and the system evacuated to 10^{-3} mm. This was placed in a metal bath at 270°C for one minute and a yellow solid immediately condensed on the cooler parts of the system. After cooling to room temperature *in vacuo* the product was dissolved in warm benzene, insoluble material removed by filtration, and the filtrate stripped *in vacuo*. This was repeated an additional two times and the benzene soluble portions were combined. The product was chromatographed on alumina (Woelm, II, neut.) in benzene and eluted with benzene-ethyl acetate (9:1). The eluent was collected under N_2 and solvent was removed *in vacuo* to give 179.0 mg (64%) of dihydrocoptisine (7) as a yellow solid: mp 175-179°C (lit[15] 194-196°C); R_f 0.84 (SiO_2, $CHCl_3$-EtOAc 1:1); nmr (60 MHz) ($CHCl_3$) δ 7.20 (s, 1, C-1H), 6.67 (d, 1, J=8 Hz, C-12H), 6.61 (s, 1, C-4H), 6.52 (d, 1, J=8 Hz, C-11H), 6.02 (s, 1, C-13H), 5.97 (s, 2, OCH_2O), 5.95 (s, 2, OCH_2O), 4.28 (s, 2, C-8H), 3.04 (m, 4, C-5H and C-6H).

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13-Hydroxy-2,3,9,10-bismethylenedioxy-5,6-dihydro-dibenzo[a,g]quinolizine (13-Hydroxy-coptisine) (6). A standard solution of m-chloroperbenzoic acid was prepared by dissolving 192.7 mg (1.11 mmole) in CH_2Cl_2 (25 ml) under N_2 and the solution cooled to -78°C. The peracid was slowly added dropwise from a burette and progress of the reaction was monitored by tlc. Dihydrocoptisine could not be detected after the addition of 1.2 equivalents of peracid. The reaction mixture was warmed to room temperature, washed with satd. NaCl (30 ml), dried ($MgSO_4$), and solvent removed *in vacuo* to give a yellow-orange solid. Recrystallization from 95% EtOH containing several drops of 1% HCl gave 159.4 mg (78%) of the phenol as small orange needles: mp 285°C; uv λ_{max}(95% EtOH) 457 (ε 8,493), 358 (20,692), 345 (19,879), 288 infl (10,451), 237 (28,614).

Anal. Calcd for $C_{19}H_{14}NO_5Cl$: C, 61.44; H, 3.79; N, 3.77. Found: C, 61.21; H, 3.84; N, 3.12.

(±)-13β-Hydroxystylopine (2, R=OH). The phenol (8) (74.2 mg, 0.2 mmole) was dissolved in 60 ml of EtOH-H_2O (5:1) at room temperature and $NaBH_4$ (30 mg) was added under N_2. After 1 hr an additional 30 mg of borohydride was added and the mixture was stirred overnight before carefully acidifying with 10% HCl.

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The residue obtained upon distillation of the solvent was diluted with H_2O (100 ml), washed with benzene (50 ml), and the acidic extract was basified with 6N KOH (pH 9). The precipitated solid was taken up in $CHCl_3$ (2 x 60 ml), the combined organic extracts were washed with H_2O (60 ml), NaCl soln. (60 ml), dried ($MgSO_4$), and solvent removed *in vacuo* to give 47 mg (69%) of a light yellow foam. Recrystallization from 95% EtOH gave (±)-13β-Hydroxystylopine as fine white needles, mp 219-221° (dec), with chromatographic (R_f 0.58, SiO_2-5% K_2CO_3, CHCl,EtOAc 1:1 1x); R_f 0.47, SiO_2-5% K_2CO_3, C_6H_6-EtOAc 4:1 2x) and spectral properties (ms, nmr) identical with naturally occurring material.

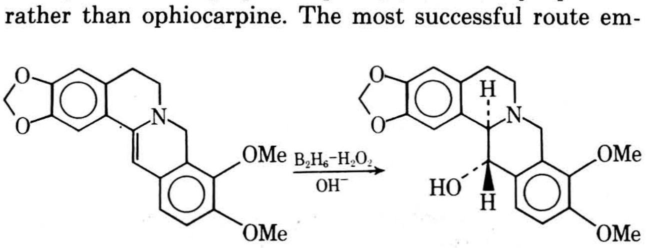
Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.04; N, 4.12. Found: C, 67.20; H, 5.03; N, 3.94.

(±)-13β-Acetoxystylopine

(±)-13β-Hydroxystylopine (24.5 mg, 0.07 mmole) was dissolved in dry pyridine (1 ml) and freshly distilled acetic anhydride (2 ml) and stirred under N_2 for 4 hrs. Work-up in the usual manner gave 27.4 mg (99%) of the acetate as a yellow oil. Recrystallization from CH_2Cl_2-pet. ether gave small plates, mp 242-243° (dec), which proved indistinguishable chromatographically R_f 0.75, SiO_2, $CHCl_3$-EtOAc 9:1v/v, 2x) from (-)-13β-acetoxystylopine.

plain negative dispersion curve subsequently determined for 13β-hydroxystylopine served to establish its absolute stereochemistry as 13*R*,14*R* as depicted in structure **2** (R = OH).

Final verification of the structure of 13β-hydroxystylopine has been achieved by a stereoselective synthesis from protopine. Although there have been several synthetic approaches described to ophiocarpine which are potentially adaptable to the synthesis of 13β-hydroxystylopine they suffer from certain disadvantages. The procedure of Govindachari[12] is both lengthy and nonstereoselective while Elliott's[13] method of hydroboration–oxidation of the enamine **4** provides 13-epiophiocarpine (**5**) as the major product rather than ophiocarpine. The most successful route em-

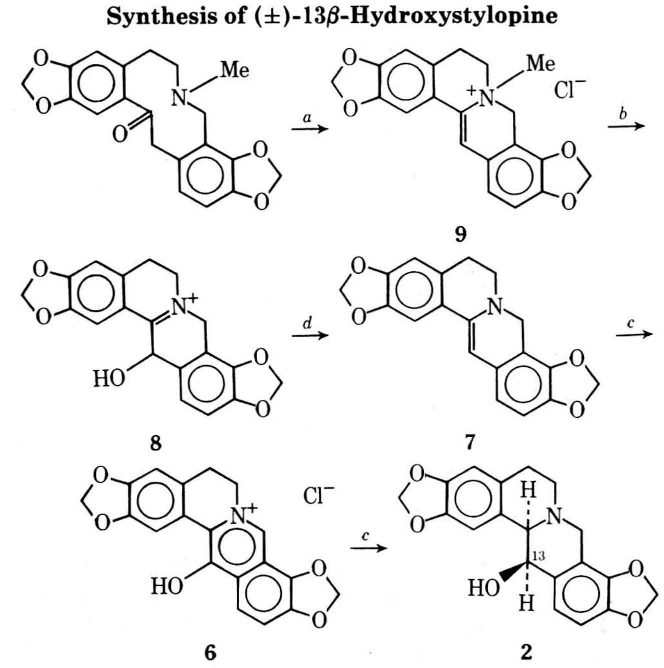


4 **5**

ploys the phenol–betaine, 13-hydroxyberberinium chloride (*cf*. **6**), which is obtained from berberine as first described by Pyman.[14] Reduction of 13-hydroxyberberinium chloride with sodium borohydride is reported[15] to proceed in a highly stereoselective manner to afford (±)-ophiocarpine.

It appeared that it might be possible to devise a more convenient route to the analogous phenol–betaine **6** required for the synthesis of 13β-hydroxystylopine than by employing the original procedure of Pyman. Our approach was based upon the rationale that the enamine **7** should

Scheme I
Synthesis of (±)-13β-Hydroxystylopine



^{a} $POCl_3$. ^{b} Δ *in vacuo*. ^{c} *m*-Chloroperbenzoic acid. ^{d} O_2. ^{e} $NaBH_2$.

react with an electrophilic oxygen, such as a peracid, to afford the hydroxylated iminium salt **8**, which should undergo a facile oxidation to the required phenol–betaine **6** (see Scheme I).

Dihydrocoptisine (**7**) required for the synthesis was obtained by the procedure of Haworth and Perkin[16] by treatment of protopine with $POCl_3$ followed by pyrolysis of the resulting salt **9** *in vacuo*.[17] Addition of 1.2 equiv of *m*-chloroperbenzoic acid to dihydrocoptisine at −78° led to rapid oxidation as evidenced by the disappearance of starting material when monitored by tlc.[18] The stoichiometry suggests that the iminium salt 8 is formed initially in this reaction. However, after allowing to come to room temperature, the product isolated in 78% yield after crystallization is 13-hydroxycoptisine chloride (**6**) as yellow-orange crystals, mp 285°. The latter is presumably formed by a highly efficient air oxidation of **8**. Reduction of **6** with sodium borohydride in aqueous ethanol gave (±-13β-hydroxystylopine, mp 219–220°, identical in its chromatographic and spectral properties with the natural alkaloid.

Careful examination of the borohydride reduction failed to show the presence of any of the 13α-hydroxy epimer of 2 (R = OH) in this reaction. The high stereoselectivity of this reduction is presumably a simple consequence of steric factors governing "approach control" of the borohydride. Alternatively, similar arguments can be made assuming a product-like transition state where, in the case of the 13α-hydroxy isomer, it is destabilized by nonbonded interactions of the C-13α hydroxyl with the C-1 hydrogen. Furthermore, if a product-like transition state is involved, the 13β-hydroxy system may gain additional stabilization by the development of an intramolecular hydrogen bond (*cf.* **3**) with the incipient electron pair on nitrogen.

Acknowledgments. We are indebted to the Duke University Research Council and the National Science Foundation (GP 9436) for grants in support of this work. Dr. David Rosenthal and Mr. Fred Williams, Research Triangle Mass Spectrometry Center, are thanked for providing the high-resolution mass spectral data. The Duke University Phytotron Facility is supported by National Science Foundation Grants GB 19634 and GB 28950 and we gladly acknowledge the use of this facility.

Registry No.—(−)-**2** (R = OH), 53777-76-7; (−)-**2** (R = OAc), 53777-77-8; (±)-**2** (R = OH), 53833-90-2; (±)-**2** (R = OAc), 53798-26-8; 6, 53798-64-4; **7**, 53777-78-9; 8, 53798-65-5; **9**, 53777-79-0; protopine, 130-86-9; phosphoryl chloride, 10025-87-3; *m*-chloroperbenzoic acid, 937-14-4.

Miniprint Material Available. Full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-75-644.

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(1) This work was supported through a Career Development Award (GM 42342) and a research grant from the National Science Foundation (GP-9436).
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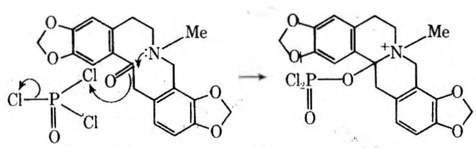
(17) It would seem that the conversion of protopine to **9** proceeds *via* the dichlorophosphate ester i reflecting the known propensity of this system to undergo transannular cyclization.



i

(18) The study of the oxidation of enamines with peracids appears not to have been investigated.[19] Preliminary experiments on the peracid oxidation of simple enamines have indicated that the conversion $COCH_2$ to COCHOH may be accomplished through this reaction (E. J. Rauckman, unpublished observation).
(19) A referee has drawn our attention to the peracid oxidation of steroidal $\Delta^{17(20)}$-20-enamines and enamides (J. Schmidt-Thomé, and W. Fritsch, *Justus Liebigs Ann. Chem.*, **622**, 27 (1963); W. Fritsch J. Schmidt-Thomé, and W. Haede, *Chem. Ber.*, **96**, 68 (1963)).
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The Isolation and Structural Elucidation of Bruceantin and Bruceantinol, New Potent Antileukemic Quassinoids from *Brucea antidysenterica*[1]

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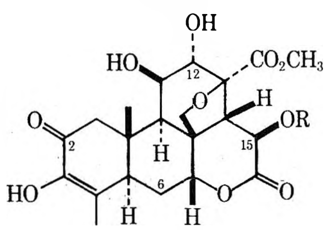
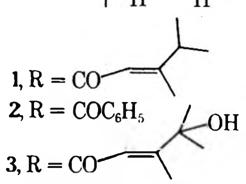
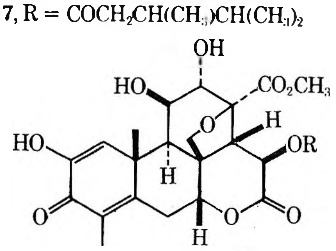
The isolation and structural elucidation of the new potent antileukemic principles, bruceantin (1) and bruceantinol (3), and the new companion quassinoids, bruceantarin (2), dehydrobruceantin (8), dehydrobruceantarin (9), dehydrobruceine B (10), dehydrobruceantol (11), and isobruceine B (12), are reported. Bruceantin (1), bruceantinol (3), and bruceantarin (2) were shown by hydrolysis to be *trans*-3,4-dimethyl-2-pentenoate, *trans*-4-hydroxy-3,4-dimethyl-2-pentenoate, and benzoate esters, respectively, of bruceolide (5). The dehydro compounds were shown to have a 2-hydroxy-3-keto-4-methylcyclohexa-1,4-diene A ring, a feature new to the quassinoids. Isobruceine B (12) was shown to be an A-ring isomer of the known bruceine B (4).

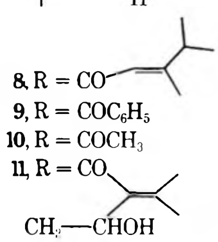
Brucea antidysenterica Mill. is a Simaroubaceous tree which is used in Ethiopia in the treatment of cancer.[2] In the course of a continuing search for tumor inhibitors from plant sources, we found that an alcoholic extract of *Brucea antidysenterica*[3] showed significant inhibitory activity *in vitro* against cells derived from human carcinoma of the nasopharynx (KB), against Walker 256 intramuscular carcinosarcoma in the rat, and against P-388 lymphocytic leukemia in the mouse (PS). A preliminary communication[4] outlined the structural elucidation of the potent antileukemic (PS) principle, bruceantin (1), and the companion quassinoid, bruceantarin (2). Interest in the chemical and





4, R = $COCH_3$
5, R = H
6, R = $COCH{=}C(CH_3)C(OH)(CH_3)_2$
7, R = $COCH_2CH(CH_3)CH(CH_3)_2$





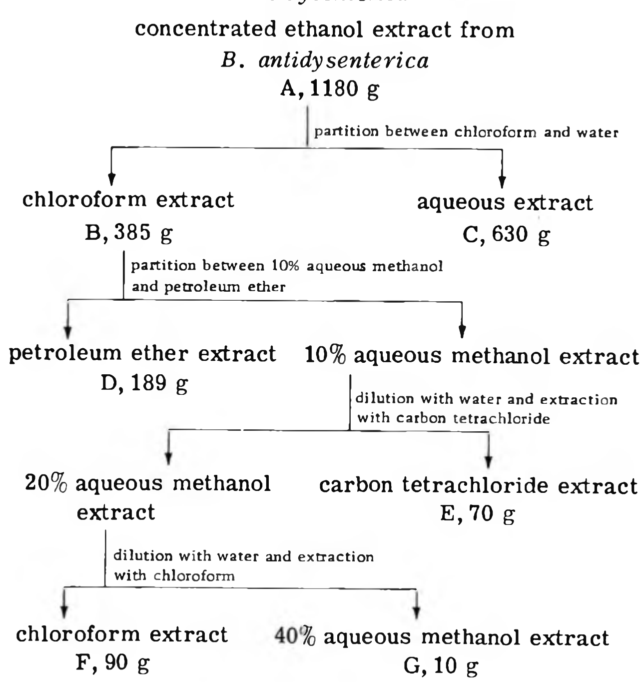
biological properties of bruceantin and related compounds has been heightened by recent findings. Thus, bruceantin also shows significant inhibitory activity against the L-1210 lymphoid leukemia, and against two solid murine tumor systems, the Lewis lung carcinoma and the B-16 melanocarcinoma.[5] Furthermore, bruceantin has been selected for toxicological investigation in preparation for clinical trials. It is the purpose of this paper to present in detail the isolation and structural elucidation of bruceantin (1), bruceantarin (2), the new potent antileukemic principle bruceantinol (3), and the companion quassinoids, dehydrobruceantin (8), dehydrobruceantarin (9), dehydrobruceine B (10), dehydrobruceantol (11), and isobruceine B (12).[6]

Fractionation (Chart I) of the alcohol extract, guided by assay (Table I) against KB tissue culture and PS leukemia

Table I
Activity of Fractions of *B. antidysenterica* against KB Tissue Culture

Fraction	ED_{50}, μg/ml	Fraction	ED_{50}, μg/ml
A	0.45	F	0.021
B	0.34	G	38.0
C	18.5	H	0.031
D	17.0	I	0.05
E	1.6	J	0.34

Chart I
Fractionation of the Active Extract from *Brucea antidysenterica*



in mice, revealed that the inhibitory activity was concentrated, successively, in the chloroform layer of a chloroform–water partition, the methanol layer of a 10% aqueous methanol–petroleum ether partition, the methanol layer of a 20% aqueous methanol–carbon tetrachloride partition and, finally, in the chloroform layer (F) of a chloroform–40% aqueous methanol partition. Column chromatography of fraction F on SilicAR yielded two KB and PS active fractions (H, I) upon elution with 1% methanol in chloroform. Continued elution with 2% methanol in chloroform gave a third KB-cytotoxic fraction (J).

Careful chromatography of fraction H on SilicAR with 20% ether in benzene as eluent gave bruceantin (**1**), as previously described.[4] Continued elution with 30% ether in benzene gave dehydrobruceantin (**8**) and isobruceine B (**12**). Column chromatography of fraction I on SilicAR, eluting with 30% ether in benzene, gave bruceantarin (**2**) and a fraction which on further separation by preparative tlc on ChromAR gave dehydrobruceantarin (**9**), bruceantinol (**3**) and dehydrobruceantol (**11**). Chromatography of fraction J in a similar manner gave the known bruceine B (**4**)[7] and dehydrobruceine B (**10**).

Bruceantin (**1**) and bruceantarin (**2**) displayed in their uv spectra the large bathochromic shift (from 280 to 330 nm) with alkali characteristic of diosphenols. The mass spectra of **1** and **2** displayed as primary fragmentation peaks corresponding to a loss of $C_7H_{11}O$ (*m/e* 438) and C_7H_5O (*m/e* 437), and base peaks corresponding to $C_7H_{11}O$ (*m/e* 111) and C_7H_5O (*m/e* 105), respectively. Except for the abovementioned base peaks in the mass spectra of **1** and **2**, peaks in the region from *m/e* 438 to 69 were almost identical with those present in the mass spectrum of bruceine B (**4**). Inspection of the nmr spectra of bruceantin (**1**), bruceantarin (**2**), and bruceine B (**4**) revealed that all three displayed peaks corresponding to an angular methyl group in the region τ 8.3–8.6, a vinyl methyl at τ 8.0–8.2, a methoxyl at τ 6.2–6.5, and a sharp one-proton doublet (J = 13 Hz) between τ 3.2 and 3.6 (assigned to H-15 in bruceine B (**4**)[7]). The major differences between the nmr spectra of bruceantin (**1**) and bruceine B (**4**) were the additional signals for **1** of a six-proton doublet (J = 6.5 Hz) at τ 8.88, a vinyl methyl signal at τ 7.82, and a vinyl proton singlet at τ 4.39. These data and the presence of the base peak at *m/e* 111 in the mass spectrum supported formulation of bruceantin as the 3,4-dimethyl-2-pentenoic acid ester (**1**) of bruceolide[7] (**5**).

Catalytic reduction of bruceantin (**1**) gave dihydrobruceantin (**7**), in which the double bond of the side-chain ester was reduced. That only the side-chain double bond was reduced was indicated by the uv spectrum, which still showed the diosphenol absorption and alkaline shift, and by the nmr spectrum, which showed no olefinic proton but a new three-proton doublet (J = 6.5 Hz) at τ 9.06. Mild alkaline hydrolysis of **7** gave bruceolide (**5**). In addition, alkaline hydrolysis of bruceantin (**1**) and esterification of the steam-distillable acid with diazoethane gave ethyl *trans*-3,4-dimethyl-2-pentenoate.[8] In the nmr spectrum of ethyl *cis*-3,4-dimethyl-2-pentenoate the vinyl methyl signal appears at τ 8.25, whereas the corresponding peak for the trans isomer occurs at τ 7.90. The peak attributed to the ester vinyl methyl in **1** appears at τ 7.82, indicative of trans stereochemistry in bruceantin (**1**).

The sharp one-proton doublet at τ 3.79 (J = 13 Hz) in the nmr spectrum of **1** indicated C-15 as the point of attachment of the ester side chain. The corresponding peak in the spectrum of dihydrobruceantin (**7**) appeared at τ 3.14 (J = 13 Hz) and in that of bruceine B (**4**) at τ 3.28 (J = 13 Hz).

In the nmr spectrum of bruceantarin (**2**), a complex A_2B_2X system centered at τ 2.3 was indicative of the presence of a benzoate group. In addition, the sharp one-proton doublet (J = 13 Hz) at τ 3.58 and the base peak at *m/e* 105 in the mass spectrum supported for bruceantarin the C-15 benzoate ester structure **2**. The postulated structure was confirmed by mild alkaline hydrolysis of bruceantarin (**2**) to benzoic acid and bruceolide (**5**). In this way bruceantin (**1**) and bruceantarin (**2**) were shown to be esters (3,4-dimethyl-2-pentenoate and benzoate, respectively) of bruceolide (**5**). These two natural esters and the alcohol bruceolide gave a specific grey to black color when treated with ferric chloride on tlc. Bruceantinol (**3**) gave a very similar coloration with ferric chloride, while dehydrobruceantin (**8**), dehydrobruceantarin (**9**), dehydrobruceine B (**10**), and dehydrobruceantol (**11**) gave a distinctive brown color under the same conditions. Isobruceine B (**12**), however, did not react with ferric chloride.

The uv spectrum of bruceantinol (**3**) revealed the presence of an α,β-unsaturated ester in addition to a diosphenol; the latter was indicated by a bathochromic shift with alkali similar to bruceantin (**1**). The mass spectrum showed major ions at *m/e* 546, 438, 420, 297, 151, 127, and the base peak at 109, and the peaks 438–151 were almost identical with those of bruceantin (**1**). The presence of strong mass spectral ions at *m/e* 127 ($C_7H_{11}O_2$) and 109 (C_7H_9O), along with elemental analysis, supported the view that bruceantinol (**3**) is a $C_7H_{11}O_2$ ester of bruceolide (**5**). Treatment of bruceantinol (**3**) with hydrogen over a palladium catalyst resulted in reduction and hydrogenolysis, giving dihydrobruceantin (**7**), thus indicating that the bruceantinol side chain has the same carbon skeleton as that of bruceantin (**1**).

The nmr spectra of bruceantinol (**3**) and bruceantin (**1**) further confirmed their similarity. Both displayed resonances corresponding to the bruceolide (**5**) skeleton [*i.e.*, for the angular methyl, vinyl methyl, and methoxy methyl groups, and the H-15 proton (a one-proton doublet)], but, in addition, both showed signals for a vinyl proton and a vinyl methyl group assignable to the side chain. Instead of the isopropyl six-proton doublet of bruceantin (**1**), bruceantinol (**3**) displayed two methyl singlets at τ 8.60 and 7.98.

Based on these spectral data, the partial structure of bruceantinol could be written as in **6**. This partial structure is identical with that reported for bruceine C.[7] The structural elucidation of the bruceine C side chain by Polonsky, *et al.*, involved ozonolysis of the side-chain double bond to give isopropyl methyl ketone. In this way, the center of geometric isomerism of the side-chain double bond was destroyed, and the exact structure of bruceine C (**6**) was not determined.

A comparison in our laboratory of bruceantinol (**3**) and a sample of bruceine C (**6**), kindly supplied by Dr. Polonsky, showed that the two compounds were different. Their nmr spectra, although very similar, differed in the peaks assigned to the terminal methyl groups of the side chain. The spectrum of bruceine C (**6**) displays a six-proton singlet at τ 8.59 for these two methyls, while that of bruceantinol (**3**) clearly shows them as two distinct three-proton singlets, when the spectra are taken in the same solvent at the same concentration. Furthermore, bruceine C (**6**) and bruceantinol (**3**) could be differentiated by mixture tlc in two different systems.

Alkaline hydrolysis of bruceantinol (**3**) at 0° followed by esterification with diazomethane gave the known bruceolide (**5**) and methyl *trans*-4-hydroxy-3,4-dimethyl-2-pentenoate, identical with an authentic synthetic sample. The synthetic ester was prepared from methyl *trans*-3-methyl-4-oxo-2-pentenoate by a Grignard reaction with methyl magnesium iodide.

The companion ferric chloride active compounds, dehydrobruceantin (**8**), dehydrobruceantarin (**9**), dehydrobruceine B (**10**), and dehydrobruceantol (**11**), displayed in their uv spectra a bathochromic shift with alkali, and gave an almost identical mass spectral fragmentation pattern from *m/e* 436 to 151. Inspection of the nmr spectra of the four compounds revealed that each displayed resonances corresponding to an angular methyl group (in the region τ 8.4–8.6), a vinyl methyl (at τ 8.0), a methoxy methyl (at τ 6.2–6.6), a one-proton doublet (J = 13 Hz, at τ 3.9–4.1), and a one-proton singlet (at τ 3.5). These spectral data supported the formulation that all four of these compounds are esters of the same alcohol.

The uv and nmr spectra are consistent with a diosphenol A ring as in **8**, where the downfield singlet can be assigned to the C-1 proton. A similar diosphenol system, but lacking a 4-methyl group, has been reported in a number of synthetic steroids,[9,10] which display the same uv maximum (254 nm). Dehydrobruceantin (**8**) forms a triacetate which neither reacts with ferric chloride nor gives a bathochromic shift with alkali in the uv spectrum, as expected for a blocked diosphenol.

In addition to the foregoing spectral data, dehydrobruceantin (**8**) displayed in the mass spectrum a parent ion at *m/e* 546 ($C_{28}H_{34}O_{11}$), a peak at 436, corresponding to the loss of $C_7H_{10}O$, and a base peak at 111 ($C_7H_{11}O$). Furthermore, the uv (225 nm) and the nmr (six-proton doublet, vinyl methyl and vinyl proton) spectra indicated that the side-chain ester of dehydrobruceantin (**8**) is identical with that of bruceantin (**1**), that is, a 3,4-dimethyl-2-pentenoate.

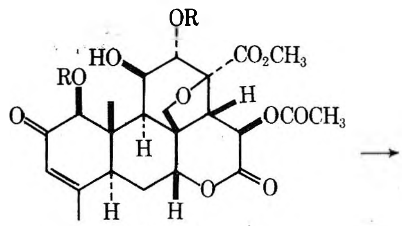
The relationship between bruceantin (**1**) and dehydrobruceantin (**8**) was confirmed through interconversion. Bruceantin (**1**) was oxidized with DDQ in benzene to give dehydrobruceantin (**8**), identical with the natural material.

In addition to the spectral data mentioned above for the dehydro alcohol, dehydrobruceantarin (**9**) and dehydrobruceine B (**10**) displayed in their mass spectra peaks corresponding to parent ions of $C_{28}H_{28}O_{11}$ (540) and $C_{23}H_{26}O_{11}$ (478) and base peaks of *m/e* 105 (C_7H_5O) and 43 (C_2H_3O), respectively. These data, together with the presence in the nmr of an A_2B_2X system of aromatic protons for dehydrobruceantarin and a three-proton acetate signal for dehydrobruceine B, confirmed their structures as **9** and **10**, respectively.

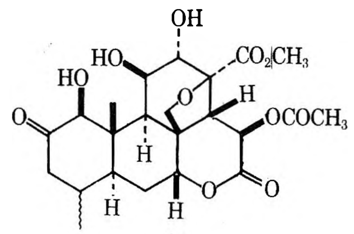
The molecular formula, $C_{28}H_{34}O_{12}$, was advanced for dehydrobruceantol (**11**) based on elemental and mass spectral analyses. The formula represents a $C_7H_{11}O_2$ ester of the dehydro skeleton alcohol. The ester, which was shown to be α,β-unsaturated by its uv spectrum, displayed nmr signals for vinyl methyls at τ 8.4 and 7.9, and for a methyl group (τ 8.62, doublet, J = 6 Hz) coupled to one proton (τ 4.64, quartet, J = 6 Hz), consistent with the presence of a methyl carbinol group. The geminal nature of the vinyl methyls in dehydrobruceantol (**11**) was proven by oxidation. Treatment of dehydrobruceantol (**11**) with excess ozone in aqueous dioxane gave acetone as the only volatile product. Structure **11** is consistent with all of the chemical and spectral properties of dehydrobruceantol.

Accompanying the ferric chloride active compounds was a KB-active and marginally PS-active crystalline material (**12**). The molecular formula $C_{23}H_{28}O_{11}$ was advanced on the basis of elemental and mass spectral analyses. That isobruceine B (**12**) was an A-ring isomer of bruceine B (**4**) was suggested by the similarity of mass spectral fragmentation pattern and nmr spectrum of **12** (which displayed signals for an angular methyl, a vinyl methyl, an acetate, and a carbomethoxy methyl, in addition to a downfield one-proton doublet) to those of **4**. The uv maximum (242 nm) was indicative of a β-disubstituted α,β-unsaturated ketone. In addition the upfield shift of the nmr signal for the vinyl methyl (from τ 8.1 in bruceine B (**4**) to 8.3 in isobruceine B (**12**)) and the appearance of two one-proton singlets at τ 5.93 and 4.08, assignable to the C-1 and C-3 protons, respectively, further supported the A-ring assignment as in **12**.

To prove the α-ketol nature of the A ring in isobruceine B (**12**), the compound was converted to a diosphenol. The double bond of **12** was catalytically reduced and the product, **14**, was subsequently oxidized with bismuth trioxide to the diosphenol, **15**. The product displayed a mass spectrum



12, R = H
13, R = $COCH_3$



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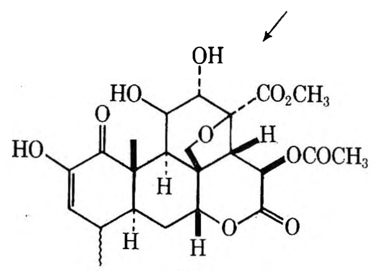

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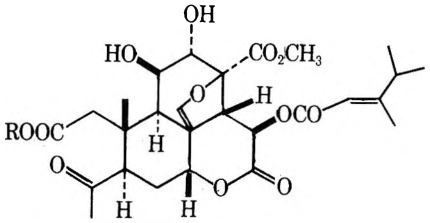
very similar to that of isobruceine B (**12**), and a uv spectrum and ferric chloride activity typical of diosphenols.

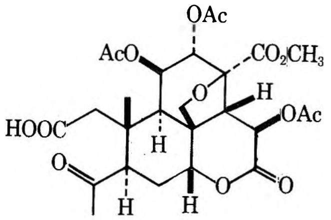
Acetylation of **12** with acetic anhydride–pyridine gave a 1,12-diacetate (**13**). This suggests that the C-1 alcohol is β in orientation and the resulting β-acetate causes sufficient steric hindrance to preclude acetylation at C-11. Moreover, all naturally occurring quassinoids with a C-1 alcohol have the 1-β configuration,[11] a fact which supports the presence of the 1-β-alcohol in **12**.

Column chromatography of fraction H, which had previously yielded bruceantin (**1**), gave a carboxylic acid (**16**). The same material was formed in varying, but small, amounts when pure bruceantin (**1**) was either aerated in a chloroform solution for 10 days, exposed to air and light on a tlc plate overnight, or even kept at low temperature and in the dark for a month or more. To further purify and characterize the acid (**16**), it was treated with diazomethane to give the methyl ether (**17**).

The molecular formula $C_{28}H_{38}O_{12}$ was advanced for **17**, based on elemental and mass spectral analyses. The presence of the bruceantin ester, *i.e.*, 3,4-dimethyl-2-pentenoate, in **16** and **17** was indicated by the uv maximum at



16, R = H
17, R = CH_3



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225 nm and by the presence of resonances in the nmr spectrum for a vinyl proton, a vinyl methyl, and an isopropyl group. The presence of other features in the nmr spectrum, such as signals corresponding to an angular methyl group, a carbomethoxy methyl group, and a C-15 proton, indicated that the B, C, and lactone rings were intact. The lack of ferric chloride activity and the absence of a conjugated ketone, indicated by the uv spectrum, suggested that the A ring of bruceantin (**1**) was changed significantly.

In the nmr spectrum, the signal for the C-4 methyl group (a vinyl methyl signal at τ 8.11 in bruceantin (**1**)) was shifted downfield to τ 7.77, consistent with the presence of a methyl ketone. The formation of a methyl ester, along with the spectral data mentioned above, is consistent with a cleaved A-ring acid as in **16**. The acid was evidently formed by oxidative cleavage of the 3,4 bond and loss of carbon-3. This compound is directly analogous to the product (**18**) of ozonolysis of bruceolide tetraacetate.[7]

The wood of stems and stem bark of *Brucea guineensis* G. Don, collected in Ghana in March, 1973, were extracted and fractionated by a procedure almost identical with that described for *B. antidysenterica*. Bruceantin (**1**), bruceantarin (**2**), bruceantinol (**3**), bruceine B (**4**), and dehydrobruceantin (**8**) were all isolated in yields comparable to those from *B. antidysenterica*.

The antileukemic activity of the bruceolide derivatives varies greatly with the nature of the ester substituent. Thus, bruceantin (**1**) and bruceantinol (**3**), which bear α,β-unsaturated esters, demonstrate potent antileukemic activity. Bruceantarin (**2**), which bears a benzoate ester, and dihydrobruceantin (**7**), which bears a saturated aliphatic ester moiety, both show moderate activity. Bruceine B (**4**), which bears the smaller acetate ester, and bruceolide (**5**), which bears no ester at all, show only marginal antileukemic activity. The limited results to data are consistent with the view that the ester moiety may serve as a carrier group involved in processes such as transport or complex formation. Investigations are in progress to determine the significance of the unsaturated ester, the diosphenol, and of other structural features in relation to the tumor inhibitory activity of bruceantin and bruceantinol.

Experimental Section

General Experimental. Melting points were determined on a Fisher-Johns melting point apparatus and are corrected. Ultraviolet absorption spectra were determined on Beckman Model DK-2A and Coleman Hitachi Model EPS-3T recording spectrophotometers. Infrared spectra were determined on a Perkin-Elmer Model 257 recording spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian HA-100 spectrometer or a JOEL PS-100 p FT NMR spectrometer interfaced to a Texas Instrument JEOL 980A computer, with tetramethylsilane as an internal standard. Mass spectra were determined on Hitachi Perkin-Elmer Model RMU-6E and AEI Model MS-902 spectrometers. Values of $[\alpha]D$ were determined on a Perkin-Elmer Model 141 automatic polarimeter. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. Petroleum ether refers to the fraction with bp 60–68°. All thin-layer chromatography was carried out on prepared plates (Brinkmann, Mallinckrodt, and Camag). Visualization of tlc was effected with 5% ferric chloride in 95% ethanol followed by vanillin (25% vanillin in 1:5 ethanol–concentrated sulfuric acid).

Brucea antidysenterica. **Extraction and Preliminary Fractionation.** Continuous extraction of 10 kg of *Brucea antidysenterica* dried ground stem bark was carried out at 72° with 95% ethanol in a Soxhlet extractor. The concentrated alcoholic extract (A, 1180 g) was partitioned between water (6 l.) and chloroform (6 l.). The water layer was washed with chloroform (6 l.) and the combined chloroform layers were evaporated to give a brown tar (B, 385 g). Evaporation of the water layer gave a brown tar (C, 630 g). Fraction B was partitioned between 10% aqueous methanol (6 l.) and petroleum ether (4 × 4 l.). Concentration of the petroleum ether layer gave a dark green tar (D, 189 g). The 10% aqueous methanol layer was diluted with water to 20% aqueous methanol and extracted with carbon tetrachloride (4 × 3.8 l.). The combined carbon tetrachloride layer was evaporated to give a green tar (E, 70 g). The 20% aqueous methanol layer was diluted with water to 40% aqueous methanol and extracted with chloroform (5 × 2.4 l.). The combined chloroform layer was evaporated to give a brown tar (F, 90 g) and the 40% aqueous methanol layer was evaporated to give a brown powder (G, 10 g). In this way all of the activity (KB and PS) was effectively concentrated in the final chloroform layer (fraction F). Fraction F was chromatographed on a column of SilicAR (5.4 kg) and eluted first with chloroform and then increasing amounts of methanol in chloroform. Fractions were combined on the basis of tlc similarity on ChromAR developed with 2:3 ether in benzene and visualized with ferric chloride and vanillin sprays. Elution with 1% methanol in chloroform gave a fraction (H, 8.1 g) which was active against PS and KB. Continued elution with 1% methanol in chloroform gave a PS and KB active fraction (I, 4.8 g) and elution with 2% methanol in chloroform gave a fraction (J, 3.6 g) active against KB.

Bruceantin (1). Careful column chromatography of fraction H on SilicAR (600 g) with benzene as eluent followed by benzene containing increasing amounts of ether gave, in the fractions eluted with 20% ether in benzene, bruceantin (**1**, 2.0 g, 0.02%): mp 225–226° (from ether[12]); $[\alpha]^{25}D$ −43° (*c* 0.31, pyridine); uv max (EtOH) λ (ϵ) 280 (8680), 221 (18,000) nm; uv max (EtOH + NaOH) λ (ϵ) 328 (7290), 221 (28,600) nm; ir (KBr) 2.90, 5.76, 6.05, 6.13, 8.70, 9.45 μ; nmr ($CDCl_3$) τ 8.88 (6 H, d, J = 6.5 Hz, $CH(CH_3)_2$), 8.56 (3 H, s, 10-CH_3), 8.11 (3 H, br s, 4-CH_3), 7.82 (3 H, s, $CH{=}C(CH_3)$), 7.29 (1 H, br m, OH), 6.47 (1 H, br s, OH), 6.24 (3 H, s, OCH_3), 4.29 (1 H, br s, $OCOCH{=}C$), 3.87 (1 H, br s, OH), 3.79 (1 H, d, J = 13 Hz, 15-H); mass spectrum *m/e* 548 (M^+), 438, 420, 402, 297, 151, 111.0819 (calcd for $C_7H_{11}O$, 111.0809).

Anal. Calcd for $C_{28}H_{36}O_{11}$: C, 61.30; H, 6.62. Found: C, 61.45; H, 6.65.

Dehydrobruceantin (8). Continued column chromatography of fraction H by elution with 30% ether in benzene gave dehydrobruceantin (**8**, 375 mg, 0.003%): $[\alpha]^{25}D$ +79.0° (*c* 0.62, pyridine); uv max (EtOH) λ (ϵ) 259 (8900), 225 (12,000) nm; uv max (EtOH + NaOH) λ (ϵ) 340 (1800), 263 (6900), 225 (15,000) nm; ir (KBr) 2.90, 5.78, 6.18, 8.07, 8.62, 9.45 μ; nmr ($CDCl_3$) τ 8.95 (6 H, d, J = 7 Hz, $CH(CH_3)_2$), 8.38 (3 H, s, 10-CH_3), 8.01 (3 H, s, 4-CH_3), 7.92 (3 H, s, $CH{=}C(CH_3)$), 6.32 (3 H, s, OCH_3), 4.46 (1 H, br s, $OCOCH{=}C$), 4.13 (1 H, d, J = 13 Hz, 15-H), 3.51 (1 H, s, 1-H); mass spectrum *m/e* 546 (M^+), 528.204 ($M^+ - H_2O$, calcd for $C_{28}H_{32}O_{10}$, 528.200), 436, 418, 400, 297, 151, 149, 111.079 (calcd for $C_7H_{10}O$, 111.081), 95.

Dehydrobruceantin was further characterized as its triacetate: mp 167–170° (crystallized from methylene chloride–ether); mass spectrum *m/e* 672 (M^+), 630, 472, 111, 43.

Anal. Calcd for $C_{34}H_{40}O_{14}$: C, 60.71; H, 5.99. Found: C, 60.49; H, 6.17.

Isobruceine B (12). Continued column chromatography of fraction H by elution with 30% ether in benzene gave a colorless glass (600 mg) which was crystallized from ether–methylene chloride to afford needles (12, 360 mg, 0.004%): mp 243–246°; $[\alpha]^{25}D$ −36.2° (c 0.24, pyridine); uv max (EtOH) λ (ε) 242 (8850) nm; ir (KBr) 2.85, 5.75, 6.01, 6.08, 8.00, 8.20, 8.65, 9.42, 10.3 μ; nmr (pyridine-d_5) τ 8.74 (3 H, s, 10-CH_3), 8.30 (3 H, br s, 4-CH_3), 8.02 (3 H, s, $OCOCH_3$), 6.38 (3 H, s, OCH_3), 5.93 (1 H, s, 1-H), 4.08 (1 H, br s, 3-H), 3.52 (1 H, d, J = 13 Hz, 15-H); mass spectrum m/e 480 (M^+), 462, 438, 420, 402, 346, 314, 297, 151, 135, 95.

Anal. Calcd for $C_{23}H_{28}O_{11} \cdot H_2O$: C, 55.41; H, 6.06. Found: C, 54.96; H, 6.07.

Bruceantarin (2). Careful column chromatography of fraction I (4.8 g) on SilicAR (330 g) using benzene followed by benzene containing increasing amounts of ether gave, on elution with 30% ether in benzene, crystalline 2. The crystalline fraction was treated with activated charcoal in chloroform and recrystallized from methylene chloride–benzene to give bruceantarin (2, 280 mg, 0.003%): mp 182–185°; $[\alpha]^{25}D$ −20.7° (c 0.60, pyridine); uv max (EtOH) λ (ε) 278 (7000), 231 (10,500) nm; uv max (EtOH + NaOH) λ (ε) 330 (4480), 230 (9030) nm; ir (KBr) 2.90, 5.78, 6.03, 6.08, 6.12, 7.88, 8.70, 9.00, 9.45, 13.8 μ; nmr ($CDCl_3$) τ 8.63 (3 H, s, 10-CH_3), 8.20 (3 H, br s, 4-CH_3), 6.56 (3 H, s, OCH_3), 3.58 (1 H, d, J = 13 Hz, 15-H), 2.60 (3 H, m, B_2X portion of A_2B_2X, m- + p-benzoate protons), 2.07 (2 H, d of d, J = 7.5, 1.5 Hz, A_2 of A_2B_2X, o-benzoate protons); mass spectrum m/e 542 (M^+), 437, 420, 402, 297, 151, 105, 77.

Anal. Calcd for $C_{28}H_{30}O_{11}$: C, 61.99; H, 5.57. Found: C, 62.06; H, 5.60.

Dehydrobruceantarin (9). Continued column chromatography of fraction I by elution with 30% ether in benzene gave a fraction rich in dehydrobruceantarin (100 mg). Preparative tlc on ChromAR developed with 2% isopropyl alcohol in methylene chloride gave dehydrobruceantarin (9, 40 mg, 0.0004%): $[\alpha]^{24}D$ +68.0° (c 0.15, pyridine); uv max (EtOH) λ (ε) 257 (8640), 231 (13,000) nm; uv max (EtOH + NaOH) λ (ε) 332 (2300), 265 (4500), 228 (17,850) nm; ir (KBr) 2.92, 5.77, 6.15, 7.93, 9.46 μ; nmr ($CDCl_3$) τ 8.37 (3 H, s, 10-CH_3), 7.99 (3 H, s, 4-CH_3), 6.58 (3 H, s, OCH_3), 3.85 (1 H, d, J = 13 Hz, 15-H), 3.48 (1 H, s, 1-H), 2.62 (3 H, m, B_2X of A_2B_2X, m- + p-benzoate protons), 2.08 (2 H, d of d, J = 7.5, 1.5 Hz, A_2 of A_2B_2X, o-benzoate protons); mass spectrum m/e 540 (M^+), 522.148 ($M^+ - H_2O$; calcd for $C_{28}H_{26}O_{10}$, 522.153), 418, 400, 151, 105.

Dehydrobruceantarin was further characterized as its triacetate: mp 181–184° (crystallized from benzene–ether); mass spectrum m/e 666 (M^+), 624, 372, 313, 105, 43.

Anal. Calcd for $C_{34}H_{34}O_{14} \cdot H_2O$: C, 59.64; H, 5.30. Found: C, 59.90; H, 5.00.

Bruceantinol (3). Continued column chromatography of fraction I by elution with 30% ether in benzene gave a fraction (490 mg) enriched in bruceantinol. Preparative tlc on ChromAR, with 2% isopropyl alcohol–methylene chloride as eluent, gave 3 (150 mg, 0.0015%): $[\alpha]^{24}D$ −14.5° (c 0.44, pyridine); uv max (EtOH) λ (ε) 278 (6650), 225 (14,100) nm; uv max (EtOH + NaOH) λ (ε) 328 (3230), 225 (10,000) nm; ir (KBr) 2.88, 5.79, 6.10, 6.95, 7.97, 9.46 μ; nmr ($CDCl_3$) 8.60, 7.98 (each 3 H, s, C(OH)(CH_3)$_2$), 8.43 (3 H, s, 10-CH_3), 8.15 (3 H, br s, 4-CH_3), 7.86 (3 H, s, CH=C(CH_3)), 6.18 (3 H, s, OCH_3), 4.23 (1 H, s, OCOCH=C(CH_3)), 3.74 (1 H, d, J = 13 Hz, 15-H); mass spectrum m/e 546.2106 ($M^+ - H_2O$; calcd for $C_{28}H_{34}O_{11}$, 546.2100), 438, 420, 402, 297, 151, 127.0765 (calcd for $C_7H_{11}O_2$, 127.0759), 109.

Anal. Calcd for $C_{28}H_{36}O_{12}$: C, 59.56; H, 6.43. Found: C, 59.50; H, 6.41.

Dehydrobruceantol (11). The preparative tlc which gave bruceantinol also gave dehydrobruceantol (11, 50 mg, 0.005%): $[\alpha]^{23}D$ +30.0° (c 0.11, $CHCl_3$); uv max (EtOH) λ (ε) 257 (8730), 219 (15,450) nm; uv max (EtOH + NaOH) λ (ε) 330 (1440), 262 (5900), 221 (22,000) nm; ir (KBr) 2.93, 5.73, 6.12, 8.00, 9.50 μ; nmr ($CDCl_3$) τ 8.62 (3 H, d, J = 6 Hz, CH(OH)CH_3), 8.50 (3 H, s, 10-CH_3), 8.27, 7.93 (each 3 H, s, =C(CH_3)$_2$), 8.01 (3 H, s, 4-CH_3), 6.16 (3 H, s, OCH_3), 4.64 (1 H, q, J = 6 Hz, =CCH(OH)CH_3), 4.14 (1 H, d, J = 13 Hz, 15-H), 3.49 (1 H, s, 1-H); mass spectrum m/e 544 ($M^+ - H_2O$), 526, 436, 418, 400, 151, 127, 109.

Anal. Calcd for $C_{28}H_{34}O_{12}$: C, 59.78; H, 6.09. Found: C, 59.65; H, 6.20.

Bruceine B (4). Careful chromatography of fraction J (3.6 g) on SilicAR (360 g) gave, on elution with 60% ether in benzene, a fraction rich in bruceine B. Further purification by preparative tlc (ChromAR, 1:1 ether–benzene) and crystallization from methylene chloride–ether gave needles (4, 83 mg, 0.0008%): mp 264–268°; mmp 262–264° [lit.[7] mp 262–266°; $[\alpha]D$ −77.2°]; $[\alpha]^{25}D$ −76.0° (c 1.01, pyridine); uv max (EtOH) λ (ε) 279 (8250) nm; uv max (EtOH + NaOH) λ (ε) 330 (7650)nm; ir (KBr) 2.90, 5.78, 6.04, 6.18, 7.90, 8.25, 9.45 μ; nmr (pyridine-d_5) τ 8.44 (3 H, s, 10-CH_3), 8.10 (3 H, br s, 4-CH_3), 7.96 (3 H, s, $OCOCH_3$), 6.30 (3 H, s, OCH_3), 3.26 (1 H, d, J = 13 Hz, 15-H); mass spectrum m/e 480 (M^+), 462, 438, 420, 402, 297, 151, 43.

Dehydrobruceine B (10). The mother liquors from the crystallization of bruceine B, which were subjected to ptlc (ChromAR, 1:1 ether–benzene), gave dehydrobruceine B (10, 8 mg, 0.00008%): $[\alpha]^{24}D$ +40.5° (c 0.20, chloroform); uv max (EtOH) λ (ε) 257 (8900) nm; uv max (EtOH + NaOH) λ (ε) 330 (3300), 264 (8170) nm; ir (KBr) 2.88, 5.75, 6.12, 7.28, 8.06, 9.51 μ; nmr ($CDCl_3$) τ 8.39 (3 H, s, 10-CH_3), 8.02 (3 H, s, $OCOCH_3$), 8.00 (3 H, s, 4-CH_3), 6.22 (3 H, s, OCH_3), 4.02 (1 H, d, J = 13 Hz, 15-H), 3.52 (1 H, s, 1-H); mass spectrum m/e 478 (M^+), 460, 436, 418, 201, 151, 43.

Anal. of high-resolution CIMS (Ar–H_2O). Calcd for $C_{26}H_{26}O_{11}$ + H: 479.160. Found: 479.154.

Keto Acid (16) and Methyl Ester (17). Column chromatography of fraction H, from which bruceantin had been isolated, was continued by elution with acetone. The fraction obtained was submitted to ptlc, with 4% isopropyl alcohol in methylene chloride as eluent, which gave 16 (36 mg): nmr ($CDCl_3$) τ 8.93 (6 H, d, J = 6 Hz, CH(CH_3)$_2$), 8.51 (3 H, s, 10-CH_3), 7.87 (3 H, s, CH=C(CH_3)), 7.75 (3 H, s, $COCH_3$), 6.26 (3 H, s, OCH_3), 4.35 (1 H, br s, CH=C(CH_3)), 3.71 (1 H, d, J = 13 Hz, 15-H); mass spectrum m/e 552 (M^+), 534, 442, 424, 111.

The acid 16 (10 mg) was methylated with ethereal diazomethane to give, after ptlc (ChromAR, 3% isopropyl alcohol in methylene chloride), 17 (7 mg): $[\alpha]^{23}D$ +44° (c 0.11, $CHCl_3$); uv max (EtOH) λ (ε) 220 (15,550) nm; ir (KBr) 2.73, 5.76, 6.09, 6.95, 8.25, 8.74, 13.3 μ; nmr ($CDCl_3$) τ 8.93 (6 H, d, J = 6 Hz, =CH(CH_3)$_2$), 8.74 (3 H, s, 10-CH_3), 7.85 (3 H, s, CH=C(CH_3)), 7.77 (3 H, s, $COCH_3$), 6.29, 6.25 (each 3 H, s, OCH_3), 4.36 (1 H, br s, CH=C(CH_3)), 3.87 (1 H, d, J = 12 Hz, 15-H); mass spectrum m/e 566 (M^+), 548, 535, 456, 111.

Anal. Calcd for $C_{28}H_{38}O_{12}$: C, 59.35; H, 6.76. Found: C, 59.38; H, 6.75.

Dihydrobruceantin (7). Bruceantin (1, 20 mg, 0.0365 mmol) was subjected to atmospheric pressure hydrogenation in absolute ethanol (5 ml) using 10% palladium on charcoal (20 mg) as catalyst. After 1 hr the catalyst was removed by filtration and the solvent was evaporated to afford a colorless glass (27 mg). Preparative tlc (ChromAR, 1:1 ether–benzene) and crystallization from ether afforded needles (7, 18.8 mg, 94%): mp 137–140°; $[\alpha]^{24}D$ −64.5° (c 2.90, pyridine); uv max (EtOH) λ (ε) 281 (10,300) nm; uv max (EtOH + NaOH) λ (ε) 332 (6450) nm; ir (KBr) 2.90, 5.77, 6.03, 6.13, 7.95, 8.70, 9.50 μ; nmr (pyridine-d_5) τ 9.23 (6 H, d, J = 7 Hz, CH(CH_3)$_2$), 9.06 (3 H, d, J = 6.5 Hz, $OCOCH_2CH(CH_3)$), 8.42 (3 H, s, 10-CH_3), 8.10 (3 H, br s, 4-CH_3), 6.22 (3 H, s, OCH_3), 3.14 (1 H, d, J = 13 Hz, 15-H); mass spectrum m/e 550 (M^+), 438, 420, 402, 392, 297, 151, 113.

Anal. Calcd for $C_{28}H_{38}O_{11}$: C, 61.08; H, 6.96. Found: C, 60.98; H, 6.94.

Bruceolide (5). A. From Dihydrobruceantin (7). To a cooled solution of 5 N sodium hydroxide (0.45 ml) and methanol (1.65 ml) was added dihydrobruceantin (7, 55 mg) and the reaction mixture was kept at −20° for 42 hr. The reaction mixture was neutralized with dilute hydrochloric acid and evaporated on the rotary evaporator. The residue was dissolved in chloroform and saturated sodium chloride solution and the aqueous layer was reextracted with chloroform. The combined chloroform layers were dried over magnesium sulfate and treated with excess ethereal diazomethane, and then evaporated to afford a colorless glass (22 mg). This material was applied to one ChromAR plate and developed with 5% isopropyl alcohol in methylene chloride to give, in the major band, 15.1 mg of a colorless foam, which was crystallized from ether–methylene chloride to afford bruceolide (5, 8.5 mg, 20%): mp 299–300°, mmp 299.5–300.5° (lit.[7] mp 300–302°); $[\alpha]^{25}D$ −92.5° (c 0.18, pyridine), (lit.[7] $[\alpha]D$ −95.4°); uv max (EtOH) λ (ε) 280 nm (8500); uv max (EtOH–NaOH) λ (ε) 330 nm (7750); ir (KBr) 2.85, 2.90, 5.78, 6.03, 6.13, 7.95, 8.23, 8.62, 9.35 μ; mass spectrum m/e 438 (M^+), 420, 402, 392, 297, 151, 91.

B. From Bruceine B (4). Bruceine B (4, 20 mg) was hydrolyzed and the product isolated as described above for dihydrobruceantin (7) to give crystalline bruceolide (5, 2.4 mg, 13%): mp 301–301.5°; identical by spectral comparisons with 5 described above.

C. From Bruceantarin (2). Bruceantarin (2, 37 mg) was hydrolyzed as described above for dihydrobruceantin (7) and after 42 hr was neutralized with dilute hydrochloric acid and evaporated to dryness. The residue was extracted with chloroform and the combined chloroform layer was dried over magnesium sulfate and evaporated to afford benzoic acid (5 mg, 60%): mp 122–123°; mmp

122–123°; identical by spectral comparisons with an authentic sample. A small amount of concentrated hydrochloric acid was added to the remaining aqueous layer and the aqueous layer was saturated with sodium chloride and then extracted with chloroform. The chloroform layer was dried over magnesium sulfate and treated with ethereal diazomethane to give, after evaporation of solvent, 4 mg of a colorless glass. This material was crystallized from ether–methylene chloride to give bruceolide (**5**, 2 mg, 7%): mp 298–300°; mmp 298–300°; identical by spectral comparisons with **5** described above.

Ethyl *trans*-3,4-Dimethyl-2-pentenoate. The ester was prepared essentially by the literature procedure using the Emmons reaction[8,13] and the mixture of cis:trans (10:90) isomers was separated by vapor phase chromatography on a 10% Carbowax 20M column (0.25 in. × 6 ft) at 95° to give pure ethyl *trans*-3,4-dimethyl-2-pentenoate: ir (film) 3.38, 5.83, 6.10, 8.13, 8.20, 8.55, 9.58 μ; mass spectrum *m/e* 156, 141, 113, 111, 95, 83, 67, 55, 41; nmr ($CDCl_3$) τ 8.97 (6 H, d, *J* = 7 Hz, $CH(CH_3)_2$), 8.76 (3 H, t, *J* = 7 Hz, OCH_2CH_3), 7.92 (3 H, br s, $CH{=}C(CH_3)$), 7.70 (1 H, septet, *J* = 7 Hz, $CH(CH_3)_2$), 5.95 (2 H, q, *J* = 7 Hz, OCH_2CH_3), 4.42 (1 H, br s, $OCOCH{=}CH(CH_3)$).

Ethyl *trans*-3,4-Dimethyl-2-pentenoate from Bruceantin (1). A solution of bruceantin (**1**, 140 mg) in a mixture of methanol (4.95 ml) and 5 *N* sodium hydroxide (1.35 ml) was stirred at room temperature overnight. The solvents were removed at aspirator pressure and the residue was acidified with dilute hydrochloric acid and then steam distilled. The steam distillate was saturated with sodium chloride and extracted with ether. The ether layer was dried over magnesium sulfate and treated with excess ethereal diazoethane. The solvent was removed at aspirator pressure and the residue (17 mg) was purified by preparative vapor phase chromatography (same conditions as above) to give ethyl *trans*-3,4-dimethyl-2-pentenoate (8 mg, 20%) identical with the synthetic sample.

Dihydrobruceantin (7) from Bruceantinol (3). Bruceantinol (**3**, 2 mg) was subjected to atmospheric pressure hydrogenation in absolute ethanol (2 ml) with 10% palladium on charcoal (4 mg) as catalyst. After 1 hr, the catalyst was removed by filtration, and the solvent was evaporated. The residue was submitted to ptlc (ChromAR, 3% isopropyl alcohol in methylene chloride) and gave dihydrobruceantin (**7**, 0.9 mg), identified by comparison of its ir, mass spectrum, tlc (5% isopropyl alcohol–methylene chloride on silica gel, and 1:1 ether–benzene on ChromAR) behavior, and high-pressure liquid chromatography (Corasil II, 1.5% methanol–methylene chloride) retention time with authentic **7** obtained from bruceantin.

Methyl *trans*-4-Hydroxy-3,4-dimethyl-2-pentenoate. 3-Methyl-4-oxo-2-pentenoic acid (Aldrich) was esterified with methanol containing 3% HCl. The resulting mixture of cis:trans (1:3) isomers was separated by vapor phase chromatography on a 10% Carbowax 20M column (0.25 in. × 6 ft) at 180° to give pure methyl *trans*-3-methyl-4-oxo-2-pentenoate: uv max (EtOH) λ (ε) 232 (12,500) nm; ir (KBr) 5.78, 5.90, 6.08, 6.97, 7.32, 9.59 μ; nmr ($CDCl_3$) τ 7.84 (3 H, d, *J* = 2 Hz, $C{=}C(CH_3)$), 7.67 (3 H, s, $C({=}O)CH_3$), 6.28 (3 H, s, OCH_3), 3.53 (1 H, q, *J* = 2 Hz, $C{=}CH$); mass spectrum *m/e* 142 (M^+), 127, 111, 110, 99, 85, 67, 59, 43.

To methyl *trans*-3-methyl-4-oxo-2-pentenoate (71 mg, 0.5 mmol) in ether (5 ml) at 0° under nitrogen was added dropwise with stirring methyl magnesium iodide (177 μl, 2.82 *M* in hexane, 0.5 mmol, Alfa Inorganics). The mixture was maintained at 0° for 30 min, then allowed to warm to room temperature. Hydrochloric acid (5%, 5 ml) was added and the ether layer was separated. The aqueous layer was extracted twice with ether; the combined ether extracts were dried ($MgSO_4$) and evaporated to give a yellow oil. Purification by vpc, as above, gave methyl *trans*-4-hydroxy-3,4-dimethyl-2-pentenoate, as a colorless liquid (50 mg, 63%): uv max (EtOH) λ (ε) 216 (14,000) nm; ir (KBr) 2.87, 5.81, 6.08, 6.97, 8.47, 9.65 μ; nmr ($CDCl_3$) τ 8.64 (6 H, s, $C(OH)(CH_3)_2$), 7.86 (3 H, d, *J* = 2 Hz, $C{=}C(CH_3)$), 7.82 (1 H, s, OH), 6.38 (3 H, s, OCH_3), 3.98 (1 H, q, *J* = 2 Hz, $C{=}CH$); mass spectrum *m/e* 158 (M^+), 143, 140, 115, 111, 83, 59, 43; vpc retention times: (a) 10.0 min (0.25 in. × 6 ft Carbowax on Chromosorb W, 180°, 60 ml/min gas flow); (b) 2.20 min (1/8 in. × 6 ft 3% SE-30 on 100–120 mesh Porapac 30, 100°, 40 ml/min gas flow).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.53; H, 8.83.

Methyl *trans*-4-Hydroxy-3,4-dimethyl-2-pentenoate and Bruceolide (5) from Bruceantinol (3). A solution of bruceantinol (**3**, 70 mg) in a mixture of methanol (2.4 ml) and sodium hydroxide (5*N*, 0.6 ml) was allowed to stand at 0° for 48 hr. After acidification (HCl), the aqueous layer was extracted with ether, salted (NaCl), and reextracted with ether. The combined ether extracts were dried ($MgSO_4$) and treated with ethereal diazomethane. Preparative tlc of the reaction mixture on ChromAR with 4% isopropyl alcohol in methylene chloride as eluent gave methyl *trans*-4-hydroxy-3,4-dimethyl-2-pentenoate (10.7 mg, 55%), identical by ir, nmr, mass spectrum, and vpc retention times to the synthetic material. The ferric chloride active band from the ptlc gave crystalline bruceolide (**5**, 2.2 mg, 2%), identical in all respects with authentic bruceolide obtained from the hydrolysis of bruceantin.

Dehydrobruceantin (8) from Bruceantin (1). To bruceantin (**1**, 20 mg, 0.037 mmol) in dry benzene (2 ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (10 mg, 0.044 mmol) and the mixture was heated under reflux for 6 hr. Evaporation of the solvent and ptlc of the residue (ChromAR, 2% isopropyl alcohol in methylene chloride) gave dehydrobruceantin (**8**, 8.8 mg, 44%), identical with natural dehydrobruceantin in nmr, ir, uv, $[\alpha]_D$, and mass spectrum.

Ozonolysis of Dehydrobruceantol (11). Dehydrobruceantol (**11**) was ozonized and the volatile product identified by the method of Moore and Brown.[14] Thus, a solution of dehydrobruceantol (**11**, 0.6 mg) in methylene chloride (1.0 ml) was treated with excess ozone, and after addition of excess triphenylphosphine, the solution was submitted to vpc analysis. Acetone was identified as the only volatile product by comparison of vpc retention times (1/8 in. × 10 ft, 10% β,β'-oxidipropionitrile on Chromosorb B).

Isobruceine B Diacetate (13). To isobruceine B (**12**, 15 mg, 0.031 mmol) in pyridine (1 ml) was added acetic anhydride (1 ml), and the mixture was kept at room temperature for 3 days. The mixture was evaporated to dryness and the residue was submitted to ptlc (ChromAR, 2% isopropyl alcohol in methylene chloride). Crystallization of the major component from ether–methylene chloride gave needles (**13**, 11 mg, 63%): mp 264–267°; uv max (EtOH) λ (ε) 238 (12,200) nm; ir (KBr) 2.83, 5.73, 5.95, 7.30, 8.13, 9.65 μ; nmr ($CDCl_3$) τ 8.86 (3 H, s, 10-CH_3), 8.12 (3 H, s, 4-CH_3), 8.05, 7.97, 7.84 (each 3 H, s, $OCOCH_3$), 6.31 (3 H, s, OCH_3), 4.85 (1 H, d, *J* = 15 Hz, 15-H), 4.05 (1 H, br s, 3-H); mass spectrum *m/e* 564 (M^+), 522, 504, 489, 135, 95, 91, 60, 43.

Anal. Calcd for $C_{27}H_{32}O_{13}$: C, 57.44; H, 5.71. Found: C, 56.97; H, 5.96.

Diosphenol (15) from Isobruceine B (12). A solution of isobruceine B (**12**, 20 mg) in ethanol (20 ml) was subjected to atmospheric pressure hydrogenation for 15 hr using 5% palladium on charcoal (20 mg) as catalyst. The catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The residue, after ptlc (ChromAR, 3% isopropyl alcohol in methylene chloride) and crystallization from methylene chloride–ether, gave dihydroisobruceine B (**14**, 15 mg, 74%): mp 294–296°; mass spectrum *m/e* 482 (M^+). Dihydroisobruceine B (**14**) was then oxidized by the method of Kupchan, *et al.*[15] To dihydroisobruceine B (**14**, 15 mg) in acetic acid (2 ml) was added bismuth(III) oxide, freshly prepared from bismuth subcarbonate (19.5 mg), and this mixture was heated at reflux for 30 min. The reaction mixture was cooled, diluted with water, and extracted three times with chloroform. The combined chloroform layers were dried ($MgSO_4$) and evaporated. Ptlc and crystallization of the major fraction gave the diosphenol 15 (0.9 mg): mp 184–187°; uv max (EtOH) λ (ε) 269 (7600) nm; uv max (EtOH + NaOH) λ (ε) 314 (4800) nm; mass spectrum *m/e* 480 (M^+), 462, 400, 325, 151, 43.

Registry No.—**1**, 41451-75-6; **2**, 41451-76-7; **3**, 53729-52-5; **4**, 25514-29-8; **5**, 25514-28-7; **7**, 41328-90-9; **8**, 53662-98-9; 8 triacetate, 53662-99-0; **9**, 53663-00-6; **9** triacetate, 53663-01-7; **10**, 53730-90-8; **11**, 53663-02-8; **12**, 53663-03-9; **13**, 53663-05-1; **14**, 53663-04-0; **15**, 53663-06-2; **16**, 53663-07-3; **17**, 53663-08-4; ethyl *trans*-3,4-dimethyl-2-pentenoate, 21016-44-4; ethyl *cis*-3,4-dimethyl-2-pentenoate, 21016-45-5; methyl *trans*-4-hydroxy-3,4-dimethyl-2-pentenoate, 53663-09-5; 3-methyl-4-oxo-2-pentenoic acid, 53663-10-8; methyl *trans*-3-methyl-4-oxo-2-pentenoate, 53663-11-9; methyl *cis*-3-methyl-4-oxo-2-pentenoate, 53663-12-0.

References and Notes

(1) (a) Tumor Inhibitors. 100. Part 99: S. M. Kupchan, R. L. Baxter, M. F. Ziegler, P. M. Smith, and R. F. Bryan, submitted for publication. (b) This investigation was supported by grants from the National Cancer Institute (CA-11718) and American Cancer Society (CI-102J), and by a contract with the National Cancer Institute (N01-CM-12099).

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wood of stems from Ethiopia also yielded active extracts. We thank Dr. Robert E. Perdue, Jr., USDA, Beltsville, Md., for supplying the plant material.
(4) S. M. Kupchan, R. W. Britton, M. F. Ziegler, and C. W. Sigel, *J. Org. Chem.*, **33**, 178 (1973).
(5) Tumor-inhibitory activity and cytotoxicity were assayed under the auspices of the National Cancer Institute, by the procedures described by R. I. Geran, N. H. Greenberg, M. M. McDonald, A. M. Schumacher, and B. J. Abbott [*Cancer Chemother. Rep., Part 3*, **3**, 1 (1972)].
(6) Bruceantin and bruceantinol showed potent antileukemic activity against P-388 lymphocytic leukemia, and were active over a 50- to 100-fold dosage range at the microgram per kilogram level. Bruceantarin showed moderate activity against P-388, and dehydrobruceantin, dehydrobruceantarin, isobruceine B, and the previously isolated[7] bruceine B showed only marginal activity against this system. Bruceantin, bruceantinol, bruceantarin, and isobruceine B showed cytotoxicity (ED_{50}) against KB cell culture at 10^{-2}–10^{-3} μg/ml, and dehydrobruceantin and dehydrobruceantarin at 10^{-1} μg/ml.
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Notes

Dehydroailanthinone, a New Antileukemic Quassinoid from *Pierreodendron kerstingii*[1–3]

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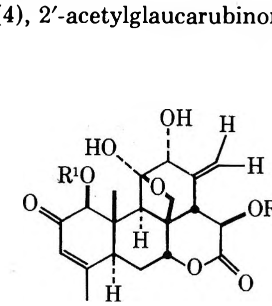
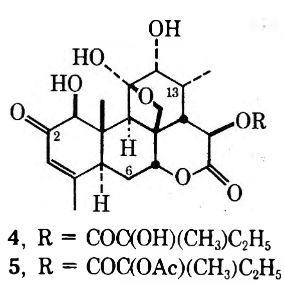
The antileukemic activity of *Brucea antidysenterica* and its active principles, bruceantin[2,4] and bruceantinol,[2] prompted us to investigate other plants of the Simaroubaceae family. An alcohol extract of *Pierreodendron kerstingii* Little[5] was found to show significant activity *in vivo* against P-388 lymphocytic leukemia in the mouse (PS) and *in vitro* against cells derived from human carcinoma of the nasopharynx (KB).[6] We report herein the fractionation of an active extract of *P. kerstingii* and the isolation and structure elucidation of a new antileukemic quassinoid, dehydroailanthinone (1),[7] and the companion quassinoids, glaucarubinone (4), 2′-acetylglaucarubinone (5), and ailanthinone (6).



1, $R^1 = H$; $R^2 = COCH(CH_3)C_2H_5$
2, $R^1 = CH_3$; $R^2 = COCH(CH_3)C_2H_5$
3, $R^1 = R^2 = H$



4, $R = COC(OH)(CH_3)C_2H_5$
5, $R = COC(OAc)(CH_3)C_2H_5$
6, $R = COCH(CH_3)C_2H_5$
7, $R = H$

Fractionation of an alcohol extract, guided by assay against KB and PS, revealed that the inhibitory activity was concentrated, successively, in the ethyl acetate layer of an ethyl acetate–water partition, and the aqueous methanol layer of a 10% aqueous methanol–petroleum ether partition. Column chromatography of the aqueous methanol solubles on SilicAR CC-7 yielded KB and PS active fractions, F and G, on elution with chloroform and 2% methanol in chloroform, respectively. Rechromatography of fraction G on SilicAR CC-7 using 2% ethanol in dichloromethane gave the known glaucarubinone (**4**, 0.05%).[8]

Further fractionation of F was effected with two successive high-ratio chromatographic columns on SilicAR CC-7, first with isopropyl alcohol in dichloromethane, and then with ether in benzene as eluents, giving three major components: dehydroailanthinone (**1**), 2′-acetylglaucarubinone (**5**),[9] and ailanthinone (**6**).[9]

The molecular formula $C_{25}H_{32}O_9$ was advanced for dehydroailanthinone (**1**) on the basis of elemental analysis and mass spectral data. The presence of an α-methylbutyrate ester was indicated by the loss of 84 amu in the mass spectrum and the presence of peaks at *m/e* 85 $[O{\equiv}CCH(CH_3)CH_2CH_3]^{\cdot+}$ and 57 $[CH(CH_3)CH_2CH_3]^{\cdot+}$. Furthermore, there appeared in the nmr spectrum signals for primary and secondary methyl groups assignable to the ester and corresponding in chemical shift to the peaks assigned to the α-methylbutyrate of ailanthinone (**6**). The presence of the ring A moiety as in **1** was supported by the uv spectrum, the vinyl methyl signal in the nmr spectrum (τ 8.26), and the mass spectral fragment ions at *m/e* 247 and 151, which are common ions in quassinoids with a similar A ring and an 11,30-hemiketal in the C ring.[9]

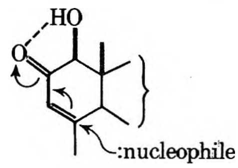
Alkaline hydrolysis of dehydroailanthinone (**1**) gave $\Delta^{13,18}$-glaucarubolone (**3**)[10] which displayed resonances in the nmr spectrum for the C-4 and C-10 methyl groups but lacked a signal corresponding to the C-13 methyl group. The presence of an AB quartet at τ 4.77 in the nmr spectrum of **1** was consistent with the presence of a 13,18-double bond. Except for these nmr spectral differences, the close similarity of all other nmr signals in the spectra of **1** and **6** strongly supported the same stereochemistry at all other positions in dehydroailanthinone (**1**) and ailanthinone (**6**).

By an isolation procedure very similar to that described, glaucarubinone (**4**) and 2′-acetylglaucarubinone (**5**) were also isolated from the wood of stems of *Picrasma excelsa* Planch., in 0.007 and 0.001% yields, respectively.

Earlier studies[11] in this laboratory have demonstrated the importance of Michael-type additions of model biological nucleophiles to highly electrophilic conjugated systems, especially methylene lactones and α,β-unsaturated esters, in relation to the cytotoxicity of several classes of terpenoids. An extension to selective alkylation of biological macromolecules has been proposed for unsaturated ketones in the cucurbitacins.[12]

Saturation of the conjugated Δ^3 double bond in the quassinoids is accompanied by a profound lessening in cytotoxicity of the resulting dihydroquassinoid derivatives.[13] It is suggested that reactions of the conjugated ketone with biological nucleophiles may play an important role in the mechanism by which quassinoids exert their biological activity. *In vitro* models for such Michael-type additions have been reported.[14]

Methylation of the C-1 alcohol of dehydroailanthinone (1) results in a diminution of cytotoxicity and of *in vivo* antileukemic activity. The decrease in activity which accompanies methylation suggests that the free hydroxyl in 1 may also play an active role in the mechanism of biological action. Possibly the hydroxyl group enhances the reactivity of the conjugated ketone toward biological nucleophiles through intramolecular hydrogen bonding, as shown. The



lowered biological activity of the methyl ether 2 may result from the diminished reactivity of the conjugated ketone.

Investigations are in progress to explore further the significance of the α,β-unsaturated ketone and of other structural features in relation to the tumor-inhibitory activity of the quassinoids.

Experimental Section

General. Melting points were determined on a Fisher-Johns melting point apparatus and are corrected. Ultraviolet absorption spectra were determined on Beckman Model DK-2A and Coleman Hitachi Model EPS-3T recording spectrophotometers. Infrared spectra were determined on a Perkin-Elmer Model 257 recording spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian HA-100 spectrometer or a JEOL PS-100 p FT NMR spectrometer interfaced to a Texas Instrument JEOL 980A Computer, with tetramethylsilane as an internal standard. Mass spectra were determined on Hitachi Perkin-Elmer Model RMU-6E and AEI Model MS-902 spectrometers. Values of $[\alpha]D$ were determined on a Perkin-Elmer Model 141 automatic polarimeter. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. Petroleum ether refers to the fraction with bp 60–68°. All thin-layer chromatography was carried out on prepared plates (Brinkmann, Mallinckrodt, and Camag). Visualization of tlc was effected with ceric ammonium sulfate solution.

Extraction and Preliminary Fractionation. The dried ground stem bark of *P. kerstingii* (2.1 kg)[5] was continuously extracted with hot 95% ethanol for 24 hr and the ethanol extract was concentrated under reduced pressure to a dark brown residue (A, 182 g). Fraction A was partitioned between water (1.5 l.) and ethyl acetate (1.5 l.), and the aqueous layer further extracted (2×) with ethyl acetate (1.5 l.). The aqueous layer was evaporated to give fraction B (132 g), as a brown foam. The combined ethyl acetate layers were evaporated to give C (50 g), which was then partitioned between 20% aqueous methanol (1 l.) and petroleum ether (3 × 1 l.). The combined petroleum ether layers and the aqueous methanol layer were evaporated to give D (24 g) and E (25 g), respectively.

Fraction E was subjected to column chromatography (SilicAR, 940 g) and eluted with chloroform followed by chloroform containing increasing amounts of methanol. Elution with chloroform gave fraction F (3.8 g) and elution with 2% methanol in chloroform gave fraction G (3.5 g).

Glaucarubinone (4). Fraction G was further fractionated by column chromatography on SilicAR (175 g) with 2% ethanol in dichloromethane as eluent, to yield a residue which gave needles from acetone–hexane (4, 1.07 g, 0.05%). The material was identified by comparison of its melting point, $[\alpha]D$, uv, ir, and nmr spectra with those reported.[8]

2'-Acetylglaucarubinone (5). Fraction F was subjected to column chromatography on SilicAR (760 g). Elution with 1% isopropyl alcohol in methylene chloride gave a two-component mixture (H, 895 mg), while elution with 2% isopropyl alcohol in methylene chloride gave, after crystallization from acetone–hexane, 5 (0.20 g, 0.01%): mp 170–172°; $[\alpha]^{23}D$ +77.0° (c 0.10, $CHCl_3$) (lit.[9] mp 173°, $[\alpha]D$ +74°); uv max (EtOH) λ (ϵ) 240 (10,700) nm; ir (KBr) 2.82, 2.93, 3.05, 5.75, 5.98, 8.78 μ; nmr ($CDCl_3$) τ 9.03 (3 H, t, J = 7 Hz, CH_2CH_3), 8.87 (3 H, d, J = 6 Hz, 13-CH_3), 8.79 (3 H, s, 10-CH_3), 8.38 (3 H, s, 2'-CH_3), 7.99 (3 H, s, 4-CH_3), 7.93 (3 H, s, C(=O)CH_3), 6.41 (1 H, m, 12-H), 6.38, 6.12 (each 1 H, d, J = 8 Hz, CH_2O), 6.01 (1 H, s, 9-H), 5.32 (1 H, br s, 7-H), 4.90 (1 H, d, J = 12 Hz, 15-H), 3.95 (1 H, br s, 3-H); mass spectrum 536 (M^+), 518, 394, 247, 151, 43.

Anal. Calcd for $C_{27}H_{36}O_{11}$: C, 60.43; H, 6.76. Found: C, 60.30; H, 6.81.

Ailanthinone (6). Separation of the remaining two-component mixture (H) was effected with a SilicAR column (90 g), eluting with ether–benzene (1:1). The first material from the column was crystallized from acetone–hexane as needles (6, 0.008%, 0.17 g): mp 227–230°; $[\alpha]^{27}D$ +90.0° (c 0.10, $CHCl_3$) (lit.[9] mp 231°, $[\alpha]D$ 88°); uv max (EtOH) λ (ϵ) 239 (11,550) nm; ir (KBr) 2.82, 5.70, 5.74, 5.93, 8.18, 9.4 μ; nmr ($CDCl_3$) τ 9.03 (3 H, t, J = 7 Hz, CH_2CH_3), 8.88 (3 H, d, J = 6 Hz, 13-CH_3), 8.83 (3 H, d, J = 7 Hz, 2'-CH_3), 8.80 (3 H, s, 10-CH_3), 7.99 (3 H, s, 4-CH_3), 7.25 (1 H, s, 9-H), 6.45 (1 H, d, J = 3 Hz, 12-H), 6.34, 6.04 (each 1 H, d, J = 8 Hz, CH_2O), 5.91 (1 H, s, 1-H), 5.36 (1 H, br s, 7-H), 4.41 (1 H, d, J = 11 Hz, 15-H), 3.85 (1 H, br s, 3-H); mass spectrum m/e 478 (M^+), 394, 377, 247, 151, 85, 57.

Anal. Calcd for $C_{25}H_{34}O_9$: C, 62.75; H, 7.16. Found: C, 62.78; H, 7.27.

Dehydroailanthinone (1). Continued column chromatography of fraction H by elution with ether–benzene (1:1) gave, after further purification by ptlc (ChromAR, 2% isopropyl alcohol in dichloromethane), dehydroailanthinone (1, 270 mg, 0.015%) as a colorless glass: $[\alpha]^{23}D$ +39.6° (c 0.24, $CHCl_3$); uv max (EtOH) λ (ϵ) 238 (10,900) nm; ir (KBr) 3.08, 5.71, 6.00, 8.45, 9.5 μ; nmr (pyridine-d_5) τ 9.05 (3 H, t, J = 7 Hz, CH_2CH_3), 8.85 (3 H, d, J = 7 Hz, 2'-CH_3), 8.50 (3 H, s, 10-CH_3), 8.26 (3 H, br s, 4-CH_3), 6.43 (1 H, s, 9-H), 6.32, 5.92 (each 1 H, d, J = 8 Hz, CH_2O), 5.79 (1 H, s, 1-H), 5.48 (1 H, s, 12-H), 5.25 (1 H, br s, 7-H), 4.84, 4.70 (each 1 H, d, J = 2 Hz, =CH_2), 3.95 (1 H, br s, 3-H), 3.67 (1 H, d, J = 12 Hz, 15-H); mass spectrum m/e 476 (M^+), 458, 447, 432, 392, 330, 247, 151, 85, 57.

Anal. Calcd for $C_{25}H_{32}O_9$: C, 63.01; H, 6.77. Found: C, 62.79; H, 6.83.

$\Delta^{13,18}$-Glaucarubolone (3) from Dehydroalilanthinone (1). A solution of dehydroailanthinone (1, 25 mg, 0.0525 mmol) in sodium hydroxide (1*N*, 0.4 ml) was allowed to stand at room temperature for 30 min. The mixture was neutralized (5% hydrochloric acid), evaporated to dryness, and extracted with methanol. The alcohol solubles were submitted to preparative tlc (ChromAR, 5% methanol–chloroform) and the major component was crystallized from methanol to give $\Delta^{13,18}$-glaucarubolone (3, 7.4 mg, 36%). Recrystallization from methanol gave an analytical sample: mp 224–226° (lit.[9] mp 230°); $[\alpha]^{24}D$ +55.0° (c 0.20, MeOH); uv max (EtOH) λ (ϵ) 239 (8850) nm; ir (KBr) 2.80, 2.93, 5.79, 5.94, 8.27, 9.52 μ; nmr ($CDCl_3$) τ 8.43 (3 H, s, 10-CH_3), 8.22 (3 H, s, 4-CH_3), 6.39 (1 H, s, 9-H), 6.31 (1 H, s, 12-H), 6.23, 5.87 (each 1 H, d, J = 9 Hz, CH_2O), 5.53 (1 H, s, 1-H), 5.29 (1 H, br s, 7-H), 4.59 (1 H, d, J = 11 Hz, 15-H), 4.52, 4.48 (each 1 H, br s, =CH_2), 3.85 (1 H, br s, 3-H); mass spectrum m/e 392 (M^+), 374, 248, 151.

Anal. Calcd for $C_{20}H_{24}O_8 \cdot H_2O$: C, 58.53; H, 6.39. Found: C, 58.51; H, 6.61.

Dehydroailanthinone 1-Methyl Ether (2). A solution of dehydroailanthinone (1, 30 mg, 0.063 mmol) in methanol (5 ml) was treated with excess ethereal diazomethane for 5 hr. The solution was evaporated and submitted to preparative tlc on ChromAR with 3% methanol–chloroform as eluent, to give a slightly yellow crystalline product. Recrystallization from acetone–hexane gave dehydroailanthinone 1-methyl ether (**2**, 14 mg, 45%): mp 272–273.5°; $[\alpha]^{26}D$ −8° (*c* 0.11, $CHCl_3$); uv max (EtOH) λ (ε) 239 (11,650) nm; ir (KBr) 2.86, 3.08, 5.82, 5.95, 8.30, 13.3 μ; nmr ($CDCl_3$) τ 9.04 (3 H, t, *J* = 7 Hz, CH_2CH_3), 8.81 (3 H, d, *J* = 7 Hz, 2′-CH_3), 8.73 (3 H, s, 10-CH_3), 8.02 (3 H, s, 4-CH_3), 7.06 (1 H, s, 9-H), 6.45, 6.07 (each 1 H, d, *J* = 8 Hz, CH_2O), 6.27 (1 H, s, 1-H), 6.22 (3 H, s, OCH_3), 5.94 (1 H, s, 12-H), 5.40 (1 H, br s, 7-H), 4.80, 4.62 (each 1 H, s, =CH_2), 4.28 (1 H, d, *J* = 12 Hz, 15-H), 3.94 (1 H, br s, 3-H); mass spectrum *m/e* 490 (M^+), 390, 261, 229, 165, 135, 85, 51.

Anal. Calcd for $C_{26}H_{34}O_9 \cdot 0.5H_2O$: C, 62.50; H, 7.06. Found: C, 62.51; H, 7.02.

Registry No.—**1**, 53683-70-8; **2**, 53683-71-9; **3**, 53683-72-0; **4**, 1259-86-5; **5**, 33957-83-4; **6**, 53683-73-1.

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(5) The stem bark was collected in Ghana in March 1973. The authors acknowledge with thanks receipt of dried plant material from Dr. R. E. Perdue, Jr., U.S. Department of Agriculture, in accordance with the program developed by the National Cancer Institute.
(6) Tumor-inhibitory activity and cytotoxicity were assayed under the auspices of the National Cancer Institute, by the procedures described by R. I. Geran, N. H. Greenberg, M. M. McDonald, A. M. Schumacher, and B. J. Abbott [*Cancer Chemother. Rep., Part 3*, **3**, 1 (1972)].
(7) Dehydroailanthinone showed significant antileukemic activity against P-388 lymphocytic leukemia in the mouse over a 50- to 100-fold dosage range. 2′-Acetylglaucarubinone, glaucarubinone, and ailanthinone also showed significant inhibitory activity against P-388. All four compounds showed cytotoxicity (ED_{50}) against KB cell culture at 10^{-2}–10^{-3} μg/ml.
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The Structure of Abresoline

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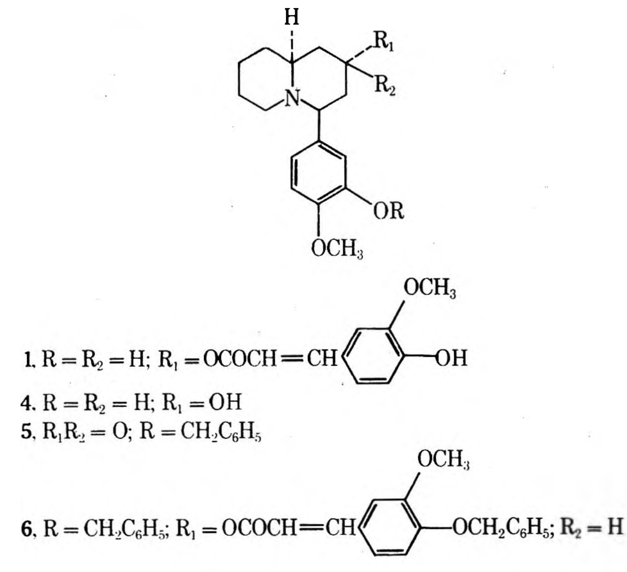
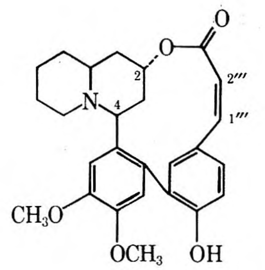
Received August 26, 1974

The alkaloids of *Heimia salicifolia* (Lythraceae) are a series of compounds which contain a quinolizidine nucleus substituted at positions 2 and 4 by a 12-membered lactone ring including a biphenyl grouping. The structures of the alkaloids are based upon chemical correlations[1–8] with lythrine (**2**) whose structure was assigned by X-ray crystallography.[9] Furthermore, there have been recent syntheses[10,11] of methyldecinine, the dihydromethyl ether of **2**, and of several lythraceous alkaloids containing biphenyl ether groupings[12–15] not found in the alkaloids of *Heimia*.

A minor alkaloid, $C_{26}H_{31}NO_6$, for which we propose the name abresoline (**1**), was isolated as a noncrystalline solid from *H. salicifolia* in very low yield. The uv spectrum, which is unlike those of the other *Heimia* alkaloids,[16] exhibits two maxima at 284 and 323 nm; the two transitions are readily correlated with those of *trans*-ferulic acid (**3**)[17] and the quinolizidol (**4**),[18] which are at 236 and 322 nm and 282 nm, respectively. Base hydrolysis of the alkaloid gave **3**





2

and **4**, and the presence of these two units in the structure of **1** could also be inferred from the mass spectrum of the alkaloid, which contained strong transitions at *m/e* 276 and 177 corresponding to the fragment ions **4** and **3**. The ir spectrum of **1** has strong bands at 1706 and 2793 cm^{-1}, the first assigned to an ester carbonyl and the second to the Bohlman bands,[19] indicative of a *trans*-quinolizidine. The nmr spectrum of abresoline is also fully compatible with the assigned structure. Thus, typical upfield absorptions are seen for the quinolizidine ring protons; H-4 appears as a quartet (J_{aa} = 10 Hz, J_{ae} = 1 Hz) supporting the trans configuration of the ring and the axial orientation of the proton.[16,20] H-2 is seen at 5.18 ppm with a half-height width of 8 Hz indicating its equatorial orientation.[16,21,22] The olefinic protons at 6.36 (H-2‴) and 7.63 (H-1‴) form an AB quartet with *J* = 18 Hz; the trans geometry of the side chain is thus established.

Since the proposed formulation **1** represents a hitherto unknown structural variation in the series of *Heimia* alkaloids, its synthesis was undertaken. Pelletierine was condensed with 3-hydroxy-4-methoxybenzaldehyde to give the *trans*-quinolizidone, which was converted to its benzyl ether (**5**) and reduced with $NaBH_4$ to a mixture of epimeric alcohols. The alcohols could not readily be separated, and were therefore converted by transesterification with methyl benzyloxyferulate to a mixture of esters which was resolved by chromatography. The axial ester **6** was debenzylated with concomitant reduction to dihydroabresoline (**7**), which was chromatographically and spectroscopically identical with the reduced form of the natural alkaloid.

In 1966, it was proposed by Ferris and his coworkers[23] that the lythraceous alkaloids might be formed in nature by a series of steps very similar to those leading to synthetic abresoline. The biphenyl system would be derived from the *trans*-cinnamyl esters by isomerization and oxidative phenol coupling. The isolation of **1** certainly provides circumstantial evidence for the biosynthetic proposal, although as yet no biphenyl alkaloid corresponding to 1 has been isolated.

Experimental Section

Nmr spectra were recorded on a Perkin-Elmer-Hitachi R24 or a Varian Associates 220 MHz in $CDCl_3$ solution. The tlc systems used throughout were silica gel with (a) benzene saturated with NH_4OH–MeOH (17:3); (b) benzene saturated with NH_4OH–MeOH (3:1); (c) chloroform–EtOH (10:1); (d) benzene–EtOAc–MeOH (5:5:1); (e) benzene–MeOH (15:4); (e) benzene–MeOH (15:4); (f) chloroform–EtOH (3:1); (g) benzene–EtOAc (3:1); (h) chloroform–EtOH (20:1); (i) toluene–$CHCl_3$–acetone (8:5:7); (j) benzene–MeOH–HOAc (23:3:2); (k) hexane–acetone–HCO_2H (10:7.5:0.5); and (l) $CHCl_3$–EtOH (19:1.5). Compounds were visualized either with modified Dragendorff's reagent or diazotized *p*-nitroaniline.

Isolation of Abresoline (1). *Heimia salicifolia* was extracted as previously described.[7] The most polar alkaloid fraction, eluted from the basic Al_2O_3 column[7] with MeOH–HOAc (20:1) and which contained some ten uncharacterized alkaloids, was further chromatographed (tlc system a). Six compounds were isolated of which one, abresoline, was isolated as an amorphous solid[24] by attempted crystallization from $CHCl_3$–hexane. The compound was homogeneous as indicated by tlc (systems a and b): mass spectrum *m/e* 453.2166 ($C_{26}H_{31}NO_6$ requires 453.2151), 435 ($M^+ - H_2O$), 276, 259, 177, and 150; uv λ_{max} 284 and 323 nm (log ϵ 3.73 and 3.76); ir ν_{max} 3356, 2933, 2793, and 1706 cm^{-1}; nmr δ 1–3 (m, 13 H), 3.22 (q, J = 10 and 1 Hz, 1 H), 3.85 (s, 3 H), 3.95 (s, 3 H), 5.18 (br s, 1 H), 6.36 (d, J = 8 Hz, 1 H), 7.63 (d, J = 18 Hz, 1 H), 7.02 (m, 6 H).

Reduction of 1. A methanolic solution of 1, reduced (10% Pd/C) to yield dihydroabresoline (7), was purified by tlc (system h), and obtained as a noncrystalline solid.

Hydrolysis of 1. The alkaloid was hydrolyzed by warming with 2 *N* NaOH for 15 min. The acidified solution was extracted with EtOAc. The organic phase was shown to contain *trans*-ferulic acid by co-chromatography with authentic material (tlc systems b and h–k). The aqueous phase was similarly proved to contain 4 (tlc system b).

2-Keto-4(e)-(3-benzyloxy-4-methoxyphenyl)-*trans*-quinolizidine (5). Compound 5 was obtained in 56% yield from the condensation of pelletierine[25] with isovanillin in 1 *N* NaOH,[15] followed by benzylation: mp 169–171° (lit.[26] 169–170°).

2(a)-(3-Methoxy-4-benzyloxycinnamoyloxy)-4(e)-(3-benzyloxy-4-methoxyphenyl)-*trans*-quinolizidine (6). A suspension of 5 as its tetraphenyl borate in MeOH was reduced to a mixture of epimeric alcohols with $NaBH_4$. The alcohols were converted to a mixture of ferulate esters by transesterification with methyl benzyloxyferulate in refluxing xylene containing an equimolar amount of NaOMe. The esters were resolved by chromatography over silica gel with C_6H_6–EtOAc (3:1) as eluting solvent; the axial ester had the lower R_f; yield from 5, 21%. The ester could not be crystallized but was shown to be homogeneous by tlc (system g): mass spectrum *m/e* 633.3078 ($C_{40}H_{43}NO_6$ requires 633.3067); ir ν_{max} 2890, 2809 (Bohlman bands), and 1712 cm^{-1}; nmr δ 1–3 (m, 13 H), 3.25 (q, 1 H), 3.80 (s, 3 H), 3.87 (s, 3 H), 5.10 (s, 5 H), 6.40 (d, J = 16 Hz, 1 H), 7.68 (d, J = 16 Hz, 1 H), 7.10 (m, 6 H), 7.34 (br s, 10 H).

Dihydroabresoline (7). Compound 6 was reduced in MeOH (10% Pd/C) to yield 7 in quantitative yield. The alkaloid could not be crystallized, but was homogeneous (systems a–g), and was identical with the reduced natural product: mass spectrum *m/e* 455.2298 ($C_{26}H_{33}NO_6$ requires 455.2308); uv λ_{max} 282, inf 287 (log ϵ 3.76); ir ν_{max} 3401, 2933, and 1733 cm^{-1}; nmr δ 1–3.5 (m, 18 H), 3.80 (s, 6 H), 5.01 (br s, 1 H), 5.50 (br s, exchangeable with D_2O, 2 H), 6.65 (m, 6 H).

Registry No.—**1,** 53778-14-6; **4,** 52656-92-5; **5,** 53778-15-7; **6,** 53778-16-8; **7,** 53778-17-9; pelletierine, 6302-02-9; isovanillin, 621-59-0.

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Vinyl Triflates in Synthesis. II. 1,1-Di-, Tri-, Tetrasubstituted and Deuterio Allenes from Ketones *via* Vinyl Triflates[1]

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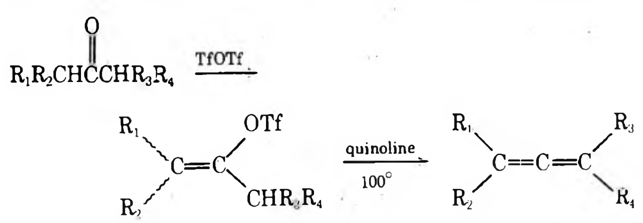
Recently we reported the preparation of *tert*-butylacetylene and certain other acetylenes from ketones *via* vinyl triflates.[3] Interest in allene chemistry[4] and the limited ways of their preparation prompts us to report in this note the ready synthesis of di-, tri-, and tetrasubstituted allenes from the appropriate ketones. Although the overall yields achieved in this preparation are only low to moderate the mild reaction conditions, and in particular the low basicity required for elimination, compare favorably with previously known procedures[4] such as the geminate dichlorination of ketones or the carbene–olefin procedures.

The reaction consists of conversion of the appropriate ketone into its vinyl triflate, 1, by previously reported procedures,[5] and the elimination of triflate, 1, by quinoline to the desired allene, 2.

Although unsymmetrical ketones give both positional as well as geometric isomers of the triflate, 1, the mixture can



1 2

Table I
Preparation and Yields of Allenes *via* Triflates from Ketones

				$R_1R_2C{=}C(OTf)CHR_3R_4$		$R_1R_2C{=}C{=}CR_3R_4$	
R_1	R_2	R_3	R_4	Compd	% yield[a]	Compd	Yield, mg[a] (%)
CH_3	CH_3	H	H	3[b]	44	4	135 (70)
CH_3	CH_3	D	D	5[c]	40	6	32 (45)
CD_3	CD_3	H	H	7[d]	35	8	85 (44)
CH_3CH_2	CH_3	H	H	9[e]	44	10	580 (85)
CH_3	CH_3	CH_3	H	11[f]	41	12	320 (76)
CH_3	CH_3	CH_3	CH_3	13[g]	48	14	130 (79)

[a] Isolated yields. [b] Prepared as previously reported.[5b] [c] Prepared from $(CH_3)_2CDC(O)CD_3$ obtained *via* exchange with D_2O. [d] Prepared from $(CD_3)_2CHC(O)CH_3$ made as previously reported.[7] [e] Prepared from 3-methyl-2-pentanone. [f] Prepared from 2-methyl-3-pentanone. [g] Prepared from 2,4-dimethyl-3-pentanone *via* the silyl enol ether.[5c]

be used directly in the elimination step as all isomers yield the same allene.[6] The procedure may, however, only be used for the preparation of 1,1-di or higher substituted allenes, as elimination from a triflate containing an olefinic hydrogen yields the isomeric acetylene as the major product with only small amounts of allene. Typical examples together with yields are summarized in Table I.

As the data in the table indicate although overall yields are low they represent *isolated yields* of small scale preparations. Moreover, control experiments demonstrated that no rearrangement of the allene to the isomeric acetylene occurs under the reaction conditions employed. The chief

$$(CH_3)_2C{=}C{=}CH_2 \;\underset{100°}{\overset{\text{quinoline}}{\not\rightleftharpoons}}\; (CH_3)_2CHC{\equiv}CH$$

usefulness of this preparation lies in the ready availability of the precursor ketones and the simplicity of the procedure. We believe this procedure to be general, limited only by the availability of starting ketones, and hence provides another manifold into allene chemistry.

Experimental Section

Boiling points are uncorrected. Nmr spectra were recorded on a Varian A-60 spectrometer using TMS as an internal standard; infrared spectra were obtained on a Beckman IR-5 spectrophotometer and mass spectra were obtained on an AEI MS-30 spectrometer. Gas–liquid chromatography was performed on a Varian Aerograph Model 90-P unit using a 15 ft × 0.375 in. column with 15% SF-96 on Chromosorb W.

General Procedure for the Preparation of Vinyl Triflates. Vinyl triflates were prepared from the appropriate ketones and triflic anhydride on a 10–50 mmol scale using pyridine as base and anhydrous CCl_4 as solvent by standard procedures.[5] Triflates **3, 5,** and **7** have been previously prepared[7] as have **11** and **13**.[8] Triflate **9** was prepared from commercial 3-methyl-2-pentanone: bp 54–55° (13 mm); ir (thin film) 2967 (CH), 1692 (C=C), 1412 (S=O), and 1211 cm^{-1} (CF); nmr (CCl_4) δ 2.06 (q, 2 H, J = 7.0 Hz, $-CH_2-$), 1.98 (br s, 3 H, α-CH_3), 1.70 (br s, 3 H, β-CH_3), 1.02 (t, 3 H, J = 7.0 Hz, CH_3CH_2).

General Procedure for the Preparation of Allenes. To a 10-ml round-bottom flask, equipped with a magnetic stirrer and containing 3–6 ml of dry freshly distilled quinoline, was added 1–10 mmol of the appropriate vinyl triflate. The flask was connected to a bulb-to-bulb distillation apparatus and a receiver flask. The reaction flask and cross arm were heated to 100° for 2–6 days and the product collected with the receiver cooled to −78°. Yields of *isolated* products are reported in the table. The products so obtained usually contained small amounts of unreacted triflate and ketone as impurities. Final purification was achieved by means of preparative glc. For **4**: nmr (CCl_4) δ 4.43 (sept, 2 H, J = 3.2 Hz, C=CH_2), 1.64 [t, J = 3.2 Hz, $(CH_3)_2C$=] [lit.[9] δ 4.43, J = 3.0 Hz, and δ 1.65, J = 3.0 Hz]; ir (thin film) 1960 (C=C=C) and 847 cm^{-1}; mass spectrum 68 (M^+, 100), 67 (54), 65 (18), 53 (52), 51 (21), 50 (20), 41 (40), 40 (22), 39 (40). For **6**: ir (CCl_4) 2941 (CH), 2288 (CD), and 1949 cm^{-1} (C=C=C); mass spectrum 70 (M^+, 61). For **8**: mass spectrum 74 (M^+, 13). For **10**: nmr (CCl_4) δ 4.50 (sext., 2 H, J = 3.0 Hz, C=CH_2), 1.90 (m, 2 H, $-CH_2-$), 1.65 (t, 3 H, J = 3.0 Hz, CH_3C=C), 0.99 (t, 3 H, J = 7.0 Hz, CH_3CH_2) [lit.[9] nmr (CCl_4) δ 4.55 (m, 2 H, C=CH_2)]; ir (thin film) 1961 cm^{-1} (C=C=C) [lit.[10] 1960 cm^{-1}]. For **12**: nmr (CCl_4) δ 4.88 (m 1 H, C=CH), 1.63 (m 6 H, $(CH_3)_2C$), 1.58 (m 3 H, CH_3CH=); ir 1965 cm^{-1} (C=C=C) [lit.[9] nmr δ 4.80 (m 1 H), 1.63 (m, 6 H), 1.57 (m 3 H); ir 1959 cm^{-1}]. For **14**: nmr (CCl_4) δ 1.75 (s, 12 H, CH_3); ir (CCl_4) 2940, 1629, 1447, 1379, 1186, and 1074 cm^{-1}; mass spectrum 96 (M^+, 87), 81 (100), 79 (38), 57 (19), 56 (25), 55 (15), 54 (50), 48 (10), 42 (75).

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Registry No.—**3**, 28143-80-8; **4**, 598-25-4; **5**, 53730-65-7; **6**, 53730-66-8; **7**, 52847-16-2; **8**, 53730-67-9; **9**, 53730-68-0; **10**, 7417-48-3; **11**, 52149-34-5; **12**, 3043-33-2; **13**, 52149-35-6; **14**, 1000-87-9; 3-methyl-2-pentanone, 565-61-7.

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Synthesis and Reactions of 6-Methylsulfonyl-9-β-D-ribofuranosylpurine

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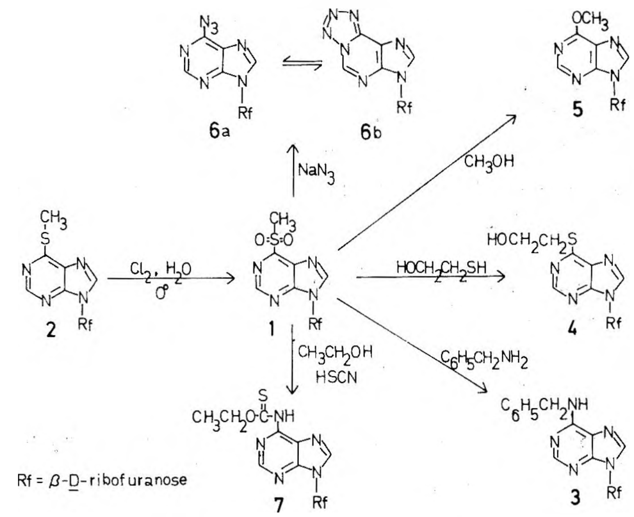
Although sulfones are generally quite stable, methyl sulfonyl substituents at low electron density positions of a pyrimidine or purine can be excellent leaving groups, and this fact has been employed in the past in nucleoside synthesis[1-4]. Early attempts to prepare 6-methylsulfonyl-9-β-D-ribofuranosylpurine (**1**) gave only its hydrolysis product inosine;[3] a similar sulfone was recently proposed as an intermediate but no attempt to characterize it was described.[1] We wish to report the isolation of pure **1** in good yield and

Scheme I



some of the physical and chemical properties of this compound.

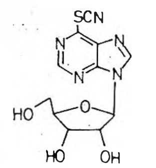
Chlorine oxidation of 6-methylthio-9-β-D-ribofuranosylpurine (2) in aqueous ethanol at 0° gives, after neutralization with $NaHCO_3$ and crystallization, the sulfone nucleoside 1 in 50% yield. This compound is stable as a solid and in neutral solution, but decomposes slowly in acidic media to form inosine. Decomposition in base, on the other hand, occurs with some cleavage of the glycosidic bond to give 6-methylsulfonylpurine, which can subsequently hydrolyze to hypoxanthine. In various pH 8 buffer systems at 37°, 1 decomposes slowly (about 20% decomposition after 2 hr) to a mixture of inosine, hypoxanthine, and 6-methylsulfonylpurine.

Compound 1 reacts readily with amines, mercaptans, and, to a lesser extent, alcohols, to give 6-substituted purine nucleosides by displacement of methylsulfinate (see Scheme I). Thus, a slight excess of benzylamine in methanol at 0° gives N^6-benzyladenosine (3)[5] in 25% yield after chromatographic separation. Mercaptoethanol in an aqueous solution of 1 reacts in a short time at 25° to give 6-(2-hydroxyethylmercapto)-9-β-D-ribofuranosylpurine (4). Methanolic ammonia at 0° converts 2 readily into 6-methoxy-9-β-D-ribofuranosylpurine (5)[6] after purification by column chromatography; this compound can also be formed in a solution of 1 in methanol after a few weeks at 25°. More basic nucleophiles tend to give hypoxanthine (see above) rather than direct displacement of methylsulfinate. Both ammonia and cyanide in water give only hypoxanthine in reactions with 1.

The reaction of 1 with sodium azide in methanol at 25° proceeds readily to give high yields of 6-azido-9-β-D-ribofuranosylpurine (6). This nucleoside, which exists predominantly in the tetrazole form **6b**,[6,7] has been previously prepared by another approach.[6] It cannot be prepared by azide displacement on a more commonly used intermediate, 6-chloro-9-β-D-ribofuranosylpurine, presumably because compound 6 is unstable at the temperatures required to effect displacement of chloride.

Compound 6 readily undergoes photodecomposition. Irradiation of a 2 m*M* aqueous solution of 6 at wavelengths higher than 280 nm[8] gives after 3 hr a compound with the UV and TLC properties of adenosine. Similar tetrazoles are known to undergo photoreactions, giving intermediate nitrenes derived from the azide tautomer of the ground-state molecule.[9]

We initially prepared 1 as a potential intermediate in the synthesis of 6-isothiocyanato-9-β-D-ribofuranosylpurine, but this approach, as with all others we attempted, failed to give any isolated isothiocyanate. Refluxing 1 in an ethanolic solution of KSCN yields a mixture consisting in part of inosine, *O*-ethyl 9-β-D-ribofuranosylpurine-6-thiocarbamate (7), and compound 7's decomposition product adenosine, but *no reaction* occurs between 1 and KSCN or AgSCN in aprotic DMSO. Compound 7 is more easily prepared by reaction of 1 in ethanolic HSCN; again, *no reaction* occurs between 1 and HSCN in aprotic solvents. Attempts to obtain the isothiocyanate by rearrangement of 6-thiocyanato-9-β-D-ribofuranosylpurine (8)[10] also failed. Compound 8 when refluxed in an ethanolic solution of



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KSCN gives only the thiocarbamate 7; in other solvents, no reaction is observed. Reaction of KSCN with 6-chloro-9-β-D-ribofuranosylpurine gives, in aprotic solvent, compound 8, and in ethanol (via 8), thiocarbamate 7.

Not only is compound 1 itself a useful synthetic intermediate, but the mild conditions of its formation and subsequent reactions make it readily applicable to nucleotide work. Phosphate derivatives of compound 2 can be oxidized to the corresponding 6-methylsulfonylpurine nucleotides and these further reacted to yield other nucleotides, without hydrolytic decomposition.[11] The stability of nucleotide derivatives of 1 in neutral solution plus their high reactivities with the common nucleophilic groups on enzymes suggest their potential use as affinity labels. The photolability of nucleotides of 6 at wavelengths above 280 nm indicates a potential use of these compounds as photoaffinity labels. We are currently exploring these possibilities in our laboratory.

Experimental

Materials and Methods. 6-Chloro-, 6-thio-, and 6-methylthio-9-β-D-ribofuranosylpurines were purchased from Papierwerke Waldhof-Aschaffenburg (Mannheim, Germany). Thin layer chromatographic R_f values were determined on DC-Microcards SI F, purchased from Riedel-De Haen Aktiengesellschaft (Seelze-Hannover, Germany). Elemental analyses were performed by Mikroanalytisches Labor Beller, Göttingen (Germany). The NMR spectra were obtained on a Bruker-Physics HFX 60 spectrometer, and the UV spectra on a CARY 16.

Synthesis of 6-Methylsulfonyl-9-β-D-ribofuranosylpurine (1). A solution of 390 mg (1.3 mmol) of 6-methylthio-9-β-D-ribofuranosylpurine in 20 ml of 90% ethanol was cooled to 0° and chlorine gas was bubbled slowly through this solution until the reaction was complete, as indicated by rough UV analysis of the reaction mixture and by the yellow tint of excess chlorine, about 10 min. At this point, nitrogen gas was bubbled through for a few minutes; then 550 mg (0.65 mmol) of $NaHCO_3$ was added. After 10–15 min of stirring at 0° with continued nitrogen bubbling, the reaction mixture was filtered to remove inorganic salts and cooled overnight to give 179 mg (0.54 mmol, 42%) of needles, melting range 97–100°. A second crop of crystals was obtained from the concentrated filtrate, giving a total yield of 50%. λ_{max}, nm ($\epsilon \times 10^{-3}$): pH 1, 278 (8.2); pH 7, 278 (8.7); pH 12, unstable. PMR (D_2O): δ 9.31 (s, 1 H), 9.16 (s, 1 H), 6.42 (d, J = 5 Hz, 1 H), 4.95 (q, J = 5 Hz, 1 H), 4.30–4.68 (m, 2 H), 4.02 (d, J = 3 Hz, 2 H), 3.62 (s, 3 H). TLC, silica gel, 9:1 EtAc–EtOH, R_f 0.18.

Anal. Calcd for $C_{11}H_{14}N_4SO_6$: C, 40.00; H, 4.24; N, 16.96; S, 9.70. Found: C, 39.83; H, 4.69; N, 17.00; S, 9.67.

Higher yields of the sulfone, with a purity sufficient for synthetic purposes, can be obtained by the following simple procedure. A solution of 1.013 g (3.37 mmol) of 6-methylthio-9-β-D-ribofuranosylpurine in 40 ml of 85% ethanol was cooled to −10° in a NaCl–ice water bath. Chlorine gas was slowly bubbled through as before, with the reaction going to completion after 15 min. Nitrogen gas was bubbled through for 5 min, during which time the sulfone dropped out of the concentrated solution as clusters of small needles. The reaction mixture was allowed to stand an additional 3–5 min at −10°, then filtered. The filtrate was washed with 10 ml of cold 85% ethanol and dried, giving 838 mg (2.54 mmol, 75% yield) of crystals melting in the range 90–96°, but chromatographically pure and giving an R_f value and UV spectrum identical with those of the material obtained by the first procedure.

Synthesis of 6-(2-Hydroxyethylmercapto)9-β-D-ribofuranosylpurine (4). To a solution of 125 mg (0.38 mmol) of sulfone 1 in 25 ml of water at 25° was added 0.1 ml of mercaptoethanol, and the solution was stirred for 4 hr. The solvent was removed under vacuum and the oil was pumped on for 0.5 hr to remove mercaptoethanol. Absolute ethanol was added and evaporated off, and the oil obtained was dissolved with warming in absolute ethanol and refrigerated. Crystals began to appear after 1 day and were collected after 4 days to give 55 mg (0.168 mmol, 44% yield) of 6-(2-hydroxyethylmercapto)-9-β-D-ribofuranosylpurine (4) as hydroscopic crystals, melting range 105–115°. λ_{max}, nm ($\epsilon \times 10^{-3}$): pH 7, 287 (16.9), 290 (16.9). PMR (DMSO-d_6): δ 8.89 (s, 1 H), 8.86 (s, 1 H), 6.11 (d, J = 5 Hz, 1 H), 5.60 (d, J = 5 Hz, 1 H), 5.00–5.35 (m, 3 H), 4.68 (q, J = 5 Hz, 1 H), 3.92–4.41 (m, 2 H), 3.47–3.84 (m, 6 H). TLC, silica gel, 9:1 EtAc–EtOH, R_f 0.18.

Anal. Calcd for $C_{12}H_{16}N_4SO_5 \cdot {}^1\!/_4H_2O$: C, 43.37; H, 4.97; N, 16.87; S, 9.64. Found: C, 43.33; H, 5.09; N, 16.67; S, 9.44.

Synthesis of 6-Azido-9-β-D-ribofuranosylpurine (6). To 700 mg (2.12 mmol) of sulfone 1 in 100 ml of anhydrous methanol was added 191 mg (2.94 mmol) of sodium azide, and the solution was stirred for 2 hr at 25°, then cooled overnight at 5°. The white amorphous solid was collected and the filtrate reduced in volume and cooled to give more solid material with the correct UV spectrum, a total of 559 mg (1.91 mmol, 90% yield). The product had a UV spectrum identical with that reported for 6-azido-9-β-D-ribofuranosylpurine (6) prepared by another route.[6] Its melting range is 212–214° (lit. 222°). PMR (DMSO-d_6): δ 10.15 (s, 1 H), 8.95 (s, 1 H), 6.18 (d, J = 5 Hz, 1 H), 5.64 (d, J = 6 Hz, 1 H), 5.00–5.37 (m, 2 H), 4.61 (q, J = 5 Hz, 1 H), 3.92–4.40 (m, 2 H), 3.50–3.83 (m, 2 H). TLC, silica gel, 9:1 EtAc–EtOH, R_f 0.25.

Synthesis of *O*-Ethyl 9-β-D-Ribofuranosylpurine-6-thiocarbamate (7). To 763 mg (2.67 mmol) of 6-chloro-9-β-D-ribofuranosylpurine in 30 ml of absolute ethanol was added 895 mg (9.2 mmol) of potassium thiocyanate, and the solution was refluxed 25 hr. The solvent was removed under vacuum and the crude mixture chromatographed on silica gel using an 8–12% linear gradient of methanol in chloroform. The product fractions were collected and the residue after removal of solvents was crystallized from hot ethanol, giving 207 mg (0.52 mmol, 19% yield) of the thiocarbamate, with ¾ ethanols of crystallization, melting range 103–106°. λ_{max}, nm ($\epsilon \times 10^{-3}$): pH 1, 305 (22.8); pH 7, 297 (20.1). PMR after exchange with D_2O and removal of ethanol of crystallization under vacuum): δ 11.94 (s, 1 H), 8.92 (s, 1 H), 8.88 (s, 1 H), 6.13 (d, J = 5 Hz, 1 H), 3.87–4.83 (m, 5 H), 3.53–3.86 (m, 2 H), 1.27 (6, J = 7 Hz, 3 H). TLC, silica gel, 9:1 EtAc–EtOH, R_f 0.32.

Anal. Calcd for $C_{13}H_{17}N_5O_5S \cdot {}^3\!/_4 CH_3CH_2OH$: C, 44.70; H, 5.51; N, 17.98; S, 8.22. Found: C, 44.70; H, 5.46; N, 18.15; S, 8.24.

Reaction of 6-Methylsulfonyl-9-β-D-ribofuranosylpurine (1) with Thiocyanic Acid Generated in Situ. To a solution of 17.5 mg (0.053 mmol) of sulfone (1) in 20 ml of ethanol were added 0.25 ml of a 1.0 *N* HCl solution and 13 mg (0.135 mmol) of potassium thiocyanate. The mixture was stirred at 25° for 9 hr, at which point a UV spectrum showed only the desired product. Thick layer chromatographic separation (silica gel, 3:1 EtAc–EtOH) gave one main nucleoside product, which was eluted and shown to be *O*-ethyl 9-β-D-ribofuranosylpurine-6-thiocarbamate (7) (0.14 mmol, 27% yield) by its TLC and UV properties.

Acknowledgment. We thank B. Seeger for the NMR spectra. Partial support for this project by the Deutsche Forschungsgemeinschaft is gratefully acknowledged. We also wish to thank Professor D. Shugar for helpful discussions.

Registry No.—1, 53821-41-3; **2**, 342-69-8; **4**, 53821-42-4; **6**, 53821-43-5; **7**, 53821-44-6; mercaptoethanol, 60-24-2; 6-chloro-9-β-D-ribofuranosylpurine, 5399-87-1; potassium thiocyanate, 333-20-0.

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Chlorination of 6-Methyl-1,6-naphthyridin-5(6*H*)-one

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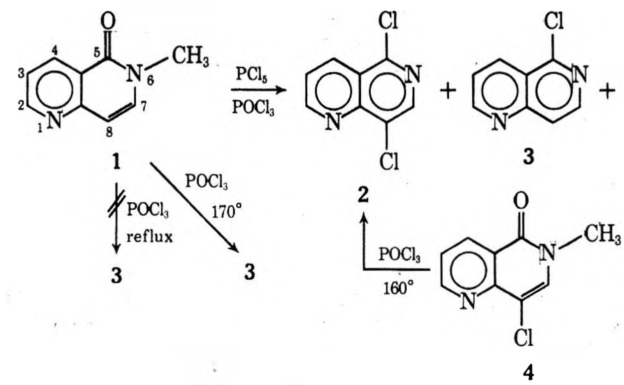
The reaction of 2-methyl-1-isoquinolone using $POCl_3$ and PCl_5 has been reported to yield 1-chloroisoquinoline.[1,2] An investigation by Haworth and Robinson[3] of this reaction found not only the major product but some 1,4-dichloroisoquinoline.

We subjected 6-methyl-1,6-naphthyridin-5(6*H*)-one (1) to the same reaction conditions as above and isolated 5,8-dichloro- (2) and 5-chloro-1,6-naphthyridine (3), 8-chloro-6-methyl-1,6-naphthyridin-5(6*H*)-one (4), and some starting material.



The structure of the major component (2) was established by spectroscopic measurement and chemical derivation. The mass spectrum indicated that the molecule contains two chlorine atoms. It was found by inspection of the nmr spectrum that the 2, 3, and 4 positions did not contain a chloro substituent since its line pattern was similar to that of the starting material and the parent ring compound.[4] The singlet absorption peak at 8.60 was assigned to the 7 proton on the following basis: (a) no cross ring coupling ($J_{4,8}$) was observed, and (b) the chemical shift of analogous protons in the isoquinoline series, 3-H (8.28) of 1,4-dichloroisoquinoline[5] and 4-H (7.80) of 1,3-dichloroisoquinoline.[6]

Since it is known that α and γ halogen substituents in quinoline[7] and isoquinoline[8] undergo nucleophilic displacement, 5,8-dichloro-1,6-naphthyridine was refluxed in a large excess of sodium methoxide in methanol for 4 hr. The mass spectrum of the product showed that the molecule now contains one methoxyl and one chloro group. The nmr spectral line pattern of the 2, 3, and 4 positions was unchanged from the starting material. The singlet proton at

8.10 ppm showed no other coupling (especially $J_{4,8}$). It is concluded from these data that the methoxy and chloro substituents are found in the 5 and 8 positions, respectively.

The second component, 5-chloro-1,6-naphthyridine, was identified by its melting point and nmr[9] and ir spectra.[10]

The third component, 8-chloro-6-methyl-1,6-naphthyridin-5(6*H*)-one, was identified by its ir spectrum and chemical conversion to (**2**). The spectrum of (**4**) indicated a carbonyl absorption at 1650, the same wavelength as found in the starting material. When (**4**) was reacted with $POCl_3$ in a sealed tube at 160°, the product was found to be identical to (**2**) by mixture melting point and nmr and ir spectra.

Since PCl_5 is a highly active chlorinating agent, reactions were attempted with $POCl_3$ under different conditions. The starting material was quantitatively isolated after a 12-hr reflux period. However, a 62.5% yield of 5-chloro-1,6-naphthyridine was obtained when the reaction took place in a sealed tube at 170° for 20 hr.

In the case of $POCl_3$ at an elevated temperature, only **3** is isolated. However, when a mixture of $POCl_3$ and PCl_5 is used, chlorination at the 8 position also occurs.

Experimental Section

1,6-Naphthyridine-6-methiodide.[4] 1,6-Naphthyridine (4.7 g, 0.036 mol) was dissolved in 40 ml of anhydrous methanol. To this was added 10.03 g (0.0724 mol) of methyl iodide, whereupon the mixture was refluxed 24 hr. The reaction mixture was cooled and 50 ml of ethyl acetate was added. A yellow precipitate was removed by filtration: yield 3.28 g; mp 154–156° (lit.[4] 153–155°). An additional 200 ml of ethyl acetate was added to the filtrate and cooled, and 2.43 g of yellow precipitate was removed: total yield 5.73 g (64%).

6-Methyl-1,6-naphthyridin-5(6*H*)-one.[4] 1,6-Naphthyridine-6-methiodide (5.50 g, 0.0202 mol) was dissolved in 50 ml of water and cooled to 0° in an ice bath. With stirring, 14.2 g (0.0435 mol) of potassium ferricyanide in 50 ml of water and 4.3 g (0.358 mol) of sodium hydroxide in 7.25 ml of water were added simultaneously. The base addition was complete in 10 min and the oxidizing agent addition was complete in 30 min. The solution was stirred at 0° for 90 min, then at room temperature for 27 hr. After continuously extracting the aqueous solution with chloroform for 24 hr, the chloroform was removed *in vacuo*. The residue was sublimed at 90°: yield 2.44 g (75.3%); mp 98–99° (lit.[4] 97–98°).

Chlorination Procedure. To a cold solution of 4.00 g (0.0192 mol) of PCl_5 and 20 ml of $POCl_3$ was added 2.25 g (0.0141 mol) of 6-methyl-1,6-naphthyridin-5(6*H*)-one. The mixture was refluxed with stirring for 24 hr. The excess $POCl_3$ was removed at reduced pressure and ice was added to the residue. After basifying with a saturated solution of sodium carbonate to pH 8, the solution was extracted with chloroform (4 × 50 ml). The chloroform extracts were dried overnight with anhydrous sodium sulfate and the chloroform was removed *in vacuo* at 20°. The residue was placed on an alumina column (Brockman Grade II, 150 g, 2.5 cm diameter) and chromatographed with 5% dichloromethane–carbon tetrachloride (50 ml in 450 ml) until the first band was isolated. Then elution was completed with ethyl acetate.

Fraction A: 5,8-dichloro-1,6-naphthyridine; yield 550 mg (23.9%); mp 113–115°; exact mass ($C_8H_4Cl_2N_2$) 197.969 (calcd 197.975); nmr 9.26 (m, 2-H), 8.67 (m, 4-H), 8.60 (s, 7-H), 7.68 (m, 3-H), $J_{2,4}$ = 1.6 Hz, $J_{2,3}$ = 4.4 Hz, $J_{3,4}$ = 8.8 Hz; ir 2970, 1600, 792, 610 cm^{-1}.

Fraction B: 5-chloro-1,6-naphthyridine; yield 38 mg (2.00%); mp 106–107° (lit.[9] 107°) (after sublimation at 60°).

Fraction C: 8-chloro-6-methyl-1,6-naphthyridin-5(6*H*)-one; yield 320 mg (14.3%); mp 199–200° (after sublimation at 155°); exact mass ($C_9H_7ClN_2O$) 194.025 (calcd 194.025); nmr 9.01 (m, 2-H), 8.68 (m, 4-H), 7.52 (s, 7-H), 7.38 (m, 3-H), 3.60 (s, $-NCH_3$) ($J_{2,3}$ = 4.6 Hz, $J_{2,4}$ = 1.7 Hz, $J_{3,4}$ = 8.0 Hz); ir 3150, 1650, 1570 cm^{-1}.

Fraction D: 6-methyl-1,6-naphthyridin-5(6*H*)-one; yield 400 mg; mp 98–99° (after sublimation at 60°); nmr and ir superimposable with starting material.

5-Methoxy-8-chloro-1,6-naphthyridine. 5,8-Dichloro-1,6-naphthyridine (100 mg, 0.502 mmol, from fraction A) and 200 mg of sodium methoxide were dissolved in 50 ml of anhydrous methanol and heated at reflux for 4 hr. The methanol was evaporated away with a stream of nitrogen and the residue was taken up in 20 ml of a saturated aqueous solution of sodium carbonate. The basic solution was extracted with chloroform (4 × 10 ml) and the extracts were dried overnight with anhydrous sodium sulfate. The chloroform was removed under a stream of nitrogen: yield 85.7 mg (88%); mp 80–82°; exact mass ($C_9H_7ClN_2O$) 194.019 (calcd 194.025); nmr (CCl_4) 8.92 (m, 2-H), 8.32 (m, 4-H), 8.10 (s, 7-H), 7.33 (m, 3-H), 3.98 (s, OCH_3) ($J_{2,3}$ = 4.8 Hz, $J_{2,4}$ = 1.6 Hz, $J_{3,4}$ = 9.4 Hz).

Conversion of 4 into 2. 8-Chloro-6-methyl-1,6-naphthyridin-5(6*H*)-one (**4**, 256 mg, 1.32 mmol) was combined with 25 ml of $POCl_3$ and heated for 16 hr in a sealed tube at 160°. The excess $POCl_3$ was removed at reduced pressure and the residue was taken up in 20 ml of an ice-cold, saturated, aqueous solution of sodium carbonate. The basic solution was extracted with chloroform (3 × 25 ml) which was dried overnight with anhydrous sodium sulfate. The chloroform was removed and the product was sublimed at 95°: yield 227 mg (88%); mp 112–114°; mp with **2** 112–113°.

Phosphorus Oxychloride with 6-Methyl-1,6-naphthyridin-5(6*H*)-one. A. 6-Methyl-1,6-naphthyridin-5(6*H*)-one was heated at reflux with 10 ml of phosphorous oxychloride for 12 hr. The isolation and work-up as described above was used. The starting material was isolated quantitatively and was identical in mp, and ir and nmr spectra.

B. Phosphorus oxychloride (5 ml) and 100 mg (0.625 mmol) of 6-methyl-1,6-naphthyridin-5(6*H*)-one were combined in a sealed tube and heated at 170° for 20 hr. The residue (81.4 mg), isolated as indicated above, was sublimed at 60–70°: yield 64 mg (62.5%); mp 106.5–107° (lit.[9] 107°); ir and nmr spectra were superimposable with that isolated earlier.

Registry No.—**1**, 19693-54-0; **2**, 53731-30-9; **3**, 23616-32-2; **4**, 53731-31-0; 1,6-naphthyridine-6-methiodide, 37960-58-0; 1,6-naphthyridine, 253-72-5; 5-methoxy-8-chloro-1,6-naphthyridine, 53731-32-1.

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Condensation of 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate with Ethyl Cinnamate and Related Compounds

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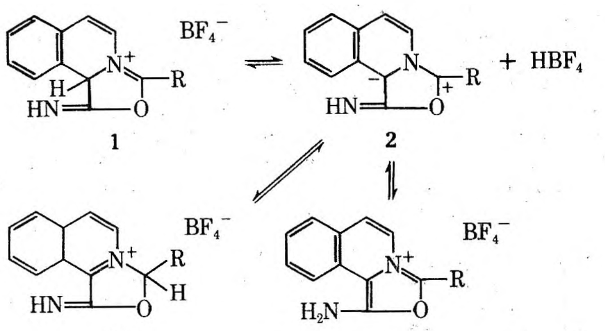
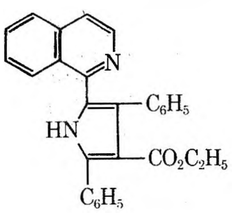
Evidence has been presented[1] that freshly prepared hydrofluoroborate salts of 2-acyl-1,2-dihydroisoquinaldonitriles (Reissert compounds[2]) have the structure **1**, but, in solution, an equilibrium mixture of **1**, **3**, and **4** results. These salts are also presumed to be in equilibrium with the 1,3-dipolar compound **2** (a mesoionic compound) and fluoroboric acid. Several studies of 1,3-dipolar addition reactions of hydrofluoroborate salts of Reissert compounds



1 2 3 4

have been reported.[3-6] Numerous examples of complex, acid-catalyzed condensation–rearrangement reactions of Reissert compounds with olefins have also been reported.[7-10] It is believed that these condensation–rearrangement reactions involve an initial Diels–Alder type of condensation of the olefin with the isomeric form **4** of the Reissert salt, and detailed mechanisms of reaction have beer suggested.[9,10] We now wish to report, as a useful synthetic procedure, the condensation of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (**1**, R = C_6H_5) with ethyl cinnamate and related compounds.

Ethyl 3,5-diphenyl-2-(1-isoquinolyl)pyrrole-4-carboxylate (**5**) has been obtained in 64% yield by treatment of 2-



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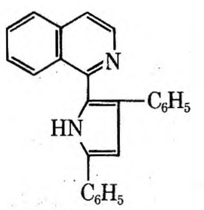

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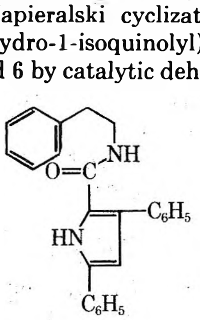
benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (**1**, R = C_6H_5) with ethyl cinnamate in dimethylformamide solution for 20 hr at room temperature. The reaction was regiospecific, and no isomeric product could be found in the reaction mixture.

The first step in the proof of structure of **5** (apart from routine spectral and elemental analyses) was its acid-catalyzed hydrolysis and decarboxylation to give 2-(1-isoquinolyl)-3,5-diphenylpyrrole (**6**). The known[11] 2,4-diphenylpyrrole was the principal starting material for an unambiguous synthesis of **6**. An exchange reaction with ethylmagnesium bromide and subsequent treatment with ethyl chloroformate provided ethyl 2,4-diphenylpyrrole-5-carboxylate. Condensation of the ester with β-phenethylamine gave *N*-(2-phenethyl)-3,5-diphenylpyrrole-2-carboxamide (**7**). Bischler–Napieralski cyclization of the amide provided 2-(3,4-dihydro-1-isoquinolyl)-3,5-diphenylpyrrole (**8**), which afforded **6** by catalytic dehydrogenation.



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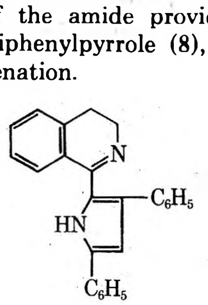

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The condensation of **1** (R = C_6H_5) with ethyl *p*-nitrocinnamate gave, in 62% yield, a single product which, on the basis of analogy and spectral comparisons, is assigned the structure of ethyl 2-(1-isoquinolyl)-3-(*p*-nitrophenyl)-5-phenylpyrrole-4-carboxylate. The condensation of **1** (R = C_6H_5) with ethyl acrylate, methylene chloride–ethanol being used as cosolvents in this case, also proceeded smoothly to give, in 67% yield, the known[10] ethyl 2-(1-isoquinolyl)-5-phenylpyrrole-3-carboxylate. Once again, no isomeric product was detected.

The herein described method for the preparation of highly substituted pyrroles appears to be reasonably general and regiospecific, and therefore it can serve as a useful synthetic procedure. Detailed kinetics studies are being initiated, and these plus other approaches should provide additional insights into the general mechanism proposed previously.[3,10,12]

Experimental Section[13]

2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (1, R = C_6H_5). This compound, mp 196–198° dec, was prepared as described previously.[5]

Condensation of 1 (R = C_6H_5) with Ethyl Cinnamate. A mixture of 2.28 g (6.55 mmol) of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (**1**, R = C_6H_5), 1.16 g (6.58 mmol) of ethyl cinnamate, and 20 ml of dimethylformamide was stirred at room temperature for 20 hr, and the mixture was then poured into 500 ml of water. The aqueous suspension was extracted five times with benzene (1 l. total). The benzene extract was dried over anhydrous magnesium sulfate, filtered, and concentrated to a small volume. This was chromatographed on neutral alumina, benzene–chloroform (1:1) being used as the eluent. Ethyl 3,5-diphenyl-2-(1-isoquinolyl)pyrrole-4-carboxylate (**5**) was obtained by evaporation of the eluent of the first light yellow band. After crystallization from 95% ethanol, this compound weighed 1.75 g (64%): mp 169–170°; ir ($CHCl_3$) 3440 (NH) and 1700 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 0.96 (t, 3 H, *J* = 10 Hz), 4.04 (q, 2 H, *J* = 10 Hz), 6.8–7.8 (m, 16 H), 13.50 (s, 1 H).

Anal. Calcd for $C_{28}H_{22}N_2O_2$: C, 80.36; H, 5.30; N, 6.69; O, 7.65. Found: C, 80.16; H, 5.38; N, 6.50; O, 7.82.

A somewhat higher yield (70%) of **5** was obtained when methylene chloride–ethanol was used as the solvent at the reflux temperature. The detailed procedure is the same as that described below for the preparation of ethyl 2-(1-isoquinolyl)-5-phenylpyrrole-3-carboxylate.

Decarbethoxylation of 5. A mixture of 0.60 g (1.4 mmol) of **5** and 6 ml of 85% phosphoric acid was refluxed for 30 min under a nitrogen atmosphere. The reaction mixture was poured onto ice and neutralized with concentrated ammonia water. A yellow solid which precipitated was collected by filtration and crystallized twice from 95% ethanol. There was obtained 0.20 g (25%) of 2-(1-isoquinolyl)-3,5-diphenylpyrrole (**6**): mp 226–228°; ir ($CHCl_3$) 3460 (NH), 3080, 3025, 1605, 1587, 1552, 1500, 1470, 1405, 1354, 830, 700 cm^{-1} (the peaks of medium intensity); nmr ($CDCl_3$) δ 6.90 (d, 1 H, *J* = 3 Hz), 7.0–8.3 (m, 16 H), 12.15 (s, broad, 1 H).

Anal. Calcd for $C_{25}H_{18}N_2$: C, 86.67; H, 5.24; N, 8.09. Found: C, 86.50; H, 5.32; N, 7.68.

Ethyl 2,4-Diphenylpyrrole-5-carboxylate. The method employed was a modification of the procedure used for the preparation of ethyl 2,3,4-trimethylpyrrole-5-carboxylate.[14]

Ethylmagnesium bromide was prepared from 14.50 g (0.134 mol) of ethyl bromide and 3.23 g (0.132 mol) of magnesium turnings in 180 ml of absolute ether. To this solution was added as rapidly as possible, consistent with frothing due to evolution of ethane, a solution of 18.0 g (0.082 mol) of 2,4-diphenylpyrrole in 400 ml of anhydrous ether, and the mixture was refluxed for 30 min. The mixture was cooled to room temperature, and a solution of 12.00 g (0.110 mol) of ethyl chloroformate in 30 ml of anhydrous ether was added dropwise. The mixture was refluxed with stirring for 2.5 hr and then allowed to stand at room temperature for 10 hr. To the cooled mixture was added 120 ml of saturated ammonium chloride solution and then 120 ml of water. The ether layer was separated from the aqueous layer and washed twice with 200 ml of water. Concentration of the ether solution, which had been dried over anhydrous sodium sulfate, led to crystallization of the product. This was washed with cold alcohol and crystallized from 95% ethanol to give 7.30 g (31%) of colorless ethyl 2,4-diphenylpyrrole-5-carboxylate: mp 140–144°; ir ($CHCl_3$) 3440 (NH), 1670 (ester C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.21 (t, 3 H, *J* = 6.7 Hz), 4.24 (q, 2 H, *J* = 6.7 Hz), 6.63 (d, 1 H, *J* = 3 Hz), 7.1–7.8 (m, 10 H), 9.67 (s, broad, 1 H).

Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.14; H, 5.70; N, 4.63.

***N*-(2-Phenethyl)-3,5-diphenylpyrrole-2-carboxamide (7).** A mixture of 6.30 g (0.022 mol) of ethyl 2,4-diphenylpyrrole-5-carboxylate and 8.47 g (0.070 mol) of β-phenethylamine was heated at 240–250° for 8 hr. The dark brown liquid was cooled to room temperature and then induced to deposit crystals by addition of small amounts of ether and Skelly B solvent. The solid was washed with ether and crystallized from 95% ethanol to give 2.80 g (35%) of **7**: mp 177–179°; ir ($CHCl_3$) 3435 (NH), 1627 (amide C=O) cm^{-1}; nmr ($CDCl_3$) δ 2.68 (t, 2 H, *J* = 6.7 Hz), 3.52 (q, 2 H, *J* = 6.7 Hz), 5.85 (t, broad, 1 H), 6.49 (d, 1 H, *J* = 3 Hz), 6.9–7.8 (m, 15 H), 10.55 (s, broad, 1 H).

Anal. Calcd for $C_{25}H_{22}N_2O$: C, 81.93; H, 6.05; N, 7.65. Found: C, 82.14; H, 6.04; N, 7.60.

2-(3,4-Dihydro-1-isoquinolyl)-3,5-diphenylpyrrole (8). A mixture of 1.0 g (2.7 mmol) of **7** and 10 g of phosphorus pentoxide in 15 ml of anhydrous *p*-xylene was heated under reflux for 6 hr. The hot *p*-xylene layer was decanted from a black, insoluble residue. The residue was added to 600 ml of ice-cold water with stirring, and a brown solid which formed was collected by filtration, washed with water, and suspended in concentrated sodium hydroxide solution. The suspension was diluted with water and then neutralized with 6 *N* sulfuric acid. The mixture was extracted with benzene, and the benzene extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated, and the residue was chromatographed on alumina by the dry column technique.[15] Elution with benzene produced a yellow band near the top of the column, and this was cut out and extracted with benzene. Evaporation of the benzene gave a brown solid, which was crystallized from 95% ethanol–Skelly B solvent. A crystalline product of mp 209–211° was recrystallized from acetone to give 0.20 g (21%) of **8**: mp 214–216°; ir ($CHCl_3$) 3440 (NH), 1601 (C=N) cm^{-1}; nmr ($CDCl_3$) δ 2.70 (t, 2 H, *J* = 7 Hz), 3.60 (t, 2 H, *J* = 7 Hz), 6.76 (s, 1 H), 6.8–7.8 (m, 14 H), 10.26 (s, broad, 1 H).

Anal. Calcd for $C_{25}H_{20}N_2$: C, 86.17; H, 5.79. Found: C, 86.14; H, 5.85.

2-(1-Isoquinolyl)-3,5-diphenylpyrrole (6). A mixture of 0.15 g (0.43 mmol) of **8** and 0.08 g of 10% palladium-on-carbon catalyst was suspended in 6 ml of decalin and refluxed in a nitrogen atmosphere, with stirring, for 5 hr. The mixture was filtered, and the filtrate was evaporated to dryness by application of a jet of air. The residue was triturated in petroleum ether, then crystallized from benzene–Skelly B solvent. The product, mp 221–223°, was chromatographed on alumina by the dry column technique.[14] Two yellow bands were developed by elution with benzene. The eluent of the first yellow band gave 0.06 g (40%) of **6** on evaporation, mp 226–228° (after recrystallization from 95% ethanol), also in admixture with the sample prepared by decarbethoxylation of **5**. The ir and nmr spectra of the two samples were identical.

Condensation of 1 (R = C_6H_5) with Ethyl *p*-Nitrocinnamate. The reaction of 2.32 g (6.66 mmol) of **1** (R = C_6H_5) with 1.45 g (6.55 mmol) of ethyl *p*-nitrocinnamate in 20 ml of dimethylformamide was carried out in the same manner as described previously for the corresponding ethyl cinnamate reaction. There was obtained 1.88 g (62%) of yellow crystals of ethyl 2-(1-isoquinolyl)-3-(*p*-nitrophenyl)-5-phenylpyrrole-4-carboxylate: mp 224–225°; ir ($CHCl_3$) 3440 (NH), 1700 (ester C=O), 1345 (NO_2), 1510 (NO_2) cm^{-1}; nmr ($CDCl_3$) δ 1.00 (t, 3 H, *J* = 7 Hz), 4.10 (q, 2 H, *J* = 7 Hz), 7.0–8.1 (m, 15 H), 13.80 (s, 1 H).

Anal. Calcd for $C_{28}H_{21}N_3O_4$: C, 72.56; H, 4.57; N, 9.07. Found: C, 72.72; H, 4.45; N, 8.89.

Condensation of 1 (R = C_6H_5) with Ethyl Acrylate. A mixture of 1.5 g (4.31 mmol) of **1** (R = C_6H_5), 3 ml of ethyl acrylate, and 30 ml of methylene chloride was heated under reflux as 95% ethanol was added slowly until the solution became clear, 70 ml being required. The solution was refluxed for another hr, and the solvents were removed by evaporation in a rotary evaporator. The reddish residue was extracted with 300 ml of benzene and chromatographed on neutral alumina to give a yellow, gummy material. This was induced to crystallize from a mixture of ethyl acetate and Skelly B solvent. There was obtained 0.99 g (67%) of ethyl 2-(1-isoquinolyl)-5-phenylpyrrole-3-carboxylate, mp 149–150°, also in admixture with a sample of the known[10] compound. The ir and nmr spectra of the two samples, taken in chloroform and deuteriochloroform, respectively, were identical.

Acknowledgment. This work was supported in part by a grant from the National Science Foundation.

Registry No.—**1** (R = C_6H_5), 33969-32-3; **5**, 53778-22-6; **6**, 53778-23-7; **7**, 53778-24-8; **8**, 53778-25-9; ethyl cinnamate, 103-36-6; ethyl 2,4-diphenylpyrrole-5-carboxylate, 53778-26-0; ethyl bromide, 74-96-4; 2,4-diphenylpyrrole, 3274-56-4; β-phenethylamine, 64-04-0; ethyl *p*-nitrocinnamate, 953-26-4; ethyl 2-(1-isoquinolyl)-3-(*p*-nitrophenyl)-5-phenylpyrrole-4-carboxylate, 53778-27-1; ethyl acrylate, 140-88-5.

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Synthesis of 2-Methylpiperidine-*2-d*. Choice of Reductive Methods from Azomethine Precursors[1]

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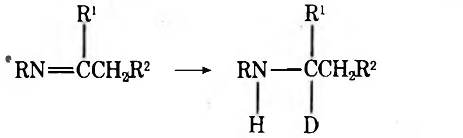
The synthesis of *2-d* 2-alkylamines by reductive methods from azomethine precursors (eq 1) is attended with some

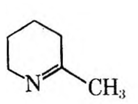


(1)

difficulties. We wish to report a simple method avoiding these problems.

Thus, catalytic deuteration (PtO_2) of 2-methyl-Δ^1-piperideine[2] in methyl acetate gave a product showing two signals of equal intensity for the methyl group in its NMR spectrum: a doublet (*J* = 6 Hz) at 1.05 ppm and a singlet at 1.05 ppm. From the ratio of methyl protons:methylene protons at C-3, 4, and 5 (m, 1.15–2.05 ppm):methylene protons at C-2 and 6 (m, 2.4–3.4 ppm), the composition of the mixture was 20% each of **2a** and **2b** and 30% each of **2c** and **2d**; mass spectral data confirmed *m/e* 99, 100, and 101.

This result may be explained by the possibility of rearrangement of the azomethine **1** to the tautomeric enamine **3**,[3] allowing hydrogen from position 3 to enter the pool. Olefins are known to isomerize on catalytic hydrogenation,[4] leading to a mixture of reduction products.[5] Alternatively, the known[4] reversibility of the hydrogenation step could result in the introduction of hydrogen (as DH) into the



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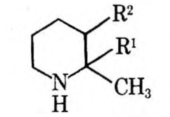
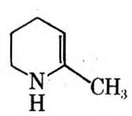


2a, $R^1 = R^2 = H$
b, $R^1 = D, R^2 = H$
c, $R^1 = R^2 = D$
d, $R^1 = H, R^2 = D$



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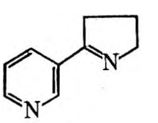

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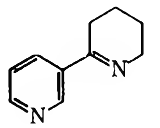

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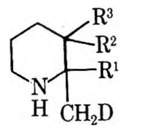

6a, $R^1 = R^2 = D, R^3 = H$
b, $R^1 = R^2 = R^3 = D$

deuterium pool, giving molecules containing more than two deuterium atoms. However, no exchange was observed (NMR) on submitting **2a** to the same catalytic deuteration conditions used above, so that the first explanation appears the more likely.

A similar effect may account for the results reported[6] on catalytic deuteration of myosmine **4** which yielded nornicotine-2-d_1 containing 65% d_1 and 35% d_0 species, and of anabasene **5** which afforded 70% d_1 and 30% d_0 species.

Sodium borohydride (usually in methanol or ethanol solution) has been shown[7,8] to be an effective reagent for the reduction of isolated Schiff bases, although this reduction is relatively slow[9,10] compared with that of aldehydes and ketones.[11] Two examples[12] of borodeuteride reduction of cyclic iminium salts are recorded in the yohimbine series, using deuteriomethanol as solvent.[13]

When **1** was reduced with sodium borodeuteride in D_2O and CH_3OD, the product showed a singlet for the methyl group (1.05 ppm) indicating the absence of hydrogen at C-2. The ratio of methyl:C-3, 4, and 5 methylene:C-6 methylene protons was, however, 2:4.6:2, and this together with mass spectral data (*m/e* 102 and 103) indicated a 1:1 mixture of **6a** and **6b**. Allylic deuterium exchange of **1** with the solvent thus appears to be a faster process than reduction.

In agreement with this conclusion, reduction of **1** with borodeuteride under identical conditions but using *aqueous methanol* gave pure **2b** in excellent yield, fully deuterated at C-2 only, as shown by the appearance of a singlet for the methyl group in its nmr spectrum.

Kinetic studies on the hydrolysis of hydroborate and of d_4-hydroborate,[14a] and of hydrogen exchange between hydroborate and water,[14b] suggested that the rate of exchange is only 6% of that for hydrolysis, and it has been shown[15] that there is very little isotopic exchange of sodium borohydride in aqueous solution at pH 9 and none[16] at pH 12. The preparation reported above confirms that borodeuteride reduction of Schiff bases, albeit slower than that of carbonyl, is fast enough to permit quantitative conversion of, e.g., **1** → **2b** to take place in protic solvents such as aqueous methanol without hydrogen exchange, double bond migration, or other side reactions.[17]

Experimental Section

2-Methylpiperidine-*2-d*. **1** (1g) was stirred with 0.42 g (1 mol) of $NaBD_4$ in 2 ml of CH_3OH and 3 ml of H_2O at 20° for 16 hr. Removal of CH_3OH, extraction with ether, and distillation of the dried (Na_2SO_4) extract gave 0.8 g (80%) of **2b**: bp 117°; mol wt, 100 (calcd for $C_6H_{12}DN$: 100), NMR ($CDCl_3$) δ 1.06 (s, 3 H), 1.15–2.05 (m, 6 H), 2.4–3.4 (m, 2 H). The product showed a single peak on GLC (10% Apiezon-L, 2% KOH on 80/100 Supelcon AW, column temp 70°) identical in retention time (2.88 min) with that of **2a** but different from that of **1** (4.3 min).

Registry No.—**1**, 1462-92-6; **2b**, 5382-40-2; $NaBD_4$, 15681-89-7.

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Communications

Marine Natural Products. Dactylyne, an Acetylenic Dibromochloro Ether from the Sea Hare *Aplysia dactylomela*

Summary: Dactylyne, a new acetylenic dibromochloro ether isolated from the sea hare, *Aplysia dactylomela,* has been determined by single-crystal X-ray diffraction analysis to be a substituted tetrahydropyran having the structure and absolute configuration shown in **1**.

Sir: Marine organisms, in particular algae, are proving to be a rich source of halogenated natural products,[1] among which are a small group of halogenated ethers characterized by a straight-chain C-15 carbon skeleton and a terminal enyne function.[2] In our continuing investigation[3] of the chemistry of a sea hare, *Aplysia dactylomela,* we have now isolated a new compound in this class and herein report its structure.[4]

Dactylyne, $C_{15}H_{19}OBr_2Cl$,[5] mp 62.2–63.3°, $[\alpha]^{25}D$ −36° (*c* 15.2, $CHCl_3$), was obtained from the hexane extracts[3] of the sea hare by chromatography first over Florisil and then repeated chromatography of selected fractions over silicic acid. The presence in dactylyne of a conjugated terminal enyne group similar to that present in laureatin and related compounds[2] was indicated by ir ($CHCl_3$) [3305, 2100 (very weak) cm^{-1}], uv [λ_{max} (isooctane), 222.5 nm (ϵ 12,000)] and nmr data (see Table I, signals at 3.18, 5.6 and 6.12 ppm). Nmr data also indicated the presence of a CH_3CH_2-$CX{=}CHCH_2$ group (δ 1.14, 2.48, and 5.8 ppm signals) in dactylyne.

The complete structure and absolute stereochemistry of dactylyne were determined by single-crystal X-ray diffraction. A suitable single crystal was obtained by recrystallization from a hexane–ether mixture. The space group is $P2_12_12_1$ with unit cell dimensions a = 8.788 (2), b = 12.1383 (8), c = 15.752 (4). The intensities of all reflections with $\theta < 65°$ were measured with Cu Kα radiation [λ (Cu Kα) = 1.5418 Å], on a CAD-4 automatic diffractometer using θ–2θ scans. Only the intensities for which $I > 1.4\sigma(I)$ were used in the structure determination. The structure was solved by the heavy-atom method. The present R value, on F, for the 1263 observed reflections is 0.109. The absolute configuration was determined using the method of Bijvoet, Peerdeman, and van Bommel.[6] A view of the molecule showing the stereochemistry and absolute configuration is given in Figure 1. The distances of 1.35 (2) Å and 1.34 (3) Å for C(3)–C(4) and C(12)–C(13) establish them as double bonds, while a distance of 1.21 (3) Å for C(1)–C(2) establishes it as a triple bond.

Table I
Nmr Spectral Data[a] for Dactylyne

δ	No. of H's	Assignment	Multiplicity, *J*
1.14	3	H-15	t, 7
3.0-2.20	8	H-5,8,11,14	m[b]
3.18	1	H-1	dd, 2, 1
3.37	1	H-10 (or 6)	dt, 7, 2
3.71	1	H-6 (or 10)	d of dd, 8, 7, 2[c]
4.12	2	H-7,9	m
5.60	1	H-3	d (11) with further fine splitting 2,1
5.8	1	H-12	t, 7
6.12	1	H-4	Complex m

[a] $CDCl_3$ solvent. [b] δ 2.3–2.65 appears as a quintet superimposed on other absorption; at 220 MHz an unambiguous quartet centered at 2.48 ppm is evident. [c] Central members overlapped.

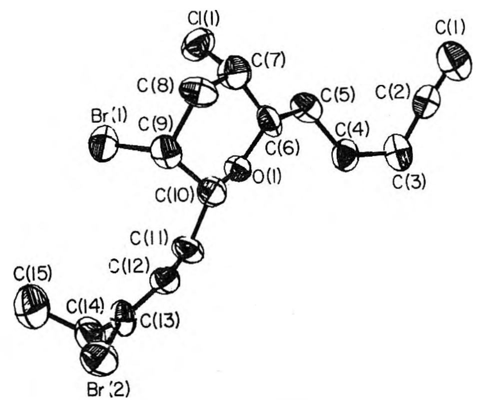
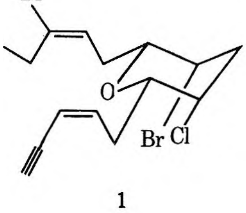


Figure 1. Computer perspective drawing of dactylyne.

Catalytic reduction (platinum/ethyl acetate) of dactylyne gave octahydromonodebromodactylyne (**2**, $C_{15}H_{28}OBrCl$).[7] Retention of both halogens on the ring was indicated by the similarity of the proton absorptions ($CDCl_3$) due to deshielding by the halogens and oxygen in **2** [δ 4.14, (2, m, CHBr, CHCl), 3.54 and 3.31 ppm (1 each, m, 2 CHO)] compared with the corresponding absorptions of **1** (see Table I) and also to the presence at δ 2.76 ppm of a distinct pair of doubled triplets whose intense inner members overlap, corresponding to the ring methylene protons flanked by halogen-substituted carbon atoms.[8] Irradiation of the δ 4.14 ppm signal collapsed the 2.76 multiplet to a broad singlet and altered each of the multiplets at 3.31 and 3.54 ppm. In the nmr spectrum of **2** taken in benzene-d_6 the ring methylene proton signals appear as a well-resolved pair of doubled triplets centered at 1.78 (J = 16, 4) and 2.45 ppm (J = 16, 2).[9]



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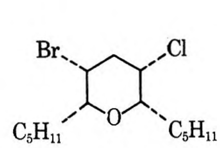

2

Dactylyne differs from all of the other reported members of the algal derived halogenated ethers having a straight-chain C-15 skeleton in that it has a six-membered ether ring rather than a four-, five-, eight-, or nine-membered ether ring as found in other members of this group. Dactylyne is similar to chondriol[2e] and rhodophytin[2f] in that it is chlorinated at C-7 rather than oxygenated as it is in all of the other members of this family, but the absolute configurations at C-6 and C-7 in **1** are opposite to those in chondriol.[2e] Dactylyne is assumed to be of algal origin since it has been demonstrated in other cases[1b,10] that halogenated compounds isolated from sea hares are present in the algae on which the animals feed.

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(3) F. J. Schmitz and F. J. McDonald, *Tetrahedron Lett.*, 2541 (1974).

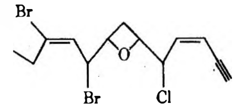
(4) In a preliminary report [F. J. Schmitz, D. C. Campbell, and F. J. McDonald, *Int. Symp. Chem. Nat. Prod., Abstr., 95th,* 12e (1974)] the structure **3**, see footnote 8 below, was proposed for dactylyne.

(5) *Anal.* Calcd for $C_{15}H_{19}OBr_2Cl$: C, 43.85; H, 4.66; Br, 38.93; Cl, 8.63. Found: C, 44.20; H, 4.73; Br, 37.61; Cl, 8.59; M^+, 412 (2%), 410 (3%), 408 (1.5%) (high resolution ms: obsvd, 407.94890; calcd, 407.94911).

(6) J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, *Nature*, **168**, 271 (1951).

(7) Mp 52-53°, $[\alpha]^{25}D$ −0.90° (*c* 5.4, $CHCl_3$). Calcd for $C_{15}H_{26}BrClO$: C, 53.10; H, 8.26; Br, 23.55; Cl, 10.44; Found: C, 53.47; H, 8.24, Br, 23.11; Cl, 10.09; M^+, 340 (6%), 338 (5%).

(8) It is interesting to note that the protons on the carbons bearing different halogens absorb at the same chemical shift position while the protons on the two ether carbons, which might be expected to absorb at the same position, in fact resonate at different positions. If the assignments of the protons on carbons bearing oxygen (C-6, C-10), see Table I and above, and those of carbons bearing halogen (C-7, C-9) are reversed, the nmr data alone (including decoupling) would suggest the structure **3**



3

for dactylyne as was proposed in a preliminary report.[4] This indicates that extreme caution must be exercised in making chemical shift assignments in this group of compounds.

(9) The marked difference in chemical shift of these two methylene protons in benzene-d_6 can be rationalized by assuming that the aromatic solvent is much more closely associated with the unhindered face of **2** and hence the axial methylene proton is shifted upfield more than its equatorial counterpart. The observed coupling constants of 4 and 2 Hz are also in accord with expectations for an axial–equatorial coupling and a diequatorial coupling, respectively [R. U. Lemieux and J. W. Lown, *Can. J. Chem.*, **42**, 893 (1964)].

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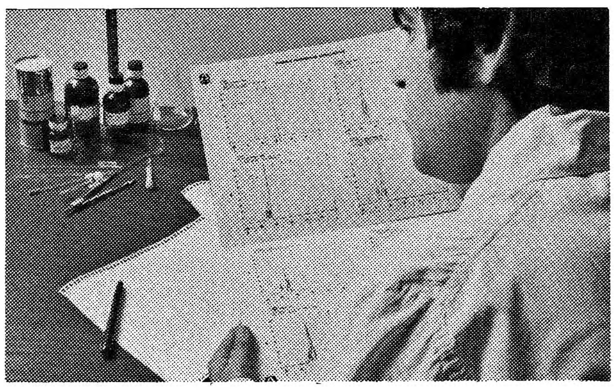

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