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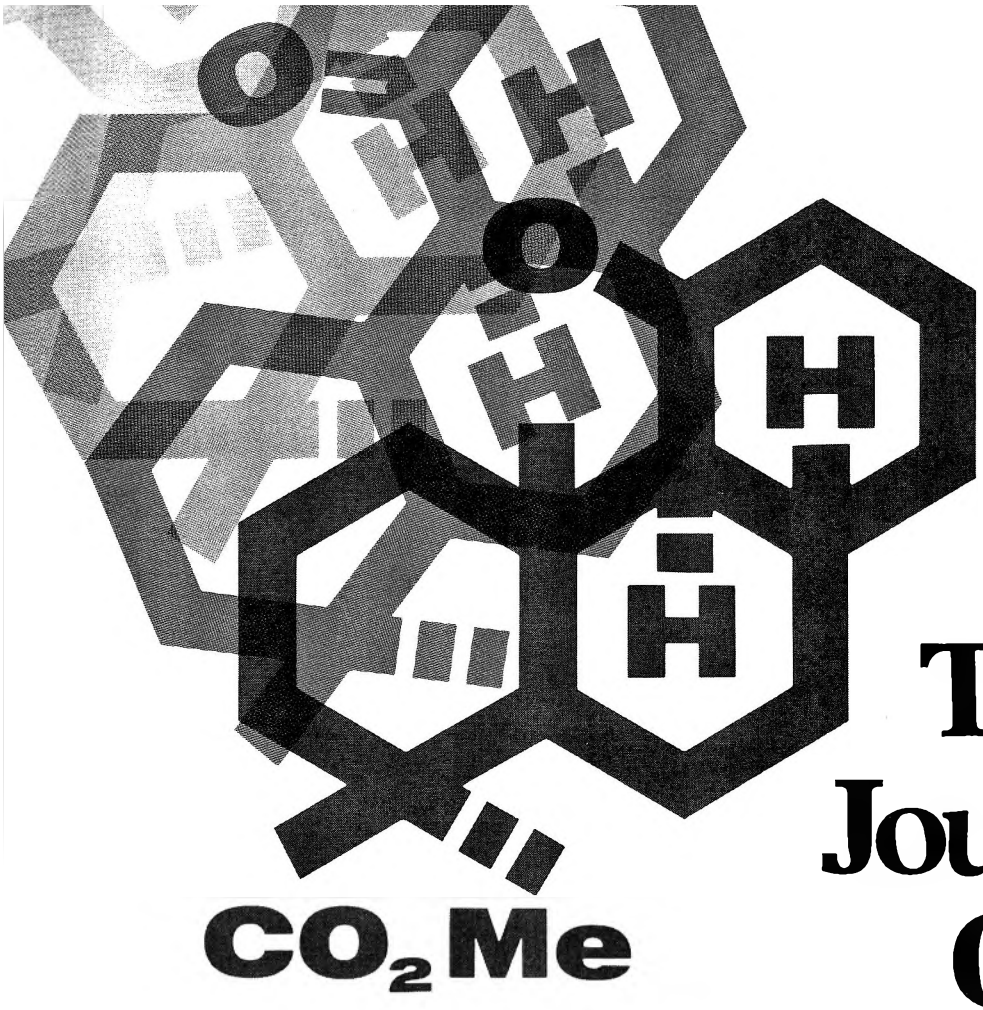

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AUGUST 8, 1975

Nickel-Catalyzed Displacement Reactions of Aryl Halides

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A series of new nickel-catalyzed displacement reactions of aryl halides is reported. The effects of variations in reaction conditions, reactant and catalyst structures, and additives were studied. Results are presented of an attempt to define the mechanism of the catalytic amination reaction. A brief account is also given of the catalysis of several of these reactions by cobalt halides.

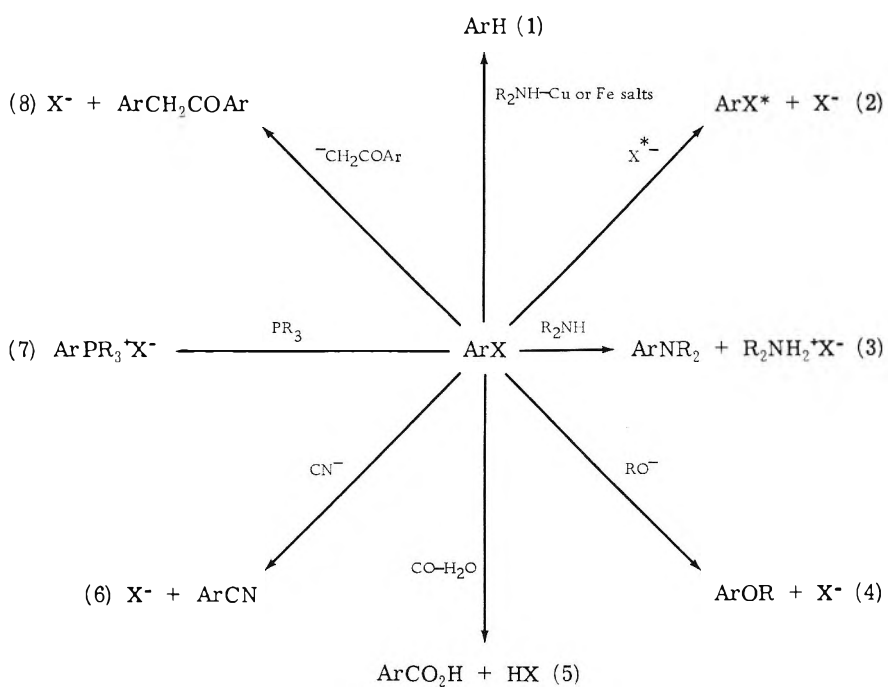
Several types of reactions of aryl halides are known[1-6] to be catalyzed by metal compounds. Among the catalysts employed, copper compounds have stood out as the most generally effective and versatile. Recently, certain nickel compounds have been reported to catalyze the syntheses of nitriles[2] (Scheme I, eq 6), carboxylic acids[3] (eq 5), aryl ketones[4] (eq 8), and phosphonium salts[5] (eq 7) from aryl halides. An early report[6] also found $NiCl_2$ to be an effective catalyst in the reaction of methylamine with chlorobenzene (eq 3). We wish to report a series of additional reactions of this type (eq 1–4) which, when added to those previously reported, comprise a group of reactions which rival the synthetic versatility of copper-catalyzed aryl halide displacement reactions.[7] Since our initial work was mostly concerned with the amination reaction (eq 3), this reaction was most extensively studied. Thus, attempts to define its mechanism are also described. Although they were inconclusive, several important phenomena were observed which we feel must be accounted for in any future mechanism study. The other displacement reactions (eq 1, 2, and 4) are described in less detail.

Experimental Section

Materials. The nickel aryls $C_6H_5NiBr[P(C_6H_5)_3]_2$ and *o*-$CH_3C_6H_4NiCl[P(C_6H_5)_3]_2$ were prepared from $Ni[P(C_6H_5)_3]_3 \cdot nP(C_6H_5)_3$ and the appropriate aryl halide according to the method described by Hidai et al.[10] The nickelate $[N(C_4H_9)_4]_2Ni_3(CO)_8$ was prepared following Cassar and Foà.[3] Other reagents were commercially available and were used without additional purification.

Experimental Techniques. Most reactions were run in sealed, thick-walled glass tubes of about 5 ml capacity. This technique avoids uncontrolled catalysis or poisoning by autoclave walls while

Scheme I
Nickel-Catalyzed Reactions of Aryl Halides



permitting experiments at superatmospheric pressures. Reactants, catalyst, and solvent were charged into the tube by pipet or by condensation and freed of air by alternately (1) freezing in liquid nitrogen and evacuating to <0.1 mm, then (2) thawing to release trapped gas. The evacuated tubes were sealed, wrapped in woven metal or fiberglass fabric for safety, and charged into an autoclave with 100 ml of water added for heat transfer and to counterbalance pressure. In order to further balance pressure that might be generated within the tubes, the autoclave was pressured to 2000 psi with nitrogen. The autoclave was then heated for specified times and its contents were agitated by reciprocal shaking along its axis. After cooling in air the tubes were chilled in liquid nitrogen and opened and the contents were analyzed by vapor phase chromatography and mass spectrometry. Since six tubes could be conveniently heated at one time, a variety of systems could be studied expeditiously.

The sealed tube technique gives the results of accumulated reaction but is not appropriate for following the course of reaction as in kinetic studies. For that work we used 100-ml globular valved glass reactors containing magnetic stirrer bars. These reactors had two inlets. One was a capillary tube which extended through the top to the bottom of the reactor. It was closed by a needle valve (with Teflon resin plunger) through which samples could be withdrawn for analysis. The other was a heavy-walled, 12-mm d. tube through which reactants were introduced. Reaction mixtures were deoxygenated as described earlier and the 12-mm inlet fused. Nitrogen was admitted (7 psig) through the valve to provide the pressure to drive analytical samples from the reactor. Most experiments designed to find reaction rates were made in the temperature range 120–170° and extended through 7 hr. Tests showed that 5–7 min was required for the reactants to reach bath temperature so sampling for analysis was started 0.5 hr after the reactor was mounted in the thermostatted bath.

Aminations. Standard Conditions. The standard charge for aminations of halobenzenes in sealed glass tubes consisted of 0.02 mmol of nickel compound, 2 mmol of aryl halide, and 20 mmol of amine in 1.2 ml of ethanol unless otherwise noted. The reasons for using excess amine and for selecting ethanol as solvent are described in the Results and Discussion.

Reduction of $NiCl_2$ and $NiBr_2$ by Dimethylamine. A sample of anhydrous $NiCl_2$ (0.25 g, 2 mmol) and dimethylamine (500 ml, 20 mmol) were placed in a tube and sealed. The tube was heated to 210° for 6 hr, giving a product consisting of two liquid phases and a black solid. The upper liquid phase proved to be completely volatile at room temperature, yielding ca. 250 ml of gas. Mass spectrometric and infrared analysis revealed the composition (mol %) 1.5% NH_3, 61% Me_2NH, and 37.5% Me_3N. The more dense liquid phase was only partially volatile, giving 120 ml of gas having the composition (mol %) 17% NH_3, 70% Me_2NH, and 13% Me_3N. The residue remaining proved to be Me_2NH_2Cl. Note that the overall ratio of Me_3N:NH_3 is ca. 5:1 while a ratio of 2:1 would be expected from the disproportionation of Me_2NH. The black solid was washed with dimethylamine until the wash was free of chloride ion. Elemental analysis showed the resulting residue to contain 3.25% C, <0.3% H, and 1.37% N, the rest presumably being nickel. X-Ray diffraction analysis indicated that it was mostly elemental Ni but Ni_3C was also present.

Similar treatment of $NiBr_2$ (0.20 g, 0.92 mmol), ethanol (1.2 ml), and dimethylamine (520 ml, 21 mmol) at 210° for 6 hr gave a mixture of volatiles whose composition (mol %) was found to be 16% Me_3N, 80% Me_2NH, and 2% each of $MeNH_2$ and $EtNMe_2$. In the absence of $NiBr_2$ there was no evidence of reaction. The amount of disproportionation appeared to increase when amination took place. Thus, when bromobenzene (0.3 ml, 2.9 mmol) was added to the above system, the mol % of Me_3N in the volatile phase increased to 68%.

Catalytic Reaction of Lithium Chloride with Bromobenzene. A solution containing LiCl (0.10 g, 2.34 mmol), $NiCl_2 \cdot 6H_2O$ (0.006 g, 0.025 mmol), and bromobenzene (0.15 ml, 1.5 mmol) in 1.2 ml of ethanol was placed in a glass tube and sealed as described previously. The tube was heated to 210° for 6 hr. The reaction product was analyzed by GLC. The peak area ratio of chlorobenzene to bromobenzene found by this procedure was 9.0.

Synthesis of Aryl Ethers. The reaction of bromobenzene with phenol was studied in sealed glass tubes by the same general procedure used in aminations. The tubes were charged with 4.2 mmol of sodium phenoxide, 2.1 mmol of bromobenzene, 0.04 mmol of catalyst, and 2 ml of solvent. Following reaction the product was analyzed by GLC.

Catalytic Reaction of Dimethylamine with Bromobenzene in the Presence of Carbon Monoxide. A mixture of bromobenzene (20.6 ml, 200 mmol) and nickel chloride (0.26 g, 2 mmol) was charged to a 240-ml autoclave containing a glass liner. The system was then charged with dimethylamine (45 g, 1000 mmol) and carbon monoxide (300 psig, unknown quantity) and heated to 190° for 6 hr. The resulting mixture was allowed to stand overnight exposed to the atmosphere, thus exhausting the bulk of the dimethylamine. The final weight was 69.6 g. This mixture was diluted with 100 ml of benzene to precipitate additional salt and was filtered. The white crystalline residue [presumably $(CH_3)_2NH \cdot HBr$] weighed 19.0 g (theoretical 25.2 g). The filtrate upon evaporation of the benzene weighed 48.9 g. GLC analysis (153 and 200°, Triton X 305, 4 ft × 0.25 in., 50 ml/min flow) revealed the following.

Product	Mmol	Wt, g
Bromobenzene	<0.01	0
N,N-Dimethylaniline	73	9.2
N-Methylaniline	23.6	2.5
N,N-Dimethylbenzamide	27	4.1
N,N-Dimethylformamide	207	15.2
Benzophenone	34	6.2
		37.2

The remaining weight may be accounted for as benzene and $(CH_3)_2NH \cdot HBr$.

Reactions of Nickel Aryls. A mixture of $C_6H_5NiBr[P(C_6H_5)_3]_2$ (0.1 g, 0.14 mmol) and dimethylamine (0.36 g, 8 mmol) was heated in a sealed tube at 100° for 6 hr. Elemental nickel precipitated and benzene and biphenyl (mole ratio 3:1) were detected by GLC and identified by mass spectroscopy but there was no evidence of an aniline in the product. Similar results were obtained from reaction of $C_6H_5NiCl[P(C_6H_5)_3]_2$ by itself or with either ammonia or dimethylamine at 200°. The benzene/biphenyl ratio tended to increase at higher temperatures (in the range 100–210°) and in the presence of dimethylamine.

When aryl halides were heated with $ArNiX[P(C_6H_5)_3]_2$, arenes and biaryls were produced in which were incorporated the aryl groups attached to nickel, halogen, and phosphorus. Elemental nickel was not formed. Thus, a mixture of *p*-chlorotoluene (0.3 g, 2.4 mmol) and $C_6H_5NiBr[P(C_6H_5)_3]_2$ (0.1 g, 0.14 mmol) heated in a sealed tube at 210° gave C_6H_6–$CH_3C_6H_5$–$(C_6H_5)_2$–$CH_3C_6H_4C_6H_5$–$(CH_3C_6H_4)_2$ in the weight ratio 1.2:0.9:8.6:2.4:5.3. Evidence for reaction of the phenyl groups of the $P(C_6H_5)_3$ ligand is provided by the following experiment. A mixture of *p*-bromotoluene (0.3 g, 1.7 mmol) and *o*-$CH_3C_6H_4NiCl[P(C_6H_5)_3]_2$ was heated in a sealed tube at 56° for 8 hr. Analysis of the product by VPC and mass spectrography showed that it contained C_6H_6–$CH_3C_6H_5$–$(C_6H_5)_2$–$CH_3C_6H_4C_6H_5$–$(CH_3C_6H_4)_2$ in the weight ratio 1.2:2.6:1.0:7.0:12.0.

Results and Discussion

Nickel-Catalyzed Aminations. Data which affirm the effectiveness of nickel catalysis are summarized in Table I. Five duplicate runs of expt 4, Table I, gave conversions to dimethylaniline of 66, 70, 89, and 68% (twice) indicating an acceptable reproducibility.

Both primary and secondary amines were used in these aminations. The greatest rates were generally shown by those amines exhibiting the least steric interference about nitrogen (see Tables I and II). Ammonia did not react with aryl halides to give anilines. In fact, ammonia inhibited amination with normally reactive amines, e.g., dimethylamine (see Table III). Other compounds which coordinate strongly to nickel(II) also interfered with the reaction of dimethylamine with chlorobenzene. For example, ethylenediamine at a dimethylamine/ethylenediamine mole ratio of 1000:10 reduced the conversion to *N,N*-dimethylaniline from 68 to 7% (conditions of Table III), while o-phenanthroline at a mole ratio of 1000:10 led to only 0.1% conversion. Both phosphites and CN^- had a similar inhibiting effect.

Amine concentration had an important effect on the rate of amination. Reaction was fastest with a large excess of

Table I
Nickel Catalysis of Amination[a]

Expt	Catalyst	Aryl halide	Amine	Conditions	% convn to subs aniline
1	None	C_6H_5Br	$(CH_3)_2NH$	170°, 6 hr	1.4
2	$[P(C_6H_5)_3]_2Ni(CO)_2$	C_6H_5Br	$(CH_3)_2NH$	170°, 6 hr	57
3	None	C_6H_5Cl	$(CH_3)_2NH$	210°, 6 hr	<1
4	$NiCl_2$	C_6H_5Cl	$(CH_3)_2NH$	210°, 6 hr	68

[a] Standard sealed tube conditions.

Table II
Amination of Bromobenzene[a]

Expt	Amine	Conditions	% convn to subs aniline
1	Piperidine	160°, 4 hr	85
2	$(C_2H_5)_2NH$	200°, 6 hr	15
3	$(C_3H_7)_2NH$	230°, 6 hr	38
4	$(n\text{-}C_4H_9)_2NH$	230°, 6 hr	12
5[b]	CH_3NH_2	200°, 6 hr	15
6	$C_6H_5NH_2$	230°, 6 hr	21
7	α- or β-$C_{10}H_7NH_2$	230°, 6 hr	<0.1

[a] $[(C_6H_5)_2PCH_2]_2Ni(CO)_2$ catalyst in all experiments. Standard sealed tube conditions except that no solvent was used. [b] Chlorobenzene used in place of bromobenzene.

Table III
Effect of Ammonia on the Reaction of Dimethylamine with Chlorobenzene

Mole ratio $NiCl_2$–C_6H_5Cl–$(CH_3)_2NH$–NH_3	% convn of chlorobenzene to *N,N*-dimethylaniline
1:100:1000:0	68
1:100:1000:20	67
1:100:1000:40	60
1:100:1000:100	20
1:100:1000:400	0.5

[a] Standard sealed tube conditions, 200°, 6 hr.

Table IV
Effect of Dimethylamine Charge on Conversion of Bromobenzene to Dimethylaniline[a]

Mole ratio $NiBr_2$–C_6H_5Br–$(CH_3)_2NH$	% convn to $(CH_3)_2NC_6H_5$
1:100:1000	97
1:100:500	91
1:100:300	76
1:100:200	46

[a] Standard sealed tube conditions except for the amount of $(CH_3)_2NH$ charged. At 200°, 6 hr in ethanol.

Table V
Effect of Substituents on the Rate of Reaction of Piperidine with Aryl Bromides[a]

Substituent on bromobenzene	Relative rate of amination
None	1.00 (def)
p-CH_3	0.78
m-CH_3	0.93
o-CH_3	<0.001
p-OCH_3	0.58
p-Cl	2.20
m-CF_3	3.68
p-CF_3	7.22

[a] $[(C_6H_5)_3P]_2Ni(CO)_2$ catalyst at 140° in valved reactor.

amine serving as both reactant and solvent and dropped on approaching the stoichiometric ratio (amine/aryl halide = 2:1) (see Table IV). Attempts to find the kinetic order of dependence of the rate of amination on amine concentration were unsuccessful. When the reaction was run (in solvents such as butyl carbitol, dimethylacetamide, *N,N*-diethylaniline, or aryl halide) with an excess of aryl halide and a limiting amine concentration, reaction was too slow to be measured accurately.

The nature of the aryl halide dramatically affected the degree of catalysis (as measured by the rate of the catalyzed reaction relative to the uncatalyzed reaction). Changing the halogen increased the degree of catalysis in the order ArF ≪ ArCl < ArBr ~ ArI. Only very slight catalysis of aminations of fluorobenzene was observed. Aminations of aryl iodides frequently led to the formation of significant amounts of arenes in addition to the expected amination products. Consequently, most experiments were run with aryl chlorides and bromides.

The effect on the rate of employing substituted aryl halides was studied briefly. As is well known,[8] electron-withdrawing substituents generally accelerate the uncatalyzed nucleophilic substitution reactions of aryl halides. A similar effect was observed in the nickel-catalyzed amination reaction (see Table V). The magnitude of this substituent effect is actually quite small, however, relative to those usually found for uncatalyzed aminations. A similar attenuation of substituent effects has been observed in the nickel-catalyzed carbonylation of aryl halides.[3]

With certain substituents an interesting effect on the amination rate was observed. When the amination rates of positional isomers of aryl halides containing *activating* substituents were compared, the meta isomers generally showed the greatest degree of catalysis. For example, moderate catalysis was observed with *o*-$CF_3C_6H_4Cl$ and dimethylamine at 210°, 6 hr (18% conversion with $NiCl_2$ vs. 9% without); uncertain, but probably no catalysis was observed with *p*-$CF_3C_6H_4Cl$ (4.5% conversion with $NiCl_2$ at 150°, 6 hr vs. 4.0% without). However, the reaction of *m*-$CF_3C_6H_4Cl$ was strongly catalyzed (99% conversion with $NiCl_2$ at 210°, 6 hr vs. 4% without). In another series, reaction of 2-chloropyridine with dimethylamine was not catalyzed by $NiCl_2$ but amination of 3-chloropyridine was strongly catalyzed (92% conversion with $NiCl_2$ at 210°, 6 hr vs. <0.1% without). Interestingly, aminations of aryl halides containing nitro substituents were *not* catalyzed by nickel compounds.

Attempts to catalyze the amination of alkyl halides did not succeed. The halides investigated included cyclohexyl chloride, neopentyl chloride, and 1,4-dihalobicyclo[2.2.3]octanes (2), where X is Cl or Br.

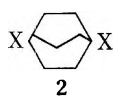


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Table VI
Effect of Initial Bromobenzene Concentration on the Rate of Amination by Piperidine[a]

Expt	Ni compd charged	Temp, °C	C_6H_5Br charge	k, min^{-1} $\times 10^4$
1	$[CH_2P(C_6H_5)_2]_2Ni(CO)_2$	130	0.40	15.7
2	$[CH_2P(C_6H_5)_2]_2Ni(CO)_2$	130	0.80	12.7
3	$[(C_6H_5)_3P]_2Ni(CO)_2$	130	0.40	11.7
4	$[(C_6H_5)_3P]_2Ni(CO)_2$	130	0.80	9.0
5	$[(C_6H_5)_3P]_2Ni(CO)_2$	140	0.40	21.7
6	$[(C_6H_5)_3P]_2Ni(CO)_2$	140	0.80	6.3
7	$[(C_6H_5)_3P]_2Ni(CO)_2$	140	4.00	3.0
8	$[(C_6H_5)_3P]_2Ni(CO)_2$	150	40.0[c]	<0.5
9	$NiBr_2$	170	1.00	8.7
10	$NiBr_2$	170	10.0	<0.5

[a] In valved reactor using 0.25 mmol of Ni compound and 40 ml of piperidine with designated C_6H_5Br charge. [b] Milliliters of C_6H_5Br. [c] A charge of 0.40 ml of piperidine was used.

The dependence of the rate of amination on the concentration of aryl halide followed a complex pattern. Within a given reaction system the rate was found to be proportional to the concentration of aryl halide. This was concluded principally from the kinetics of the reaction of a small amount of bromobenzene dissolved in piperidine with various nickel compounds as catalysts. Plots of $-\log [C_6H_5Br]$ or, equivalently, $\log [C_6H_5NC_5H_{10}]$ against time were linear through the duration of the experiment (up to 3 half-lives). However, the reaction rate, calculated from these plots, decreased when the initial charge of aryl halide in the reaction mixture was increased (see Table VI). This effect of initial bromobenzene charge was observed with all other aryl halides and nickel compounds that were tested. It also appears to increase at higher temperatures (cf. expt 3 and 4 with 5 and 6 of Table VI).

An extensive comparison of various nickel compounds as catalysts was made through rate studies. The precise order of effectiveness varies somewhat depending principally upon the temperature at which comparisons were made. The approximate order of decreasing activity is $[(C_6H_5)_2PCH_2CH_2P(C_6H_5)_2]Ni(CO)_2 > [(C_6H_5)_3P]_2Ni(CO)_2 > Ni(CO)_4 > Ni[P(C_6H_5)_3]_3{\cdot}nP(C_6H_5)_3 \approx NiBr_2 \approx [(C_6H_5)_3P]_2NiBr_2 > CH_3C_6H_4NiCl[P(C_6H_5)_3]_2 > Ni(OCOCH_3)_2{\cdot}2H_2O > NiSO_4{\cdot}6H_2O$. At 170° and in the reaction of bromobenzene with piperidine, activity ranges from a half-life of about 20 min with $[(C_6H_5)_2PCH_2CH_2P(C_6H_5)_2]Ni(CO)_2$ to about 10% conversion in 8 hr with $NiSO_4{\cdot}6H_2O$.

Cassar found[2] (and we have confirmed) that Ni(0) compounds or certain Ni aryls [which, by his mechanism, are equivalent to Ni(0)] were the catalysts of choice for the synthesis of nitriles from aryl halides. In comparison, our work shows that there is surprisingly little difference between $NiBr_2$ and Ni(0) compounds as catalysts for the reaction of bromobenzene and piperidine (Table VII). Cassar and Foà[3] report that $[Ni_3(CO)_8]^{2-}$ is a superior catalyst for carboxylation of aryl halides insofar as eliminating an induction period encountered with other catalysts. We found it somewhat more effective initially than $[(C_6H_5)_3P]_2Ni(CO)_2$ for amination of bromobenzene but short lived (about 0.5 hr at 140°).

The rate of amination was found to be approximately proportional to the amount of nickel compound employed as catalyst (see Table VIII).

Solvents were found to affect the rate of catalyzed aminations. Most of the information on this aspect of the reaction was obtained by comparing the extent to which chlorobenzene reacted with dimethylamine in sealed tube experiments. In one study using $NiCl_2{\cdot}6H_2O$ as a catalyst the conversions to *N,N*-dimethylaniline obtained were 94% (dimethylformamide), 68% (ethanol), 23% (methyl ethyl ketone or acetonitrile), 10% (benzonitrile or dimethyl sulfoxide). Conversions higher than 70% were also obtained in diethylformamide and both dimethyl- and diethylacetamide. However, interchange was observed between amine and the amide solvents. Thus, ethanol was usually employed as solvent in sealed tube aminations.

Table VII
Comparison of Nickel Compounds as Catalysts in the Synthesis of *N*-Phenylpiperidine[a]

Temp, °C	$k \times 10^4$, min^{-1} $NiBr_2$	$k \times 10^4$, min^{-1} $[(C_6H_5)_3P]_2Ni(CO)_2$
160	10.8	10.0
150	3.3	8.5
140	5.2	11.7
140		1.8[b]
140		5.7[c]

[a] In valved reactor. Initial charge contained 40 ml of piperidine, 0.25 mmol of nickel compound, and 0.8 ml (8 mmol) of bromobenzene (at 140°) or 1.60 ml (16 mmol) of bromobenzene (at 150 or 160°). [b] $4\text{-}CH_3C_6H_4NiCl[P(C_6H_5)_3]_2$ instead of $[(C_6H_5)_3P]_2Ni(CO)_2$. [c] $Ni[P(C_6H_5)_3]_3{\cdot}nP(C_6H_5)_3$[9] instead of $[(C_6H_5)_3P]_2Ni(CO)_2$.

Table VIII
Effect of [Nickel Compound] on Rate of *N*-Phenylpiperidine Formation[a]

Nickel compd (g)	$k \times 10^4$, min^{-1}	$k \times 10^3$ / g of Ni compd	Temp, °C
$[CH_2P(C_6H_5)_2]_2Ni(CO)_2$ (0.26)	5.0	1.9	140
$[CH_2P(C_6H_5)_2]_2Ni(CO)_2$ (0.05)	1.3	2.6	140
$[(C_6H_5)_3P]_2Ni(CO)_2$ (0.64)	6.0	0.94	140
$[(C_6H_5)_3P]_2Ni(CO)_2$ (0.16)	1.2	0.75	140
$[C_6H_5P(C_2H_5)_2]_2NiBr_2$ (0.56)	8.1	1.4	140
$[C_6H_5P(C_2H_5)_2]_2NiBr_2$ (0.14)	1.4	1.0	140
$NiBr_2{\cdot}4H_2O$ (0.100)	4.2	4.2	165
$NiBr_2{\cdot}4H_2O$ (0.020)	1.0	5.0	165

[a] In valved reactor. Reaction mixtures contained 40 ml of piperidine and 0.80 ml of bromobenzene.

The reduction of nickel(II) compounds by amines was examined as a possible step in catalyst activation, since nickel(0) compounds have been implicated as catalysts in a variety of organic reactions. We found that amines which aminate aryl halides reduce $NiCl_2$ or $NiBr_2$ to nickel metal at temperatures above 200° but we were not able to define the stoichiometry of the reaction. Also, extensive disproportionation of the amine component occurred during this reduction. Dimethylamine, methylamine, piperidine, diethylamine, and diethanolamine all reduced nickel halides at 200° and yielded "disproportionated" amine mixtures. *N*-Methylaniline yielded *N,N*-dimethylaniline but it did not appear that Ni(II) had been reduced nor was any other product detected. It is uncertain whether amine disproportionation is a consequence of nickel reduction; however, disproportionation is catalyzed by nickel and not by the alkylammonium halides formed in the reduction. Interestingly, neither reduction of nickel halides nor disproportionation of amines has been observed at 150° but amination, especially of aryl bromides, occurs readily at that temperature (see Table VII).

In seeking some relationship between amination and

nickel halide reduction, the effect of varying the mole ratio of aryl halide to amine was studied. In the amination of chlorobenzene with dimethylamine under $NiCl_2$ catalysis (mole ratio 10:4:1, respectively, 210°, 6 hr) no elemental nickel precipitated though 67% of the chlorobenzene was converted to products. When the charge of chlorobenzene was reduced (mole ratio 0.5:4:1) it reacted completely and elemental nickel precipitated. A tentative explanation of this observation is that the chlorobenzene was able to prevent Ni precipitation by reacting with it to give soluble nickel compounds, possibly Ni aryls.

It was found that inhibition of the aminations occurred when small amounts of either certain other transition metal salts or nitroaromatics were added to the system. Thus, in one amination employing piperidine as both a solvent and reactant (with bromobenzene) the addition of copper or iron salts in amounts as low as 25 mol % of the nickel present *completely* inhibited all catalytic reactions. Employing ethanol as the solvent diverted the reaction to yield benzene, vide infra. The addition of aromatic nitro compounds (e.g., nitrobenzene, dinitrobenzene, etc.) to the same reaction likewise completely inhibited the catalysis at Ni/nitroaromatic ratios of as low as 1:0.3. A similar, though much less dramatic, effect was noted on adding small amounts of hydroquinone. These inhibitions were observed using either Ni(II) or Ni(0) compounds as catalysts.

Mechanism of Amination. The mechanism of these nickel-catalyzed aminations is obscure. Of many possible mechanisms only those involving the intermediacy of arynes can be eliminated with certainty. This follows from the finding that nickel-catalyzed amination of either *p*- or *m*-bromotoluene gave only the corresponding *p*- or *m*-*N,N*-dimethyltoluidines. A particularly attractive mechanism for which there is recent precedent in the work of Cassar et al.[2,3] is outlined in Scheme II. In this hypothetical

Scheme II

$$NiL_2 + ArX \longrightarrow ArNiX + 2L \quad (1)$$

$$ArNiX + 2R_2NH \longrightarrow ArNiNR_2 + R_2NH_2X \quad (2)$$

$$ArNiNR_2 + 2L \longrightarrow NiL_2 + ArNR_2 \quad (3)$$

[a] For clarity only those ligands attached to nickel which participate in the reaction indicated.

mechanism a "zero" valent nickel species is responsible for the catalysis. However, the near equivalence of Ni(0) and Ni(II) compounds as catalysts for amination suggests that additional chemistry must be involved. There may appear to be no difficulty here since, as we have seen, Ni(0) species are easily generated in situ by amine reduction of Ni(II) species. However, this particular pathway to Ni(0) catalysts is not sufficient to account for the catalysis observed with Ni(II) compounds. Although both dimethylamine and piperidine have been shown to reduce Ni(II) halides at 200°, no formation of nickel metal is observed after 6 hr at 150°. Yet at this latter temperature there is significant catalytic amination of aryl halides. (See Table VII.) It might be suggested that only traces of Ni(0) species are required and that enough reduction occurred at 150° to provide it. However, in such a case an increasing reaction rate would be expected as the Ni(0) species accumulated through continued reduction of the Ni(II) precursor. This is inconsistent with the observed rates, which show relatively clean first-order amination over a period of 3 half-lives. Furthermore, no induction period was noted.

The retarding effect of aryl halide on the reaction rate noted earlier must be accounted for in any proposed mechanism. Since the aminations show a first-order dependence on a given charge of aryl halide a possible explanation for this effect may be that the aryl halides contain certain trace impurities which deactivate the catalyst. However, since a variety of aryl halides showed this effect, such an explanation would require all of them to contain such impurities.

In further evaluation of the mechanism suggested by Scheme II we examined the reactions of plausible intermediates, corresponding to ArNiX, with amines. We have found that reaction of $C_6H_5NiCl[P(C_6H_5)_3]_2$[10] with ammonia, methylamine, or dimethylamine in the temperature range of 150–200° did *not* yield anilines. Instead, the usual products observed included benzene, biphenyl, and related products resulting from the exchange of the aryl groups bonded to the nickel and the phosphorus. This latter exchange reaction has since been reported[11] by others. It should perhaps be noted that $C_6H_5NiCl[P(C_6H_5)_3]$ has been shown to exhibit catalytic activity in the aminations (see Table VII for an analogous example).

Although the evidence discussed thus far tends to rule out the intermediacy of aryl nickel species, this need not imply their absence in the aminations. Indeed, evidence supporting the existence of such species in the amination reactions comes from an examination of such a reaction carried out in the presence of carbon monoxide. When bromobenzene was reacted with dimethylamine in the presence of either Ni(II) or Ni(0) compounds *and* carbon monoxide, substantial amounts of *N,N*-dimethylbenzamide was formed along with the expected *N,N*-dimethylaniline. Since species containing nickel–carbon bonds are known to readily insert carbon monoxide resulting in the formation of aroyl derivatives,[12] it seems reasonable to suppose that nickel aryls exist under the conditions of the amination.

The spectacular inhibitions caused by the addition of nitroaromatics or the copper or iron salts to the amination systems suggest that electron-transfer processes are important. It should also be noted that an aromatic ring (or at least a π electron system) appears necessary for catalysis to occur since the amination of saturated alkyl halides did not respond to catalysis. All of this suggests that electron transfer to the aromatic ring is an important step in the catalytic aminations. It is also interesting to note that aromatic displacement reactions known to involve radical anion intermediates (e.g., via SRN1 mechanisms) have been reported[13] to also be efficiently inhibited by added nitroaromatics. Thus, it is tempting to suggest that transient metal species [possibly Ni(I) compounds] are the actual catalytic species and that they act by transferring an electron to the aromatic halide, thereby generating a free or complexed radical anion to activate the displacement process. However, the evidence supporting such a hypothesis is purely circumstantial at this point.

Halogen Exchange Reactions. Exchanges of aryl halides with halide ions have been reported[14] to be catalyzed by Cu(I) halides. However, only aryl halides containing activating groups (e.g., NO_2) have been studied previously. We have discovered that nickel compounds effectively catalyze the exchange of halide ions with nonactivated aryl halides. For example, using $NiCl_2$ as catalyst the equilibrium summarized in eq 1 was achieved in ethanol at 210°

$$C_6H_5Br + Cl^- \underset{210^\circ}{\overset{EtOH}{\rightleftharpoons}} C_6H_5Cl + Br^- \quad (1)$$

within 6 hr. An equilibrium constant of about 20 was found for this reaction. In the absence of catalyst only about 1–5% of the bromobenzene reacts under these conditions. Very low concentrations of nickel catalyst are effective. Thus,

with 0.001 mol % of $NiCl_2$ (based on bromobenzene) a 68% conversion to chlorobenzene was obtained under these same conditions. However, conversion levels are very erratic at such low catalyst concentrations.

As in amination, the extent of reaction varies with solvent. At 157° for 6 hr the conversions to chlorobenzene were 77% (dimethylformamide), 35% (ethanol), 22% (hexamethylphosphoramide), 3% (dimethyl sulfoxide or pyridine).

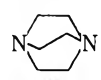
Halogen exchange and amination compete but can proceed concurrently. 4-Bromotoluene in ethanol was exposed to both LiCl and dimethylamine at 210°. With a LiCl/$(CH_3)_2NH$ ratio of 1.25:1, the ratio $CH_3C_6H_4Cl$/$CH_3C_6H_4N(CH_3)_2$ of the product was 1.75:1. With LiCl/$(CH_3)_2NH$ ratio 1:1.6, the product ratio was 1:4.4. Like amination, halogen exchange is inhibited by NH_3, CN^-, or ethylenediamine. For example, upon inclusion of ammonia (NH_3/Ni = 60:1) conversion of bromobenzene dropped from 90% to 0.7%.

Rate studies, especially with nickel halide catalysts, were largely inconclusive because of induction periods lasting up to several hours at 180°. These could be eliminated or substantially reduced by heating a mixture of LiCl and $NiBr_2$ with the solvent (dimethylacetamide or butyl carbitol) for several hours at 160° before adding the aryl bromide. This led to deposition of some elemental nickel. However, it was found that $[CH_2P(C_6H_5)_2]_2Ni(CO)_2$ was a much better catalyst for halogen exchange than was $NiBr_2$. At 140° the $[CH_2P(C_6H_5)_2]_2Ni(CO)_2$-catalyzed reaction of bromobenzene and lithium chloride had a half-life of about 4 hr whereas very little reaction could be detected after 6 hr at 140° using $NiBr_2$. This pattern is similar to the catalyst behavior in Cassar's nitrile synthesis and suggests that the mechanisms may be related.

It appears that nickel compounds catalyze halogen exchange of some alkyl halides, although the yields are usually low. For example, β-bromostyrene and LiCl gave 85% conversion to β-chlorostyrene in the presence of $NiCl_2$ but only 22% in its absence. Also, 1,4-dibromobicyclo[2.2.2]octane (2) (in ethanol solution) was completely converted to a variety of substitution products ($C_2H_5OC_8H_{12}H$, $HOC_8H_{12}H$, $C_2H_5OC_8H_{12}Cl$, $C_2H_5OC_8H_{12}Br$, and $C_2H_5OC_8H_{12}OH$) in the presence of $NiCl_2$ but was largely unchanged in its absence. 3-Bromocamphor reacted completely in the presence of $NiCl_2$ (2% chlorocamphor, 98% camphor), but without $NiCl_2$ half the bromocamphor was recovered. Neopentyl chloride was converted completely to pentenes by $NiBr_2$–LiBr but was substantially unchanged in absence of $NiBr_2$.

No perceptible catalysis by nickel compounds was observed in exchanges involving fluoride ion and aryl halides.

Reduction of Aryl Halides to Arenes. Small amounts (<2%) of arenes are formed in nickel-catalyzed aminations and we found up to 8% arene formation in corresponding CuCl-catalyzed reactions. Arene formation could be made to predominate by appropriate modification of either amination or halogen exchange systems. The modifications consist in adding either a copper or iron salt to the standard sealed tube nickel-catalyzed amination system or adding diazabicyclo[2.2.2]octane (Dabco, 3) to a sealed tube halogen exchange reaction mixture.



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Addition of catalytic amounts of ferric chloride or cupric chloride to nickel catalyzed amination systems employing ethanol as a solvent (Fe or Cu/Ni ≈ 1:1) resulted in conversion of 60–90% of the aryl halide to arene. Lower conversions were obtained by inclusion of rhodium or ruthenium chloride; chlorides of Co, Cr, Ti, V, Sn, Hg, Pd, Zn, Ir, or Pt did not promote arene formation. An amine is an essential reaction component. Dimethylamine, piperidine, methylamine, and trimethylamine are all effective. With dimethylamine, conversion to arene increases to 80% as the amine/aryl halide ratio is raised to 1:1. An inorganic base (magnesium oxide) is ineffective as a replacement for amines.

Arenes are the principal product obtained from Ni-catalyzed reaction of aryl halide in the presence of amine diazabicyclo[2.2.2]octane (3), even without added copper or iron salt. Thus, when *p*-bromotoluene was heated with nickel halide and Dabco in ethanol it was converted into toluene (99% at 265°, 6 hr; 77% at 210°; no reaction at 155°). Higher conversions were obtained in 5:1 dimethylformamide–ethanol (92% at 210°) but ethanol or methanol were generally employed as solvents. Benzene is unsatisfactory but good conversions were obtained in acetone or trimethylamine. Arene formation is inhibited by ethylenediamine (EDA); at 210° with EDA/Ni = 30:1, conversion of C_6H_5Br to C_6H_6 was less than 1%. Aryl chlorides are less reactive than bromides (55% conversion at 265°; 1% at 210°).

We have not found a substitute for Dabco. MgO, CH_3COONa, $(CH_3)_3N$, $(C_2H_5)_2NC_6H_5$, $(C_2H_5)_2NCOC_6H_{12}$, and dioxane were all ineffective. Reduction of aryl halides to arenes using a cuprous chloride catalyst has been reported by Bacon.[16] He employed *N*-methylmorpholine, 2,4-dimethylphenol, or pyridine oxide as promoters but these do not induce arene formation with $NiCl_2$. Conversely, Dabco does not produce arene when used with CuCl. Although dimethylamine itself is ineffective, it promotes arene formation when used with limited amounts of Dabco.

Some observations have been made concerning the chemistry of Dabco-promoted arene formation. We have not been able to detect (by GLC) any oxidation products of Dabco or the solvent. Tagging experiments show that the hydrogen which replaces halide could be derived from both solvent and Dabco. Reaction of *p*-bromotoluene with CD_3OD gave a 50:50 mixture of toluene-d_1 and toluene-d_0 while reaction of bromobenzene with CD_3COCD_3 gave benzene which was 25% d_0 and 75% d_1. The mass spectra of recovered haloarene and Dabco do not indicate exchange of deuterium into these compounds to produce protonated solvents, although small amounts (ca. 5%) of protonated solvents were detected from reaction of Dabco with either CD_3OD or CD_3COCD_3 in the presence of $NiCl_2$ but with no bromobenzene.

Analysis of the ^{13}C NMR spectrum of the toluene derived from the reaction of *p*-bromotoluene with CD_3OD revealed the para carbon resonance to have much less than half the intensity of either of the ortho or meta carbons. This suggests[17] that deuterium had entered the position originally occupied by bromine.

Synthesis of Aryl Ethers. The synthesis of diphenyl ether from sodium phenoxide and bromobenzene at 210° was catalyzed by $[P(C_6H_5)_3]_2Ni(CO)_2$ or $[(C_6H_5)_2PCH_2]_2Ni(CO)_2$ but *not* by $NiBr_2$ (Table IX). Tetrahydrofuran or ethylene glycol dimethyl ether were satisfactory solvents but methanol was not. A substantial amount of bromobenzene appeared to be converted to phenol. In a comparative experiment (No. 7, Table IX) cuprous bromide was much more effective than any of the nickel compounds.

Catalysis of Displacements by Cobalt Halides. Displacement reactions of aryl halides such as those shown in Scheme I, eq 1–3, are catalyzed by cobalt halides. The rates are slower (sometimes substantially slower) and we have not studied the reactions so extensively as with nickel cata-

Table IX
Diphenyl Ether from Bromobenzene and Sodium Phenoxide[a]

Expt	Added complex	Solvent	% conversions C_6H_5O-C_6H_5	To phenol	Recovered C_6H_5Br
1	None	THF	0.4	2	100
2	$[P(C_6H_5)_3]_2Ni(CO)_2$	THF	33	45	3
3	$[(C_6H_5)_2PCH_2]_2Ni(CO)_2$	Methanol	2	54	26
4	None	Glyme	1	2	98
5	$[(C_6H_5)_2PCH_2]_2Ni(CO)_2$	Glyme	7	10	68
6	$NiBr_2$	Glyme	2	4	95
7	CuBr	Glyme	95	~3	~5

[a] All experiments were run at 210°, 6 hr, with mole ratio of C_6H_5ONa-C_6H_5Br-catalyst = 100:50:1 in sealed glass ampoules.

Table X
Cobalt-Catalyzed Aminations of Bromobenzene[a]

Expt	Catalyst	Amine	Time, hr	Products (% conversion)
1	None	Me_2NH	6	$C_6H_5N(CH_3)_2$ (9)
2	$CoCl_2 \cdot 6H_2O$	Me_2NH	12	$C_6H_5N(CH_3)_2$ (58) C_6H_5Cl (3)
3	$CoCl_2 \cdot 6H_2O$	$MeNH_2$	12	$C_6H_5NH(CH_3)$ (10) C_6H_5Cl (1)
4	$CoCl_2 \cdot 6H_2O$	Me_2NH[b] + NH_3	12	$C_6H_5N(CH_3)_2$ (23)
5	$CoBr_2$	Me_2NH	6	$C_6H_5N(CH_3)_2$ (63) $C_6H_5NH(CH_3)$ (14)
6	CoI_2	Me_2NH	6	$C_6H_5N(CH_3)_2$ (30) C_6H_6 (48)

[a] Standard sealed tube conditions. In ethanol at 210°. Amine–bromobenzene–Co compound = 1000:100:1. [b] Dimethylamine–ammonia = 5:1.

lysts. The principal results are described briefly. Unless otherwise specified these experiments were run by the sealed tube technique with the same reactant ratios used in the standard nickel catalyzed reactions (see Experimental Section).

The amination of bromobenzene by dimethylamine (see Table X) was catalyzed by $CoCl_2 \cdot 6H_2O$ giving a 62% conversion at 210°, 6 hr. Modest reaction also occurred with methylamine (10% conversion) but none with ammonia. Ammonia also inhibited amination with dimethylamine. $CoBr_2$ is more effective than $CoCl_2 \cdot 6H_2O$ and CoI_2 is essentially equivalent to the chloride but promotes formation of benzene. Low conversions (7–12%) to dimethylaniline (corresponding to noncatalyzed reaction) were obtained with $Co(CN)_2 \cdot 2H_2O$. Still lower conversions or even undetectable reaction resulted using $Co(CH_3COO)_2$, $Co(NO_3)_2$, $Co(acac)_3$, $CoSO_4$, or $[(C_6H_5)_3P]_2Co(CO)_3$, suggesting that these interfere with the noncatalyzed amination.

This finding suggests the existence of a chain-type mechanism for the uncatalyzed aminations, since relatively small amounts of material were found to inhibit the reactions (ca. <0.5–3% conversions). In this connection Shein and coworkers have proposed[18] that chain mechanisms operate in certain noncatalytic aromatic displacement reactions.

Chlorobenzene is less reactive than bromobenzene (5% conversion to dimethylaniline in 6 hr at 210° with $CoCl_2 \cdot 6H_2O$ catalyst vs. <1% conversion in the absence of catalyst).

Cobalt-catalyzed halide exchange is slow. After 6 hr at 210° the conversion of C_6H_5Br to C_6H_5Cl was only 7% (C_6H_5Br–LiCl = 1:2). Conversion of C_6H_5Br to C_6H_5Cl was undetected (<0.1%) under the same conditions and equilibration (approached from C_6H_5Br + LiCl) was incomplete after 18 hr at 210°.

The reduction of aryl halides to arenes is also cobalt catalyzed. Addition of $FeCl_3$ to a $CoCl_2 \cdot 6H_2O$ catalyzed amination (such as expt 2, Table X) gave 23% conversion to arene after 12 hr at 210° with no detectable dimethylaniline. Also, reaction of bromobenzene with Dabco in the presence of $CoCl_2 \cdot 6H_2O$ resulted in 24% conversion to benzene.

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Registry No.—$C_6H_5NiBr[P(C_6H_5)_3]_2$, 41798-98-5; o-$CH_3C_6H_4NiCl[P(C_6H_5)_3]_2$, 27057-09-6; $[N(C_4H_9)_4]_2Ni_3(CO)_8$, 41948-83-8; $C_6H_5NiCl[P(C_6H_5)_3]_2$, 38413-93-3; $[P(C_6H_5)_3]_2Ni(CO)_2$, 13007-90-4; $[(C_6H_5)_2PCH_2]_2Ni(CO)_2$, 15793-01-8; 4-$CH_3C_6H_4NiCl[P(C_6H_5)_3]_2$, 53402-25-8; $Ni[P(C_6H_5)_3]_3$, 25136-46-3; $[(C_6H_5)_3P]_2Ni(CO)_2$, 13007-90-4; $NiCl_2$, 7718-54-9; $NiBr_2$, 13462-88-9; dimethylamine, 124-40-3; lithium chloride, 7447-41-8; bromobenzene, 108-86-1; p-chlorotoluene, 106-43-4; p-bromotoluene, 106-38-7; piperidine, 110-89-4; $(C_2H_5)_2NH$, 109-89-7; $(C_3H_7)_2NH$, 926-63-6; $(n$-$C_4H_9)NH$, 102-82-9; CH_3NH_2, 74-89-5; $C_6H_5NH_2$, 62-53-3; α-$C_{10}H_7NH_2$, 134-32-7; β-$C_{10}H_7NH_2$, 91-59-8; m-CH_3 bromobenzene, 591-17-3; o-CH_3 bromobenzene, 95-46-5; p-OCH_3 bromobenzene, 104-92-7; p-Cl bromobenzene, 106-39-8; p-CF_3 bromobenzene, 402-43-7; m-CF_3 bromobenzene, 401-78-5; CuBr, 7787-70-4; $CoCl_2$, 7646-79-9; $CoBr_2$, 7789-43-7; CoI_2, 15238-00-3.

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Catalytic Decomposition of Diphenyldiazomethane by Lewis Acids, Cyclopropanation Reactions of a Diphenylcarbenoid Species

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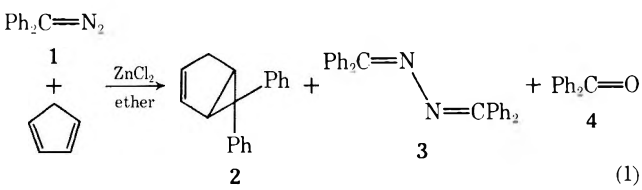
The first successful cyclopropanation reactions utilizing zinc chloride catalyzed decompositions of diphenyldiazomethane are reported. Various metal salts were surveyed for their relative activity toward diphenyldiazomethane decomposition and then several were chosen for cyclopropanation studies. Conjugated dienes and electron-rich olefins were found to be good cyclopropanation substrates. The diphenylcyclopropanation of cyclopentadiene was optimized by investigating changes of temperature, concentration, mode of addition, reaction time, the metal cation, and the anions. Mechanistic studies, including comparison with diphenylcarbene reactions, suggest that our results are best explained by a diphenylcarbenoid intermediate which reacts competitively with the olefin to produce a cyclopropane product and with diphenyldiazomethane to produce tetraphenylketazine and tetraphenylethylene.

The Lewis acid catalyzed decomposition of diphenyldiazomethane has been examined a number of times[2-4] using various catalysts, but only recently have good mechanistic studies on this reaction appeared.[3] Furthermore, we know of no survey of Lewis acids that are effective in inducing diphenyldiazomethane decomposition. Although a number of catalyzed diphenylcyclopropanations have been attempted[4] in analogy to the well-known studies[5] on monoaryldiazomethane cyclopropanations, the only successful report involved two enamines in refluxing benzene[6] with copper acetylacetonate. Gaspar's recent report[4f] that this reaction does not proceed at room temperature suggests that the mechanism of this reaction is fundamentally different from that of the monoarylcyclopropanations, which is thought to involve reactive carbenoids.[5] Although previous decomposition studies have shown little sign that a diphenylcarbenoid species thus generated would cyclopropanate olefins, a diphenylcarbenoid derived from dibromodiphenylmethane has been reported to cyclopropanate 2-butenes[7a] and ethyl vinyl ether[7b] in modest yields. A similar attempt with dichlorodiphenylmethane was unsuccessful.[7c]

An extensive amount of work has been done on photolytically generated diphenylcarbene,[8] but only recently have good studies of its cyclopropanation reactions appeared.[9] Casey's recent report of diphenylcyclopropanation on ethyl vinyl ether by use of tungsten pentacarbonyl complex of diphenylcarbene[10] and Gaspar's recent studies on catalyzed decomposition of diphenyldiazomethane[4f] compel us to report our successful cyclopropanation reactions[11] using diphenylcarbenoid species generated by catalyzed decompositions of diphenyldiazomethane, our studies on the decomposition reaction, and some comparisons among diphenylcyclopropanation reactions.

Results and Discussion

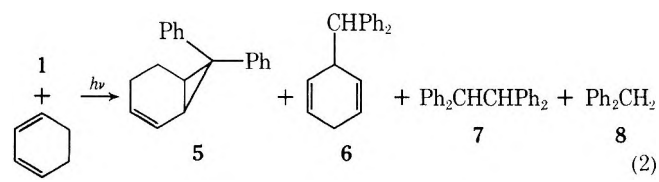
Slow addition of ethereal diphenyldiazomethane (1) under nitrogen to a stirred anhydrous ethereal mixture of zinc chloride and a fivefold excess of cyclopentadiene at 25° with concentration and extraction followed by crystallization afforded a 35% yield of 6,6-diphenylbicyclo[3.1.0]hex-2-ene (2) with tetraphenylketazine (3) and benzophenone (4) as the other principal products (cf. eq 1).



(1)

The relatively good yield, the ease of isolation, and the ease of scaling up compared with the carbene route[12] make this the preferred method for synthesizing 6,6-diarylbicyclo[3.1.0]hex-2-enes. The most favorable reaction conditions were worked out using cyclopentadiene and were then applied to other olefins (cf. Table I). Conjugated cyclic dienes gave diminishing yields with increasing ring size; 1,3-cyclooctadiene did not react under these conditions. Although no reaction is seen with isoprene at 0°, results at 25 and 40° show a temperature-dependent regioselectivity for attack at the more electron-rich double bond. Use of the electron-rich ethyl vinyl ether in analogy to the previously mentioned enamines[6] gave a gratifying 52% yield of 1-ethoxy-2,2-diphenylcyclopropane.

The isolation of 3-benzhydrylcyclohexa-1,4-diene (6) from the diphenylcarbene reaction with cyclohexadiene has analogy in the formation of 9-benzhydrylfluorene.[2h] The benzhydryl radical produced by hydrogen abstraction can couple with the cyclohexadienyl radical to produce 6 competitively with self-coupling to produce 1,1,2,2-tetraphenylethane (7), and further hydrogen abstraction to produce diphenylmethane (8).[13] The uv and NMR spectra were particularly useful in the structure elucidation of compound 6. The ultraviolet spectrum, 217 nm (ε 14,400) and 260 (962), is more reminiscent of that of diphenylmethane, 260 (501), than of 1,3-cyclohexadiene, 259 (10,000). The bisallylic and bisbenzylic methine ^{1}H NMR signals at δ 3.7 agree well with the methylene ^{1}H NMR signals of diphenylmethane at δ 4.0. The ^{1}H NMR absorption at δ 2.6 assigned to the bisallylic methylenes is much closer to those of 1,4-cyclohexadiene at δ 2.7 than to the methylenes of 1,3-cyclohexadiene at δ 2.1.



(2)

Our studies, summarized in Table I, indicate that anhydrous conditions, the correct mode of addition, 25° instead of 0°, zinc chloride instead of other Lewis acids, and extra reaction time all favor cyclopropanation. These conditions are too mild to induce a dipolar addition by diphenyldiazomethane, and no disappearance of diazo compound is seen without a Lewis acid. Tetraphenylketazine is a major product while tetraphenylethylene is usually quite minor and none of the tetraphenylethane characteristic of the diphen-

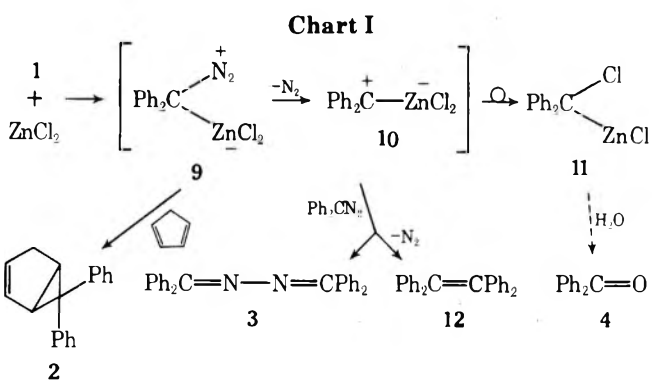
Table I
Reactions of Diphenylcarbene and Diphenylcarbenoid Species

System[a]	Method	Temp, °C	Time[b]	Cyclopropane[c]	Ketazine	Benzophenone	Other[d]
CPD	$ZnCl_2$	22	2 hr	35	24	29	
CPD	$ZnCl_2$	22	9 hr	34.8	27	29	
CPD	$ZnCl_2$	22	10 min	23	28	25	
CPD	$ZnCl_2$	0–5	15 min	23 (28)	51	15	
CPD	$ZnCl_2$	28	5 min	5[e]	75		
CPD	$ZnCl_2$	0–5	45 min	0[f]	91		
CPD	ZnI_2	0–5	10 min	(1.5)	76		
CPD	$CuBr_2$	22	2 hr	0	28	50	15, TPY
CPD	$h\nu$	0–5		19	1.2	25	36, TPE
CHD	$h\nu$	0–5		18	7.9	6	35, TPE
CHD	$ZnCl_2$	0–5	1 hr	0 (0)	43		
CHD	$ZnCl_2$	25	11 min	2	34	39	
CHPD	$ZnCl_2$	22	15 min	0.4	25	52	
COD	$ZnCl_2$	25	15 min	0 (0)	35	56	
ISOP	$ZnCl_2$	0–5	15 hr	0 (0)	68		
ISOP	$ZnCl_2$	24	10 min	2.4 (≥5:1)[g]	34	16	
ISOP	$ZnCl_2$	40	20 min	5.5 (2.4:1)[g]	31	26	
ISOP	$h\nu$	24		73 (1.1:1)[g]	0		0
EVE	$ZnCl_2$	25	2 hr	52	3.6	12	0
EVE	$h\nu$[h]			18.5	55.2	12	8.9, TPE
EVE	Ph_2CBr_2–MeLi[h]			4.8	0	16.5	20.6, TPY
EVE	$W(CO)_5$ complex[i]	37	3 hr	65			

[a] CPD, cyclopentadiene; CHD, 1,3-cyclohexadiene; CHPD, 1,3-cycloheptadiene; COD, 1,3-cyclooctadiene; ISOP, isoprene; EVE, ethyl vinyl ether. [b] The time the reaction was stirred after addition was completed. [c] Isolated percentages of corresponding cyclopropane product, parentheses indicate HPLC yields determined against cumene internal standard. [d] TPY, 1,1,2,2-tetraphenylethylene; TPE, 1,1,2,2-tetraphenylethane; ketazine, tetraphenylketazine. [e] Undistilled ether used as solvent. [f] Stirring the reactants without catalyst for 1 hr at 0° gave no reaction but nitrogen evolution was complete 15 min after addition of 0.1 mol % zinc chloride. [g] Ratio of disubstituted to monosubstituted double bond attack. [h] Reference 7b. [i] Reference 10.

ylcarbene is seen. Since changing the cation or its anions changes both the rate of decomposition (see below) and the amount of cyclopropanation, it is clear that the catalyst is involved in the decomposition reaction as well as the subsequent reactions. The best explanation for these results is a diphenylcarbenoid intermediate, and the overall mechanism (Chart I) follows the various modifications[3a,4d] of Wittig's original suggestion[14] about diazomethane decompositions.

Chart I



The initial reaction of the Lewis acid with diphenyldiazomethane depends on the relative strength of the Lewis acid and the basic property of diphenyldiazomethane. Very strong Lewis acids like boron trifluoride etherate and aluminum chloride react very fast and tend to give larger amounts of tetraphenylethylene.[2i] Bethell argued[3a] for the partitioned intermediate **10** based on a low degree of charge development on the diazo carbon, but this would not exclude the initial adduct **9** which could merely lose nitrogen on subsequent reaction.

Table II
Relative Activity toward Diphenyldiazomethane Decomposition in Air

Very fast[a]	$AlCl_3$, $TiCl_4$, $SnCl_4$, BF_3•OEt_2
Fast	$HgCl_2$, $Hg(NO_3)_2$, $CuBr_2$, $FeCl_3$, ZnI_2, $(i\text{-}PrO)_3P$•CuI, CuCl[MeCN][b]
Moderate	HgI_2, $ZnCl_2$, CuCl[ether], $CuCl_2$•$2H_2O$, $SnCl_2$•$2H_2O$, Hg_2Cl_2[MeCN]
Slow	CuCN, $CrCl_3$•$6H_2O$, $AlCl_3$•$6H_2O$
No reaction	Hg_2Cl_2[ether], $CdCl_2$, $Zn(CN)_2$, $Cr(OAc)_3$•$6H_2O$, $NiCl_2$•$6H_2O$, $Co(NO_3)_2$•$6H_2O$, $CoCl_2$•$6H_2O$, $MgCl_2$•$6H_2O$, $CaCl_2$, LiCl, LiBr, NH_4Cl, tetraphenylethylene

[a] Very fast, reacts completely in less than 1 min; fast, in less than 15 min; moderate, in less than 4 hr; and slow, reacts while standing for 24 hr. [b] Brackets indicate solvent where differences occurred.

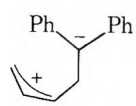
Diphenyldiazomethane shows no reaction with lithium bromide at 25° (see below)[5a] or with zinc chloride below −15° in ether, while phenyldiazomethane reacts with lithium bromide at 0° and with zinc chloride at −50°.[4d] This decreased basicity can be attributed to inductive electron withdrawal and to the additional steric hindrance of the second phenyl ring.

The results of our qualitative survey of the reactivities of various metal salts toward diphenyldiazomethane in ether–hexane and acetonitrile solution are listed in Table II. Since hydration does lower the reactivities, some of the strongly hydrated salts might change position if anhydrous samples were used, but within a series, the comparisons are probably sound. These relative values agree with published kinetic data for zinc chloride, zinc iodide, and cupric bromide.[3]

We note that salts of main groups I and II showed no

reaction and that salts of transition metals having stable lower oxidation states (Cr^{3+}, Fe^{3+}, and Cu^{2+}) reacted while others did not (Co^{2+} and Ni^{2+}). This supports Gaspar's suggestion[4f] about initial electron transfer, and parallels Nozaki's observation that product distributions vary with the aqueous reduction potential for several salts.[4e] The ligand effects on zinc(II) and mercury(II) decompositions correlate with their binding strengths to the metal ions. Thus the most tightly bound salts are least reactive. Hard–soft acid–base theory[15] suggests that the soft iodide ion binds more strongly to mercury(II) than to zinc(II), so $HgCl_2$ reacts faster than HgI_2, while ZnI_2 reacts faster than $ZnCl_2$ even though the equilibrium acidities for zinc halides in ether are in the reverse order.[16] Tighter binding could reduce reactivity because of lower solubility or because tighter ligands are less easily displaced during reaction.

Mixing a fivefold excess of cyclopentadiene with ethereal diphenyldiazomethane at 0° gave no reaction, but addition of 0.1 mol % zinc chloride quickly gave 91% tetraphenylketazine (3) with no trace of cyclopropane (2). Clearly the competition between olefin and excess diazo compound for the carbenoid greatly favors the more polarizable diazo compound. Previous workers[4] found no cyclopropanation because they used unreactive olefins. Apparently diene reactivity is determined by both electron density and by planarity, or the ability to attain a planar conformation. A planar conformation would facilitate the formation of an allylic carbonium ion on the diene residue after electrophilic attack. This type of intermediate, **13** or **14**, allows one to pre-



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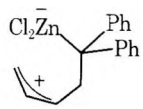

14

dict stereochemical results for closure of unsymmetrical carbenoids.[17] Initial work with unsymmetrically substituted diphenyldiazomethanes suggests that the syn–anti selectivities are the same for both the phenylarylcarbene and the phenylarylcarbenoid cyclopropanation reactions.[18] This will be discussed in a subsequent publication.

For cyclopropanation Zn(II) is much better than Cu(II) or Hg(II) and the more tightly bound zinc chloride promotes cyclopropanation better than zinc iodide. This correlates with the tendency to rearrange to the α-halo metal halide intermediate. Mercury(II) is known to form these derivatives readily and they are not particularly reactive toward cyclopropanation at or below 25°.[19] Furthermore, both chlorodiphenylmethylmercuric chloride[2c] and iodofluorenylzinc iodide[3a] have been isolated.

Our interest in the source of benzophenone oxygen led to separate ether extraction of the reaction mixture both before and after aqueous hydrolysis. Less than 10% of the benzophenone was present in the extract before hydrolysis, and this small amount could come from a small amount of water in the commercial anhydrous ether used for extraction. Perhaps the α-chloro zinc chloride (**11**) or some similar intermediate produces benzophenone during hydrolysis.

With the very reactive olefin ethyl vinyl ether, the diphenylcyclopropanation reactions appear to be dependent more on temperature than on the nature of the specific reagent. At −20° the methyllithium reaction with dibromodiphenylmethane gave only 4.8% cyclopropanation,[7b] while the zinc chloride catalyzed reaction with diphenyldiazomethane gave 52% at 25°, and the tungsten pentacarbonyl complex gave 65% at 37°.[10] However, on the less reactive 2-butenes, the methyllithium reaction gave 10–15% cyclopropanation at −20° [7a] when the tungsten complex[10] gave only a trace at 50°. In agreement with previous work,[7c] we found no cyclopropanation reaction with 1,3-cyclohexadiene using Olofson's method[5b] with chlorodiphenylmethane. Apparently the 2-butenes show some real reactivity differences that ethyl vinyl ether does not show. Furthermore, cyclopentadiene would be a better substrate for future reactivity comparisons.

The similarity of the cyclopropanation yields for diphenylcarbene reacting with cyclopentadiene, cyclohexadiene, and ethyl vinyl ether is probably caused by the competition with hydrogen abstraction that occurs in all three cases. The ratio of cyclopropanation to abstraction varies in the direction predicted by steric effects:[9a] ethyl vinyl ether (2:1); cyclopentadiene (1:2); and cyclohexadiene (1:3.4).

The regioselectivity of attack on isoprene was obtained by integrating the vinyl region of the ^1H NMR spectra for the cyclopropane products. The zinc chloride carbenoid gave a 5:1 preference at 24° and a 2.4:1 preference at 40° for the more electron-rich disubstituted double bond. Diphenylcarbene showed little selectivity.

The best explanation for the isoprene results is that the less reactive diphenylcarbenoid must rely more on electron density to promote complexation with the olefin than the more energetic diphenylcarbene does. We are continuing our work on the nature of cyclopropanation transition states.

Experimental Section

General. All melting points were determined on a hot stage apparatus and are corrected. Unless otherwise noted, magnesium sulfate was employed as a drying agent. The ir spectra were determined on a Beckman IR-5A or Acculab 1. NMR spectra were recorded on a Varian A-60A or EM-360. All diazo reactions were run under a nitrogen atmosphere. All HPLC work was done on a Waters ALC-202 with 1000 psig pump and 254-nm uv detector. Analytical determinations were done on a 6 ft × 0.125 in. Corasil C-18 (27–50 μ) reversed phase column using 1:1 acetonitrile–water eluent with cumene as an internal standard. Ether solvent was dried over lithium aluminum hydride or sodium benzophenone ketyl and then distilled before use. Ultraviolet spectra were determined on a Cary 14 spectrophotometer.

General Conditions for Carbenoid Reaction of Diphenyldiazomethane with Olefins. All reactions involved slow addition (ca. 10 mmol/hr) of an ethereal diphenyldiazomethane[20] solution (5–30 mmol, 0.1–0.5 *M*) to a stirred ethereal suspension or solution of the metal salt (5–30 mmol, nominally 0.5–2 *M*) and the olefin (fivefold excess, ca. 1.7 *M*) in a one-necked flask equipped with constant-pressure addition funnel, magnetic stirring bar, nitrogen line for initial flushing, a burette for monitoring nitrogen evolution, and an external temperature bath with thermometer. After the addition was complete (100–200 ml of nitrogen evolved per 10 mmol), the reaction mixture was stirred (10 min–9 hr) before the ether and excess olefin were removed in vacuo. The crude reaction mixture was slurried with 100 ml of ether to remove the ether-soluble material. The residue was partitioned between 100 ml of ether and 10 ml of water in a separatory funnel and any insoluble material was removed by filtration before the water layer was drawn off. The insoluble material generally included some tetraphenylketazine, mp 160–163° (lit. mp 163–164°),[21] identified by melting point, ir, and TLC; variable amounts of tetraphenylethylene, mp 224° (lit.[22] mp 223–224°); and a white solid, mp 205–250°. The ether layer was then washed twice more with 10-ml portions of water.

Generally, the two ether solutions were combined, dried, and concentrated (additional ketazine often crystallized out). HPLC aliquots were removed. The residue was dissolved in a minimum amount of benzene and was then chromatographed on a slurry packed Florisil column (ca. 1 × 53 cm). Elution with hexane gave residual olefin and the cyclopropane product, 10% ether–hexane gave benzophenone and some ketazine, and elution with up to 50% ether–hexane gave the remainder of the ketazine and some slow-moving tars. The results are listed in Table I and individual experimental details are listed below for some experiments.

Control Run with Reactants Mixed. A 3.88-g (20 mmol) sample of diphenyldiazomethane in 20 ml of dry ether was mixed with 6.60 g (8.3 ml, 100 mmol) of freshly distilled cyclopentadiene. Stirring for 1 hr at 0–5° gave no evolution of nitrogen and no observable diminution of color. After adding 2.56 ml of 0.8 *M* ethereal

$ZnCl_2$ solution, nitrogen began evolving. After an additional 45 min of stirring the reaction mixture was worked up to give 3.30 g (91%) of tetraphenylketazine crystals, mp 161–162°.

Temperature Control Run. A 6.60-g (100 mmol) sample of cyclopentadiene and 25.6 ml (20 mmol, 0.8 *M*) of ethereal zinc chloride were mixed with 50 ml of dry ether as before. After cooling to −40° (internal temperature), slow addition of a 3.88-g (20 mmol) sample of diphenyldiazomethane in 200 ml of dry ether was begun but the temperature continued to drop to −50°. No nitrogen evolution or fading of the color was observed, so addition was stopped and the flask was allowed to warm up. At −15°, but not before, both diminution of color and nitrogen evolution were observed. The temperature stabilized at about 3° during the reaction. Products were not isolated for this reaction.

Large-Scale Preparation of 6,6-Diphenylbicyclo[3.1.0]hex-2-ene. Following the general procedure, an ethereal solution of 19.0 g (100 mmol) of diphenyldiazomethane in 50 ml was added to 41 ml (33 g, 500 mmol) of freshly distilled cyclopentadiene and 20.4 g (100 mmol) of fused zinc chloride in 60 ml of ether at 25° over 1 hr. After stirring for an additional 1 hr at 25°, the ethereal solution was decanted and concentrated in vacuo, and the resulting oil was extracted with hot hexane. Crystallization of the concentrated hexane solution gave 6.10 g (26.2%) of 6,6-diphenylbicyclo[3.1.0]hex-2-ene, mp 80–81° (lit.[12] mp 80–81°).

Zinc Chloride–Diphenyldiazomethane Reaction with 1,3-Cycloheptadiene. Following the general procedure an ethereal solution of 3.72 g (19 mmol) of diphenyldiazomethane in 25 ml of dry ether was added to 4.71 g (50 mmol) of 1,3-cycloheptadiene and 2.6 g (20 mmol) of fused zinc chloride in 25 ml of ether at 25° and then stirred for an additional 10 min. After concentration in vacuo, partitioning between ether and water gave 2.32 g of insoluble solid, mp 190–250°. After crystallizing out 883 mg of ketazine, mp 163–164°, from the ether-soluble fraction, the remaining 1.93 g of ether-soluble material was then chromatographed on a Florisil column to give 1.90 g of benzophenone (52%) and 20.9 mg (0.45%) of 8,8-diphenylbicyclo[5.1.0]oct-2-ene as a clear oil: NMR (CCl_4) δ 7.27 (5 H s, ArH), 7.05 (5 H s, ArH), 5.87 (1 H d with further splitting, vinyl CH), 5.6–5.1 (1 H m, vinyl CH), 2.85–0.8 (10 H envelope); ir (thin film) 3050, 3020, 2920, 2880, 1600, 1590, 1440, 1175, 1140, 1070, 1030, 745, 690 cm^{-1}.

Anal. Calcd for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 91.87; H, 7.94.

An ether-insoluble solid, 419 mg, mp 240–250°, was isolated by filtration of the initial ether–water wash. Such material was isolated from nearly every reaction in varying yield, with mp 205–250°. TLC analysis shows a trace of tetraphenylketazine but the major component moves somewhat slower with chloroform eluent; NMR ($CDCl_3$) δ 7.5 (ArH, s); ir (mull) 3360, 3320 (OH), 3090, 3060 (ArCH), 1595, 1565, 1445, 1390, 1230, 860, 690 cm^{-1}. Although elemental analyses on different samples varied, they indicated a probable $C_{26}H_{20}N_2Cl_2Zn{\cdot}2H_2O$ formula. Although this is formally a hydrated 1:1 complex of zinc chloride and tetraphenylketazine, it was not formed when ketazine was mixed with ethereal zinc chloride. The exact structure is still under investigation.

Diphenylcarbene Reaction with Cyclopentadiene. A Pyrex tube containing 1.94 g (10 mmol) of diphenyldiazomethane and 25 ml of freshly distilled cyclopentadiene was immersed in an ice bath alongside a 450-W Hanovia well and irradiated for 4 hr at 0–5°. After concentration and collection of 529 mg of tetraphenylethane, mp 208–211° (lit.[23] mp 211°), and 72 mg of tetraphenylketazine, mp 164–165°, the residue was chromatographed on a Florisil column packed with hexane to give 2.25 g of cyclopentadiene dimer, 652 mg of semisolid containing product, 296 mg of tetraphenylethane, and 457 mg of semisolid identified as benzophenone (25%) by ir and TLC. Crystallization afforded 456 mg (19.6%) of 6,6-diphenylbicyclo[3.1.0]hex-2-ene, mp 80–81°. The total tetraphenylethane yield was 36.4%.

Diphenylcarbene Reaction with 1,3-Cyclohexadiene. A 1.00-g (5.15 mmol) sample of diphenyldiazomethane dissolved in 10 ml of 1,3-cyclohexadiene was irradiated as before for 3 hr at 0–5°. After concentration 174 mg of tetraphenylethane was isolated and the residue was chromatographed on a Florisil column with hexane to give 64 mg of cyclohexadiene residue, 141 mg of diphenylmethane (16.2%), a mixture of the cyclopropane product plus an isomer, 19 mg of crystals, mp 83–84°, 1.2% of benzophenone, a total of 35.2% of tetraphenylethane, and 7.9% ketazine. The product mixture was rechromatographed to give 228 mg of clear oil identified as 7,7-diphenylbicyclo[4.1.0]hept-2-ene (18%) which afforded clear crystals: mp 49–50°; NMR (CCl_4) δ 7.26 (5 H s, ArH), 7.09 (5 H s, ArH), 6.35–6.0 (1 H m, vinyl H), 5.55–5.2 (1 H m, vinyl H), 2.35–1.15 (6 H m); uv (95% ethanol) λ_{max} (ϵ) 276 (634), 268 (1090), 226 (14,300), 260 (shoulder, 1400; ir (mull) 3040, 3020, 2910, 2850, 1600, 1490, 1440, 1060, 1020, 745, 680 cm^{-1}.

Anal. Calcd for $C_{19}H_{18}$: C, 92.63; H, 7.36. Found: C, 92.65; H, 7.42.

The following fractions afforded 145 mg of crystals, mp 83–89° (11.5%), identified as 3-benzhydrylcyclohexa-1,4-diene. Recrystallization gave mp 101–102° with NMR (CCl_4) δ 7.25 (10 H s, ArH), 5.58 (4 H d of d with overlapping inner peaks and satellites ±14 Hz and smaller coupling ca. 2 Hz visible, vinyl H's), 3.70 (2 H m, bisallylic methines), 2.60 (2 H m, bisallylic methylenes); uv (95% ethanol) λ_{max} (ϵ) 268 (736), 260 (962), 255 (800), 217 (shoulder, 14,400); ir (Nujol, fluorolube) 3030, 2090, 1600, 1490, 1450, 1410, 1090, 1030, 950, 900, 750, and 690 cm^{-1}.

Anal. Calcd for $C_{19}H_{18}$: C, 92.63; H, 7.36. Found: C, 92.61; H, 7.46.

Decomposition Studies. All reactions were run in air with 0.1 mmol of diphenyldiazomethane dissolved in 3.0 ml of commercial grade solvent. Approximately 50 mg of the metal salt was added and decomposition was followed by disappearance of color. Times for disappearance are listed in Table II. No attempt was made to dry the solvents or the salts.

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Registry No.—**1**, 883-40-9; **2**, 22524-13-6; **3**, 983-79-9; **4**, 119-61-9; **5**, 55530-27-3; **6**, 55530-28-4; **7**, 632-50-8; cyclopentadiene, 542-92-7; zinc chloride, 7646-85-7; 1,3-cycloheptadiene, 4054-38-0; 8,8-diphenylbicyclo[5.1.0]oct-2-ene, 55530-29-5; 1,3-cyclohexadiene, 592-57-4.

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Arylsulfonoxylation of Aromatic Compounds. VI. Decomposition of *m*-Trifluoromethylbenzenesulfonyl Peroxide in the Absence of Solvent and in the Presence of Ethylbenzene and Cumene[1a,b]

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m-Trifluoromethylbenzenesulfonyl peroxide (1) has been synthesized and found to be slightly more stable than the nitrobenzenesulfonyl peroxides. The thermal decomposition of 1 in ethylbenzene and cumene gives exclusively nuclear substitution with no side-chain products characteristic of a homolytic reaction. The stability and heterolytic dissociation of sulfonyl peroxides substituted with electron-withdrawing groups (NO_2, CF_3) therefore are inherent and do not require the presence of a radical trap (e.g., a nitro group). Competitive *m*-trifluoromethylbenzenesulfonoxylations gave K_{Ar}/K_B: ethylbenzene, 14.8; cumene, 12.1. The ortho, meta, and para orientations (partial rate factors) are: ethylbenzene, 33.3, 5.8, 60.9% (14.8, 2.6, 54.2); cumene, 28.5, 7.8, 63.7% (10.3, 2.8, 46.1). The reactions of 1 with these two alkylbenzenes in ethyl acetate solution are first order with respect to the arenes and the enthalpies (entropies) of activation are: ethylbenzene, 16.7 (−17.4); cumene, 16.6 (−18.2). The reaction of 1 with benzene is first order with respect to the arene in methylene chloride, but in ethyl acetate an overall order of 0.66 is due to a competition to the reaction first order with respect to benzene ($\Delta H^{\ddagger}$, 18; $\Delta S^{\ddagger}$, −20) by a reaction zero order with respect to benzene ($\Delta H^{\ddagger}$, 30; $\Delta S^{\ddagger}$, 22). The $\Delta S^{\ddagger}$ for the zero-order reaction corresponds to a homolytic mechanism. The thermal decomposition of neat 1 (1.00 mol) and treatment of the reaction mixture with ethanol produced *m*-trifluoromethylbenzenesulfonic acid (0.538), 2-hydroxy-4-trifluoromethylbenzenesulfonic acid (0.617), ethyl *m*-trifluoromethylbenzenesulfonate (0.159), *m*-trifluoromethylphenyl *m*-trifluoromethylbenzenesulfonate (0.261), and *m*-trifluoromethylphenol (0.04). These products can be explained by a series of ionic intermediates.

Of all the arylsulfonyl peroxides reported up to this time (benzene-, *p*-toluene-, *p*-chlorobenzene-, *p*-bromobenzene-, 3,4-dichlorobenzene-, and *o*-, *m*-, and *p*-nitrobenzenesulfonyl peroxides),[2,3] only the nitro derivatives are sufficiently stable at room temperature for routine laboratory use. The nitrobenzenesulfonyl peroxides have been found to undergo a heterolytic scission in the presence of aromatic substrates leading to an electrophilic substitution.

$$(O_2NC_6H_4SO_3)_2 + C_6H_5X \longrightarrow O_2NC_6H_4SO_3C_6H_4X + O_2NC_6H_4SO_3H \quad (1)$$

There are two possible reasons for the stability of the nitrobenzenesulfonyl peroxides. First, the electron-withdrawing effect of the nitro group, by reducing the electron density on the peroxidic oxygens, may suppress any tendency for homolytic scission, similar to the stabilizing influence previously observed in the nitrobenzoyl peroxides.[4] Second, all sulfonyl peroxides may be inherently susceptible to an induced homolytic decomposition and the stabilizing effect of the nitro group could be due to its ability to interrupt such a chain reaction by acting as a radical trap.[5-8]

In the present work it was planned to synthesize *m*-trifluoromethylbenzenesulfonyl peroxide (1) and study its stability and some of its reactions. The *m*-trifluoromethyl group in its electron-withdrawing ability (σ 0.42) is similar to the *m*-nitro group (σ 0.71) but it is not a radical trap; therefore any unusual stability or reactions of 1 must be attributed specifically to the inductive effect of the trifluoromethyl group.

Results and Discussion

Synthesis of 1 was successfully accomplished by established methods[9] and it was found to be sufficiently stable at room temperature for routine laboratory use. Its high stability in contrast to that of most of the other arylsulfonyl peroxides can be due only to the inductive effect of the trifluoromethyl group, and the stability of the nitrobenzenesulfonyl peroxides now can similarly be attributed to the inductive effect of the nitro group.

Thermal decomposition of 1 in ethyl acetate solutions of alkylbenzenes was undertaken next. The nitrobenzenesulfonyl peroxides have been found to react in high yields with these hydrocarbons exclusively by an electrophilic substitution of the nucleus. The absence of any side-chain attack products characteristic of a homolytic dissociation of these peroxides conceivably could be attributed again to the nitro group acting as a radical trap. It has now been found that the reaction of 1 with ethylbenzene and cumene gives only nuclear substitution (Table I), although yields of as little as 1% of 2,3-diphenyl-2,3-dimethylbutane- (the expected side-chain attack products) could have been detected. The result with cumene is particularly significant, for this hydrocarbon undergoes side-chain hydrogen abstraction readily with a variety of free-radical reagents.[10-12] Therefore, the tendency of the arylsulfonyl peroxides to undergo heterolytic scission in the presence of aromatic substrates is inherent and not dependent on the presence of a trapping agent for free radicals to prevent an induced decomposition from becoming predominant.

The relative reactivities with respect to benzene and the orientations of substitution of ethylbenzene and cumene using 1 (Table II) are characteristic of an electrophilic substitution and are similar to those obtained using *o*- and *m*-nitrobenzenesulfonyl peroxides. The greatest differences are the slightly greater ortho substitutions obtained with 1.

The kinetic orders of the reactions with respect to arene

Table I
Reaction of *m*-Trifluoromethylbenzenesulfonyl Peroxide with Mixtures of Alkylbenzenes and Benzene in Ethyl Acetate Solution

Compd or quantity	Ethylbenzene (0.10 *M*)		Cumene (0.10 *M*)		Cumene (0.20)	
	Run 1	Run 2	Run 1	Run 2	Run 1	Run 2
Peroxide, mmol	0.545	0.453	0.476	0.471	1.01	1.03
Alkylbenzene, mol	0.005	0.005	0.005	0.005	0.01	0.01
Benzene, mol	0.025	0.025	0.025	0.025	0.05	0.05
Ethyl acetate	to 50 ml	to 50 ml	to 50 ml	to 50 ml	to 50 ml	to 50 ml
Sulfonate esters						
Total, % yield	84.3	84.2	77.4	78.1	84.6	82.6
Phenyl, mmol	0.141	0.095	0.109	0.107	0.209	0.208
o-Aryl, mmol	0.139	0.095	0.075	0.075	0.177	0.177
m-Aryl, mmol	0.022	0.018	0.020	0.021	0.053	0.060
p-Aryl, mmol	0.250	0.175	0.166	0.166	0.416	0.406
k_{ar}/k_B	14.5	15.2	11.9	12.2	15.4	15.4

Table II
Competitive Relative Reactivities with Respect to Benzene, Orientations, and Partial Rate Factors for the Arylsulfonoxylation ($XC_6H_4SO_3^-$) of Ethylbenzene and Cumene

Arene and quantity measured	X = *m*-CF_3	X = *o*-NO_2	X = *m*-NO_2
	Ethylbenzene		
k_{Ar}/k_B	14.8	11.5	17.6
% (k/k_H) ortho	33.3 (14.8)	30.6 (10.5)	29.9 (15.8)
% (k/k_H) meta	5.8 (2.6)	4.4 (1.5)	4.3 (2.3)
% (k/k_H) para	60.9 (54.2)	65.0 (44.8)	65.8 (69.4)
	Cumene		
k_{Ar}/k_B	12.1	9.0	13.5
% (k/k_H) ortho	28.5 (10.3)	22.3 (6.0)	23.5 (9.5)
% (k/k_H) meta	7.8 (2.8)	8.9 (2.4)	6.5 (2.6)
% (k/k_H) para	63.7 (46.1)	68.0 (36.8)	70.0 (56.7)

were obtained by direct measurements of the rate of *m*-trifluoromethylphenylsulfonoxylations via an iodometric titration of the disappearance of the peroxide to yield the data in Table III. Simple first-order (1.01) kinetics were obtained with respect to ethylbenzene in ethyl acetate just as first-order kinetics had been obtained for the *m*- and *p*-nitrophenylsulfonoxylation of all the alkylbenzenes studied.[13]

The *m*-trifluoromethylphenylsulfonoxylation of benzene in methylene chloride was found to be first order (0.97) with respect to the arene but in ethyl acetate solution the order was 0.66. Similarly the *m*-nitrophenylsulfonoxylation of benzene has been found to be first order in methylene chloride but 0.66 order in ethyl acetate.[13] These partial orders are due (eq 2) to the pseudo-first-order rate (k_1[P]) being the sum of a first-order (k_2[P]) dissociation to a reactive species plus a bimolecular nucleophilic displacement (k_3[P][B]) by the arene on an oxygen of the peroxide.[1b]

$$\frac{-d[P]}{dt} = k_1[P] = k_2[P] + k_3[P][B] \qquad (2)$$

From a plot (Figure 1) of k_1 (Table III) vs. the concentration of benzene, k_3 (the slope) and k_2 (the intercept) were obtained at three temperatures (Table IV). From these k_2 and k_3 values, as shown in Table V, the enthalpy (entropy) of activation for the k_2 process was found to be 30 kcal mol^{-1} (22 cal deg^{-1} mol^{-1}) and for the k_3 process, 18 kcal mol^{-1} (−20 cal deg^{-1} mol^{-1}). These values are of limited accuracy for minor deviations in k_1 are magnified in deriving k_2 and k_3. However, these parameters are very similar

Table III
Dependence of the Pseudo-First-Order Rate of Disappearance of *m*-Trifluoromethylbenzenesulfonyl Peroxide (0.01 *M*) in Ethyl Acetate Solution upon the Arene Concentration and the Temperature

Arene	Arene concn, *M*	Solvent	Temp, °C	$k \times 10^5$, sec^{-1}
Benzene	1	Ethyl acetate	0	0.170
Benzene	2	Ethyl acetate	0	0.312
Benzene	3	Ethyl acetate	0	0.453
Benzene	1	Ethyl acetate	10	0.730
Benzene	2	Ethyl acetate	10	1.07
Benzene	3	Ethyl acetate	10	1.48
Benzene	1	Ethyl acetate	20	2.82
Benzene	1.5	Ethyl acetate	20	3.44
Benzene	2.0	Ethyl acetate	20	4.16
Benzene	3.0	Ethyl acetate	20	5.87
Benzene	4.0	Ethyl acetate	20	7.06
Benzene	1.0	Methylene chloride	20	3.56
Benzene	2.0	Methylene chloride	20	7.14
Benzene	3.0	Methylene chloride	20	10.3
Ethylbenzene	1.0	Ethyl acetate	0	3.81
Ethylbenzene	1.0	Ethyl acetate	10	11.75
Ethylbenzene	0.1	Ethyl acetate	20	3.38
Ethylbenzene	0.5	Ethyl acetate	20	16.6
Ethylbenzene	1.0	Ethyl acetate	20	33.4
Ethylbenzene	1.5	Ethyl acetate	20	51.5
Cumene	1.0	Ethyl acetate	0	3.21
Cumene	1.0	Ethyl acetate	10	9.81
Cumene	1.0	Ethyl acetate	20	27.7

Table IV
k_2 and k_3 for the Trifluoromethylbenzenesulfonoxylation of Benzene in Ethyl Acetate

Temp, °C	$k_2 \times 10^6$, l. mol^{-1} sec^{-1}	$k_3 \times 10^6$, sec^{-1}
0	.29	1.42
10	3.43	3.75
20	13.2	14.56

to the corresponding values for the *m*- and *p*-nitrophenylsulfonoxylation of benzene (Table V).

The kinetics with 1 are much more reproducible than with any of the nitrobenzenesulfonyl peroxides. Traces of impurities in the solvent, etc., have smaller effects upon the rates with 1, thus making it a better model reagent.

Reaction Parameters. The enthalpies of activation for

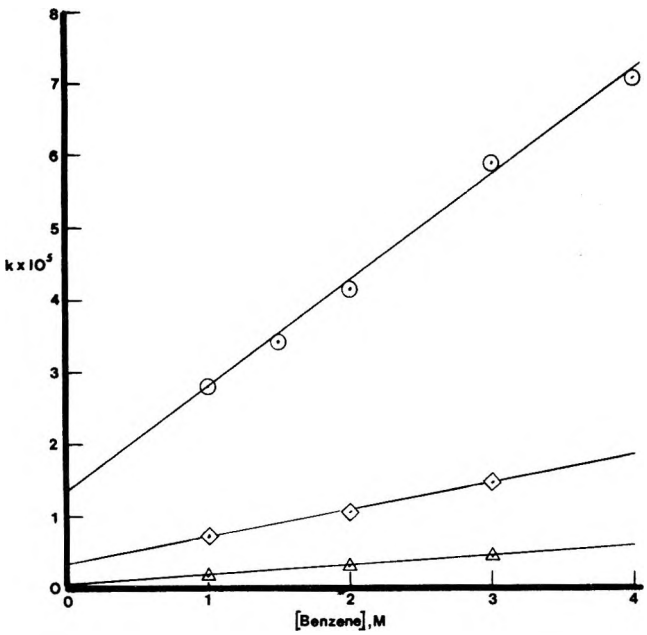


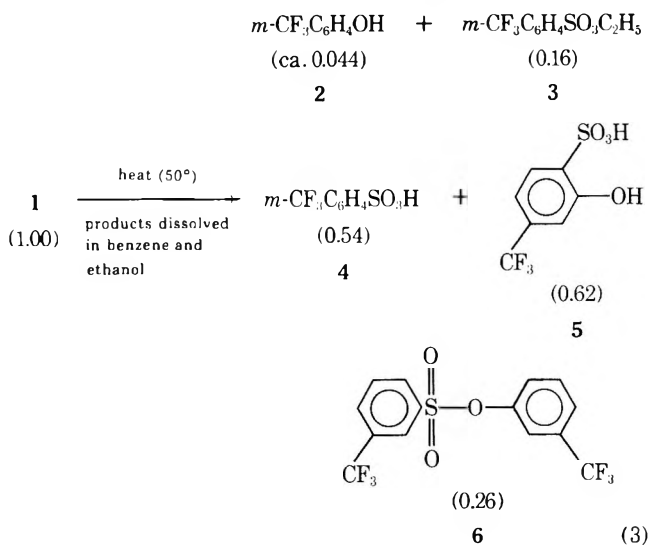
Figure 1. Plot of the pseudo-first-order rate constants for the disappearance of *m*-trifluoromethylbenzenesulfonyl peroxide in ethyl acetate solutions of benzene at the temperatures indicated: △, 0°; ◇, 10°; ○, 20°.

the *m*-trifluoromethylphenylsulfonoxylation in ethyl acetate of benzene (based on overall k_1), ethylbenzene, and cumene (Table V) are all about 1 kcal greater and the entropies of activation only a little less negative than the corresponding values for the *m*- and *p*-nitrophenylsulfonoxylation of the arenes.[13] This reflects the somewhat greater stability and longer half-lives of reaction of the trifluoromethyl peroxide observed in the laboratory as compared to the data for the nitro peroxides.

The entropies and enthalpies of activation for the bimolecular reaction of *m*-trifluoromethylphenylsulfonoxylation in ethyl acetate of benzene (based on k_3), ethylbenzene, and cumene are very similar. The differences observed based on the overall rate for benzene (k_1) result primarily from the competing (k_2) reaction. A similar relationship was observed for the nitrophenylsulfonoxylations of the arenes.[13]

The large negative entropies of activation for all the bimolecular arylsulfonoxylations are to be expected for electrophilic substitutions. The large positive entropy of activation for the k_2 *m*-trifluoromethylphenylsulfonoxylation of benzene in ethyl acetate is appropriate for a homolytic process. This is in agreement with the conclusions made with the nitrobenzenesulfonyl peroxides.[13] The similarity of competitiveness of the k_3 reactions with both the nitro and trifluoromethyl peroxides (as evidenced by the overall orders of reaction with respect to benzene) indicates that this homolytic decomposition of the peroxides is not induced, because then the nitro group, with its ability to act as a radical trap, would be expected to exert an influence different from that of the trifluoromethyl group.

Thermal decomposition of crystalline 1 in a sealed tube was undertaken as a model to determine what products might be expected from a cage reaction of 1 in solution and was found to give the products shown in eq 3. No ex-



(3)

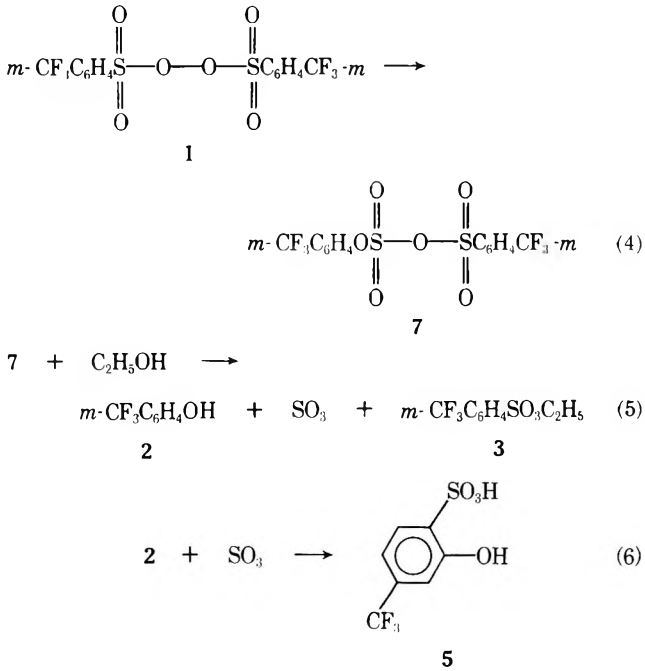
cess pressure was observed upon opening the tube on a gas manifold. Gas chromatographic analysis of the products

Table V
Reaction Parameters for the Arylsulfonoxylation of Benzene, Ethylbenzene, and Cumene

Arene and reaction	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
Benzene		
m-Trifluoromethylbenzenesulfonoxylation[a]	21.8	−4.8
m-Trifluoromethylbenzenesulfonoxylation[b]	30	+22
m-Trifluoromethylbenzenesulfonoxylation[c]	18	−20
m-Nitrobenzenesulfonoxylation[a]	20.6	−7.8
m-Nitrobenzenesulfonoxylation[b]	32	+30
m-Nitrobenzenesulfonoxylation[c]	16	−22
p-Nitrobenzenesulfonoxylation[a]	21.2	−6.2
p-Nitrobenzenesulfonoxylation[b]	d	d
p-Nitrobenzenesulfonoxylation[c]	16 ± 2	−18
Ethylbenzene		
m-Trifluoromethylbenzenesulfonoxylation	16.7	−17.4
m-Nitrobenzenesulfonoxylation	15.5	−20.0
p-Nitrobenzenesulfonoxylation	15.6	−20.1
Cumene		
m-Trifluoromethylbenzenesulfonoxylation	16.6	−18.2
m-Nitrobenzenesulfonoxylation	15.3	−20.7
p-Nitrobenzenesulfonoxylation	15.3	−21.6

[a] From the pseudo-first-order rate constants (k_1). [b] From the reaction constants (k_2) calculated for the reaction whose rate is independent of the benzene concentration. [c] From the reaction constants (k_3) calculated for the reaction first order with respect to benzene concentration. [d] The k_2 values were not reproducible enough to justify additional calculations.

showed the presence of **2** and **6**. When ethanol was added to the reaction mixture, **3** was found and the yield of **2** approximately doubled. Inasmuch as **6** does not undergo alcoholysis under these mild conditions, **3** possibly may have some type of anhydride precursor. The following scheme (eq 4–6) includes a possible concerted mechanism for the decomposition similar to the carboxyl inversion observed with *p*-methoxy-*p'*-nitrobenzoyl peroxide.[14,15] Fichter and



Stocker studied the decomposition of benzenesulfonyl peroxide in water[16] but because of the insolubility of this peroxide in water, its reaction might parallel a neat decomposition. It is therefore not surprising that they isolated benzenesulfonic acid and phenol (corresponding to **2** and **4**) as well as sulfuric acid (an alternative SO_3 product).

Experimental Section

Reagents. Anisole,[17] benzene,[17] cumene,[17] ethylbenzene,[17] nitrobenzene,[17] and ethyl acetate[18] were purified by standard procedures.

***m*-Trifluoromethylbenzenesulfonyl peroxide** was prepared by the literature method[9] for the nitro analog. A solution of *m*-trifluoromethylbenzenesulfonyl chloride[19] (12.2 g) dissolved in ethanol (10 ml) and a cold solution (−20°) of potassium carbonate (8.5 g) and 98% hydrogen peroxide (5 g) dissolved in a mixture of distilled water (100 ml) and ethanol (100 ml) were mixed at high speed in a prechilled Waring Blendor cup for about 90 sec. Ethanol (50 ml) was added and the mixture was stirred for 30 sec. The crude product (8.72 g, mp 74.5–76°) was collected by filtration, washed with water, and dried in vacuo. The peroxide was recrystallized from methylene chloride to give the pure product (4.77 g, 43%, mp 81–82°, purity 99.8% by peroxide titration[13]).

Anal. Calcd for $C_{14}H_8O_6S_2F_6$: C, 37.34; H, 1.79; S, 14.24. Found: C, 37.70; H, 2.09; S, 14.50.

Aryl Trifluoromethylbenzenesulfonates. The arenesulfonyl chloride (0.04 mol) and the phenol (0.04 mol) were heated together to 80° and a slight excess of aqueous 1 *M* potassium hydroxide was added dropwise over 30 min. The mixture was kept at 80° for an additional 1 hr and then extracted with methylene chloride. The methylene chloride solution was washed with 5% aqueous sodium hydroxide (20 ml), 5% hydrochloric acid (10 ml), and water (20 ml), and then dried with Drierite. The solvent was removed and the liquid esters were distilled at reduced pressure and the solids recrystallized from ethanol (Table VI).

2-Hydroxy-4-trifluoromethylbenzenesulfonic Acid (5). To *m*-trifluoromethylphenol (15 g) was added dropwise 20% fuming sulfuric acid (20 ml) and the mixture was kept at 100° for 1 hr. The mixture was stirred at room temperature with water (25 ml) for 2 days and then more water (100 ml) and sodium chloride were added. A tan solid (19.1 g) was collected by filtration. A portion of the product was dissolved in water and neutralized with aqueous potassium hydroxide, the mixture was cooled, and a cold solution of *S*-benzylthiouronium chloride was added. The *S*-benzylthiouronium arenesulfonate was collected by filtration and after recrystallization from hot 25% ethanol melted at 193–194°.

Anal. Calcd for $C_{15}H_{15}O_4N_2S_2F_3$: C, 44.11; H, 3.70; S, 15.70. Found: C, 44.00; H, 3.61; S, 15.67.

The structure of **5** was established from the NMR spectrum of its sodium salt, which consisted of four resonances: a singlet (H_3) at δ 7.10 overlapping a doublet (H_6) at 7.15; a doublet (H_5) at 7.70 ($J_{H_5H_6}$ = 8 Hz); and a singlet (OH) at 10.67 for an intramolecularly hydrogen-bonded phenol. These chemical shifts correspond to those of 2-amino-4-trifluoromethylbenzenesulfonic acid,[17] which similarly consist of a singlet (H_3) at δ 7.33 overlapping a doublet (H_6) at 7.25; a doublet (H_5) at 7.83; and a broad singlet at 5.67 for the amine salt hydrogens of the zwitterion, $J_{H_5H_6}$ = 7 Hz.

***S*-Benzylthiouronium *m*-trifluoromethylbenzenesulfonate** (mp 138–139°) was prepared by the method used above with hydroxysulfonic acid.

Anal. Calcd for $C_{15}H_{15}O_3N_2S_2F_3$: C, 45.91; H, 3.85; S, 16.34. Found: C, 45.82; H, 3.92; S, 16.33.

Competitive Reaction of 1 with Benzene and Cumene or Ethylbenzene in Ethyl Acetate. A solution 0.01 *M* in **1**, 0.1 *M* in arene, and 0.5 *M* in benzene was kept at 20° for 2 days. *m*-Tolyl *m*-trifluoromethylbenzenesulfonate was added as an internal standard and GLC analysis on a 20% SE-30 on Chromosorb W AW/DCMS column gave the results in Table I by comparison to chromatograms of the authentic esters.

Kinetics. The rates of disappearance of **1** in various solutions of arenes were measured by iodometric titration[13] and the data treated by a least-squares program.

Thermal Decomposition of Solid 1. A weighed amount of **1** placed in a Fischer-Porter aerosol compatibility tube half filled with glass helices was kept at 50° for 7 days. When the aerosol tube was cooled, attached to a gas manifold, and opened, no gas was evolved. The products were dissolved in methylene chloride and ethanol. This solution was washed with 5% aqueous potassium hydroxide to remove sulfonic acids and then chromatographed on silica gel, eluting with benzene. *m*-Trifluoromethylphenyl *m*-trifluoromethylbenzenesulfonate, identified by its melting point and comparison of its ir spectrum to that of an authentic sample, eluted first. Ethyl *m*-trifluoromethylbenzenesulfonate, identified by comparison of its ir spectrum to that of an authentic sample, eluted second.

Table VI
Physical Properties of *m*-Trifluoromethylbenzenesulfonic Acid Esters[a]

Ester	Registry no.	Mp or bp, °C (mm)	$n^{25}D$
Phenyl	55400-60-7	103–104 (0.2)	1.5103
o-Ethylphenyl	55400-61-8	97–98 (0.02)	1.5104
m-Ethylphenyl	55400-62-9	104–105 (0.03)	1.5065
p-Ethylphenyl	55400-63-0	107–108 (0.03)	1.5071
o-Cumyl	55400-64-1	125.5 (0.05)	1.5072
m-Cumyl	55400-65-2	122–123 (0.05)	1.5030
p-Cumyl	55400-66-3	44–45	
m-Trifluoromethylphenyl	55400-67-4	34.5–36.0	
Ethyl	55400-68-5	66 (0.08)	1.4576

[a] Analysis for the elements gave maximum deviations from the theoretical values as follows: all C values, ± 0.24; H, ± 0.14; S, ± 0.31.

A second decomposition mixture was dissolved in benzene, *m*-tolyl *m*-trifluoromethylbenzenesulfonate was added to an aliquot as an internal standard, and analysis by GLC on 5% SE-30 on Chromosorb W (Table I) showed successive peaks for *m*-trifluoromethylphenol and *m*-trifluoromethylphenyl *m*-trifluoromethylbenzenesulfonate. When absolute ethanol was added before GLC analysis, a new peak for ethyl *m*-trifluoromethylbenzenesulfonate appeared between the other two peaks and the peak for *m*-trifluoromethylphenol approximately doubled in area.

A second aliquot of the benzene solution of the reaction mixture was concentrated, methylene chloride was added, and the solution was extracted twice with water and once with 5% aqueous potassium hydroxide. The aqueous alkaline extract and the two water washes were combined and evaporated to dryness in a rotary evaporator. A portion of this residue was dissolved in 10 ml of water and adjusted to pH 6 with hydrochloric acid. This solution was cooled in an ice bath and added to a cold solution of *S*-benzylthiouronium chloride (5.0 g) in water (30 ml). The tan precipitate which formed was collected, dried, and recrystallized from hot 25% ethanol to give *S*-benzylthiouronium 2-hydroxy-4-trifluoromethylbenzenesulfonate (mp 193–194°). The mother liquor from the tan precipitate yielded *S*-benzylthiouronium *m*-trifluoromethylbenzenesulfonate (mp 133–134°). These salts were identified by melting point and ir spectra.

A new reaction mixture was prepared and concentrated, methylene chloride was added, and the methylene chloride solution was extracted twice with water and once with 5% aqueous potassium hydroxide. The combined aqueous layers were evaporated to dryness using a rotary evaporator. The solid residue was dissolved in a minimum amount of water (less than 10 ml), the solution was adjusted to pH 6 with hydrochloric acid, and a cold solution of *S*-benzylthiouronium chloride (3.0 g) in water (15 ml) was added. The precipitate which formed from this minimum amount of solution was collected by filtration, dried, and analyzed by ir using the base line technique to determine the relative amounts of the two component sulfuric acid salts.

Acknowledgment. We wish to express our thanks to Dr. Robert L. Waller for providing some of the kinetic data.

Registry No.—**1**, 35673-10-0; **5**, 55400-69-6; *m*-trifluorobenzenesulfonyl chloride, 777-44-6; phenol, 108-95-2; o-ethylphenol, 90-00-6; *m*-ethylphenol, 620-17-7; *p*-ethylphenol, 123-07-9; o-cumenol, 88-69-6; *m*-cumenol, 618-45-1; *p*-cumenol, 99-89-8; *m*-trifluoromethyphenol, 98-17-9; ethanol, 64-17-5; *S*-benzylthiouronium chloride, 538-28-3; *S*-benzylthiouronium 2-hydroxy-4-trifluoromethylbenzenesulfonate, 55400-70-9; *S*-benzylthiouronium *m*-trifluoromethylbenzenesulfonate, 2342-60-1; benzene, 71-43-2; cumene, 98-82-8; ethylbenzene, 100-41-4.

References and Notes

(1) (a) Presented at the International Conference on the Mechanisms of Reactions in Solution at the University of Kent at Canterbury, July 1970. Taken in part from the Ph.D thesis of P. K. T., 1970. (b) For the previous paper of this series see R. L. Dannley, R. V. Hoffman, P. K. Tornstrom, R. L. Waller, and R. Srivastava, *J. Org. Chem.*, 39, 2543 (1974). (c) NDEA Fellow, 1966–1969. This work supported in part by National Science Foundation Grant GP-19018.
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Preparation and Hydrolysis of Aminocyclopropyl and Aminocyclobutyl Sulfones[1]

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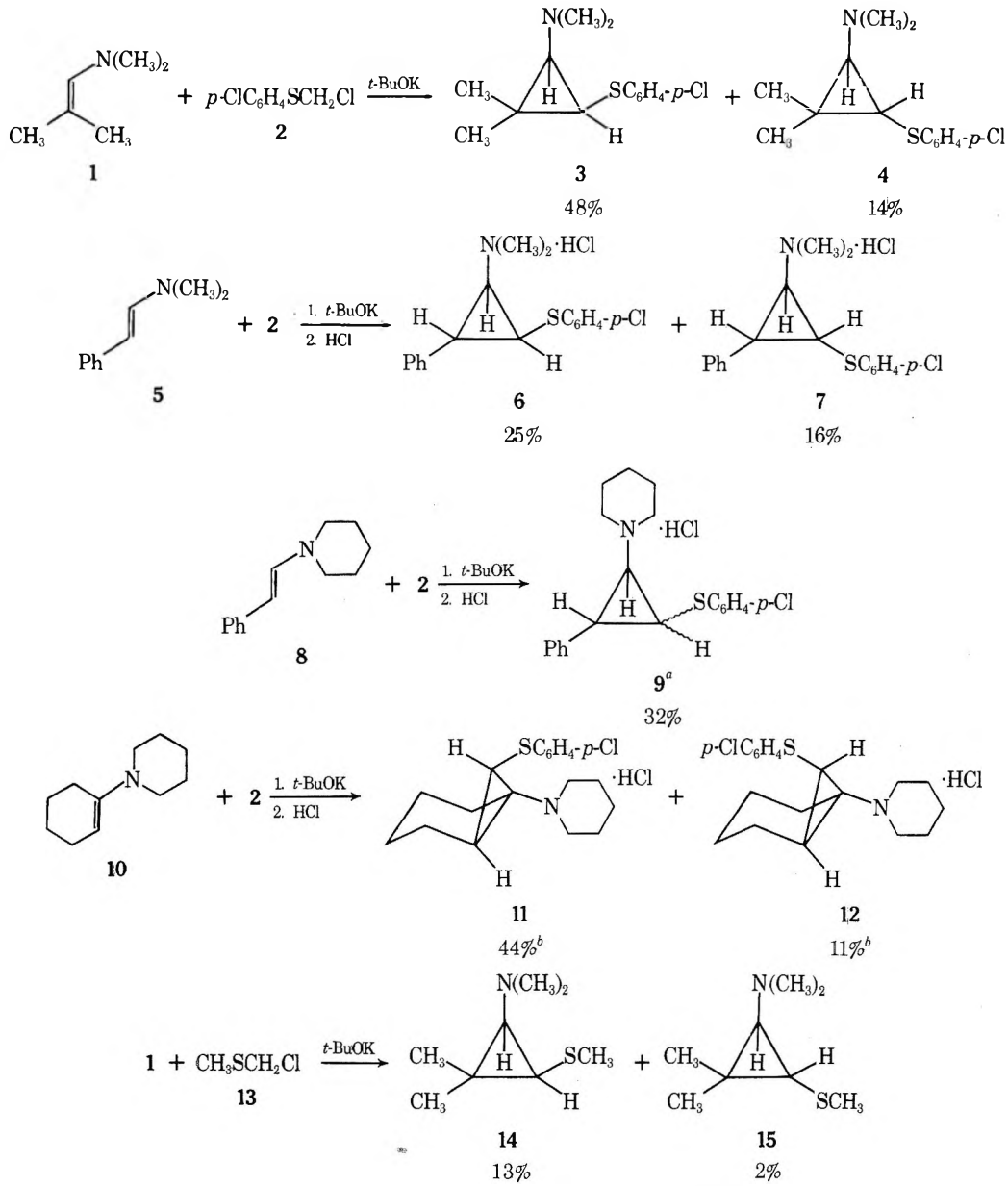
This report describes (1) the synthesis of aminocyclopropyl sulfides and their aqueous potassium permanganate oxidation to afford ring-opened sulfone acids and ketones; (2) the synthesis and facile hydrolysis of an aminocyclopropyl sulfone to afford a ring-opened aldehyde; and (3) the synthesis and hydrolysis of aminocyclobutyl sulfones to afford ring-opened aldehydes. It is proposed that these ring-opening reactions occur via zwitterionic intermediates.

There has been recent interest in the ring opening of cyclopropanes via zwitterionic intermediates.[1b-6] Ring-opening reactions of cyclopropylamines have also received recent attention.[1b,3,5-9] However, all of these systems require elevated temperatures and/or acidic or basic conditions. In contrast, we have found that aminocyclopropyl sulfones undergo a facile hydrolytic ring opening at room temperature. This report describes (1) the synthesis of aminocyclopropyl sulfides and their aqueous potassium permanganate oxidation to afford ring-opened products; (2) the synthesis and facile hydrolysis of an aminocyclopropyl sulfone; and (3) the synthesis and hydrolysis of aminocyclobutyl sulfones. We propose that these ring-opening reactions occur via zwitterionic intermediates, and discuss the factors influencing zwitterion formation.

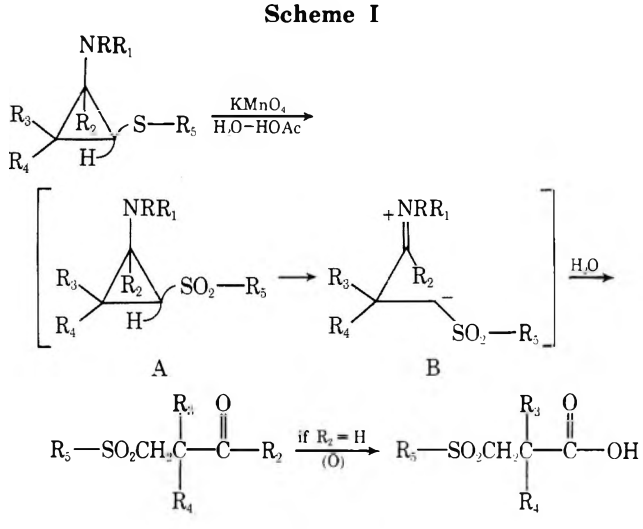
Preparation and Aqueous Potassium Permanganate Oxidation of Aminocyclopropyl Sulfides. The reaction of thiocarbenes (or carbenoids[10]), generated from chloromethyl sulfides and potassium *tert*-butoxide in ether, with enamines afforded the aminocyclopropyl sulfides shown in Table I. The yields ranged from poor to good, the lowest being observed with chloromethyl methyl sulfide. Rationale for the configurational assignments and an explanation for the observed stereoselectivities have been presented.[1a] Oxidation of the aminocyclopropyl sulfides **3**, **9**, and **11** + **12** with potassium permanganate in aqueous acetic acid at 25–30° afforded ring-opened sulfone acids and/or ketones in good yields. The products and yields are summarized in Table II. Structural proof for the products has been previously described.[1b] These conversions can be best

Table I
Conversion of Enamines to Aminocyclopropyl Sulfides

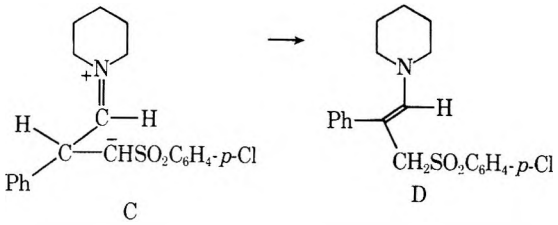


[a] Stereochemistry unassigned. [b] Isomer ratio based on ^{1}H NMR; quantitative separation not accomplished.

Scheme I

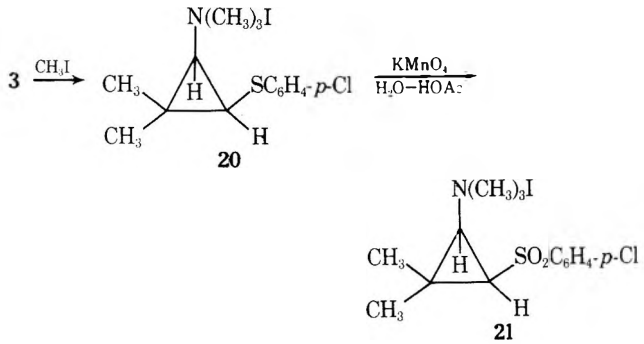


rationalized by initial formation of an aminocyclopropyl sulfone intermediate (A) which subsequently opened to a zwitterionic intermediate (B). Reaction of the zwitterion with water would afford the ring-opened aldehyde or ketone. In the cases where R_2 = H, the aldehyde would then be oxidized to the acid. This mechanistic sequence is summarized in Scheme I. The reaction of **9** to afford **18** as the major product deserves special consideration. The oxidative decarboxylation of **17** into **18** is not the major pathway for the formation of **18**, since treatment of **17** under identical reaction conditions afforded only a 14% yield of **18** with a 60% recovery of **17**. The formation of the major portion of **18** can be rationalized by the oxidative cleavage of the enamine intermediate D. Acid **17** presumably arose from intermediate C in a manner analogous to the formation of **16**. Presumably a major driving force for these ring-opening reactions is the formation of well-stabilized zwitterionic intermediates. Evidence for zwitterion involvement was ob-



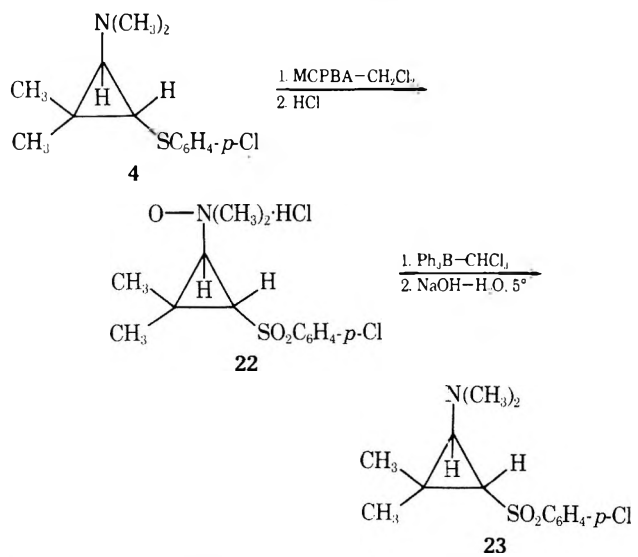
C D

tained when the quaternary ammonium salt **20,** a compound in which the electron pair of the nitrogen atom is not available for zwitterion stabilization, was submitted to similar oxidizing conditions (see Experimental Section). The product obtained (63% yield) was the unopened sulfone **21.**



20 **21**

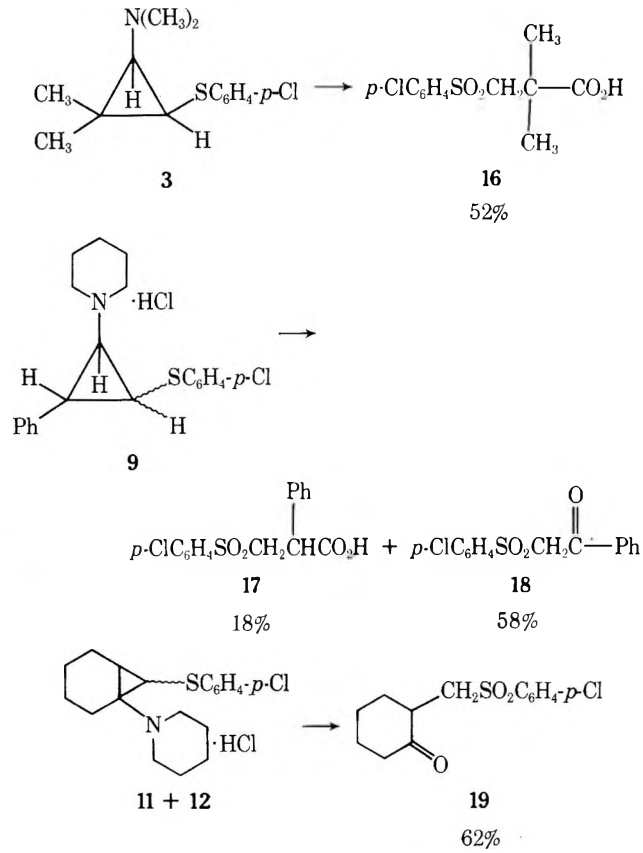
Preparation and Hydrolysis of Aminocyclopropyl Sulfones. With the presumption that aminocyclopropyl sulfones were a relatively unstable class of compounds, we set out to prepare examples of this class of compounds utilizing the mildest conditions we could envisage. Oxidation of *trans*-2-[(*p*-chlorophenyl)thio]-*N,N*,3,3-tetramethylcyclopropylamine (**4**) with 2 equiv of *m*-chloroperoxybenzoic acid (MCPBA) in chloroform at 5° afforded a complex, inseparable mixture of products. However, treatment with 4.5 equiv of MCPBA at −60° with slow warming to room temperature afforded a 75% yield of the amine oxide sulfone **22** (isolated as the hydrochloride). Amine oxides have



4 **22** **23**

been used to oxidize triarylboranes to the corresponding boric esters.[11] This suggested that a triarylborane, such as the commercially available triphenylborane,[12] could be used to reduce amine oxides to the corresponding amines under nonhydrolytic conditions. Indeed, treatment of **22** with triphenylborane in chloroform at room temperature followed by treatment with cold, aqueous sodium hydroxide solution afforded a 79% yield of *trans*-2-[(*p*-chlorophenyl)sulfonyl]-*N,N*,3,3-tetramethylcyclopropylamine (**23**). This compound was extremely sensitive to atmospheric moisture and under controlled conditions (aqueous methanol at 25° for 10 min) rapidly hydrolyzed to the ring-opened aldehyde **24** (84% yield). The identity of **24** was

Table II
Oxidation of Aminocyclopropyl Sulfides with Potassium Permanganate in Aqueous Acetic Acid

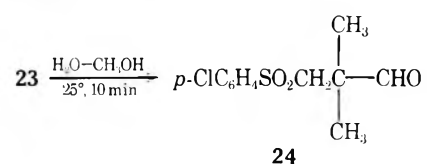


3 **16** 52%

9

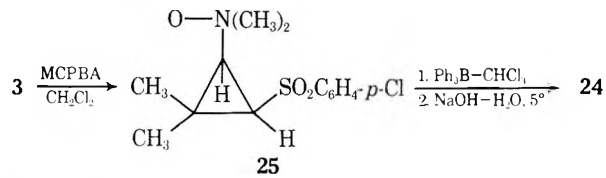
17 18% **18** 58%

11 + 12 **19** 62%



confirmed by comparison with an authentic sample prepared by the MCPBA oxidation of 3-[(*p*-chlorophenyl)-thio]-2,2-dimethylpropionaldehyde.[13] This facile hydrolysis of **23** is in accord with our proposal that aminocyclopropyl sulfones are intermediates in the aqueous potassium permanganate oxidation of aminocyclopropyl sulfides.

An analogous preparation of the corresponding cis aminocyclopropyl sulfone was attempted. Oxidation of **3** under conditions similar to those used for the trans isomer afforded the amine oxide **25** (83% yield). Reduction of **25** with triphenylborane using a cold sodium hydroxide solution work-up afforded an 86% yield of the ring-opened aldehyde **24.** An investigation of the ^{1}H NMR spectrum of the reduc-



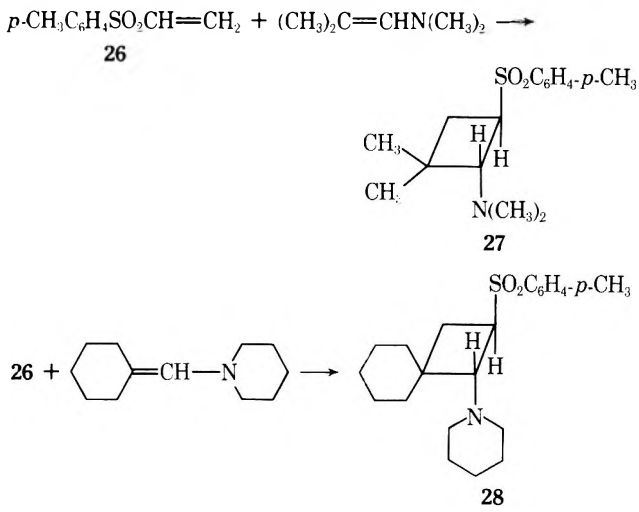
25

tion mixture before the aqueous work-up suggested that the desired cis aminocyclopropyl sulfone was present. Previous experience with aqueous sensitive compounds had shown that the chromatographic absorbent that had caused

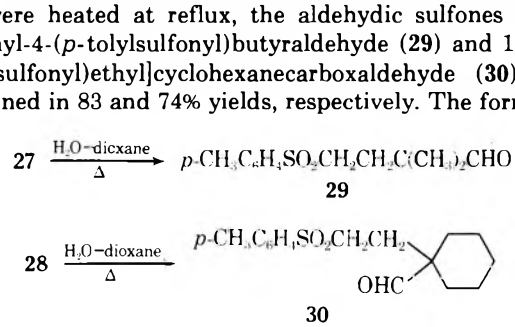
the least hydrolysis was acetylated cellulose. The crude reduction mixture was submitted to column chromatography using Woelm acetyl cellulose as the absorbent and eluted with *n*-hexane; the only identifiable product was the trans aminocyclopropyl sulfone **23** (42% yield). Thus the cis aminocyclopropyl sulfone which presumably formed on reduction of **25** isomerized to the trans isomer **24.** This isomerization and the hydrolysis of **23** can be best rationalized by the intermediacy of a zwitterion of type B.

Preparation and Hydrolysis of Aminocyclobutyl Sulfones. The next higher homologs, aminocyclobutyl sulfones, are known, stable compounds.[14] Brannock did cleave *N,N*,2,2-tetramethyl-4-(methylsulfonyl)cyclobutylamine by quaternization of the amino group followed by hydrolysis with aqueous base.[14] He attributed this cleavage to the dealdolization of a hydroxycyclobutyl sulfone intermediate.

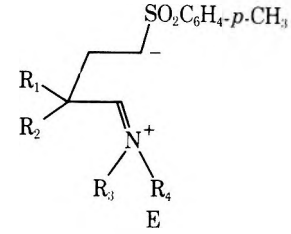
Compounds *trans-N,N*,2,2-tetramethyl-4-(*p*-tolylsulfonyl)cyclobutylamine (**27**) and *trans*-1-[2-(*p*-tolylsulfonyl)spiro[3.5]non-1-yl]piperidine (**28**) were prepared by treatment of *p*-tolyl vinyl sulfone (**26**) with the appropriate enamine in refluxing benzene. The gross structures of **27** and **28** were assigned on the basis of ir, ^{1}H NMR, mass spectra, elemental analyses, and chemical analogy.[14]



The assignment of cis or trans stereochemistry on the basis of vicinal coupling constants cannot be made with any assurance.[15,16] The assignment of a trans relationship between the amino and sulfonyl functions is based upon the commonly accepted mechanism of 1,2-cycloaddition reactions of enamines, i.e., a zwitterionic intermediate with free rotation leading to the thermodynamically more stable product.[15,17,18] When aqueous dioxane solutions of **27** and **28** were heated at reflux, the aldehydic sulfones 2,2-dimethyl-4-(*p*-tolylsulfonyl)butyraldehyde (**29**) and 1-[2-(*p*-tolylsulfonyl)ethyl]cyclohexanecarboxaldehyde (**30**) were obtained in 83 and 74% yields, respectively. The formation



of **29** and **30** can be best rationalized by formation of a zwitterionic intermediate (E), analogous to the cyclopropyl homolog, which subsequently reacts with water to form the aldehydic sulfones. The conditions required (ca. 100°, 17–18 hr) for these conversions are considerably more vigorous than those (25°, 10 min) required for the analogous aminocyclopropyl sulfone **23.** This suggests that ring strain



E

is a major driving force in the formation of such zwitterionic intermediates. The reaction sequence, **26** → **29** or **30,** represents a convenient preparation of α,α-dialkyl-γ-sulfone aldehydes.

Experimental Section

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were obtained on a Perkin-Elmer Model 421 recording spectrometer in Nujol mulls, the ^{1}H NMR spectra were recorded on a Varian A-60A spectrometer, and the mass spectra were determined on an Atlas CH-4 spectrometer.

Preparation of Aminocyclopropyl Sulfides. The following procedure for the preparation of *cis*- and *trans*-2-[(*p*-chlorophenyl)thio]-*N,N*,3,3-tetramethylcyclopropylamine (3 and 4) is representative. Chloromethyl *p*-chlorophenyl sulfide (50.0 g, 0.259 mol) in anhydrous ether (650 ml) was added dropwise over a 2-hr period to a stirred mixture of potassium *tert*-butoxide (34.8 g, 0.311 mol) and *N,N*,2-trimethylpropenylamine (77.0 g, 0.777 mol) in anhydrous ether (350 ml). The temperature was maintained at 25 ± 2° by means of a cooling bath. After stirring for an additional 2.5 hr at room temperature, the reaction mixture was diluted with water (400 ml) and the layers were separated. The ether layer was washed with water (200 ml) and extracted with 1 *N* HCl solution (3 × 500 ml). The combined HCl extracts were washed with ether (2 × 200 ml) and made strongly alkaline with 6 *N* NaOH solution. The resulting milky suspension was extracted with ether (3 × 500 ml) and the combined extracts were dried (Na_2SO_4). The solvent was removed in vacuo to afford 51.3 g (77% yield) of crude product. Chromatographic separation on silica gel (elution with 10% EtOAc in benzene) afforded 31.8 g (48% yield) of **3**, mp 59–61° (EtOH–H_2O), and 9.4 g (14% yield) of **4**, bp 100–104° (0.09 mm), respectively. The analytical and spectral data are summarized in Table III.

Oxidation of *cis*-2-[(*p*-Chlorophenyl)thio]-*N,N*,3,3-tetramethylcyclopropylamine (3) with Potassium Permanganate in H_2O–HOAc. Potassium permanganate (15.0 g, 0.094 mol) in 50% aqueous acetic acid (600 ml) was added dropwise to a stirred, cooled (20–25°) solution of **3** (10.0 g, 0.039 mol) in 50% aqueous acetic acid (200 ml). After stirring for an additional 2 hr at 20–25°, the reaction mixture was diluted with water (1200 ml) and then digested on a steam bath for 2 hr to precipitate the finely divided manganese dioxide. After standing at room temperature for 2 hr, the precipitate was removed by filtration through Celite and the solvent of the filtrate was removed in vacuo. The residue was partitioned between chloroform (250 ml) and water (100 ml). The organic layer was separated, washed with saturated $NaHCO_3$ solution (3 × 100 ml) and water (100 ml), and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was recrystallized from ether–petroleum ether to afford 5.6 g (52% yield) of 2,2-dimethyl-3-[(*p*-chlorophenyl)sulfonyl]propionic acid (**16**): mp 134–135.5°;[1b] ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 6 H), 3.47 (s, 2 H), 7.63 (q, 4 H), 12.2 (s, 1 H); mass spectrum *m/e* 276, 278 (M^+).

Anal. Calcd for $C_{11}H_{13}ClSO_4$: C, 47.74; H, 4.73; Cl, 12.81; S, 11.59. Found: C, 47.96; H, 4.72; Cl, 12.84; S, 11.43.

Oxidation of 1-[2-(*p*-Chlorophenylthio)-3-phenylcyclopropyl]piperidine Hydrochloride (9) with Potassium Permanganate in H_2O–HOAc. Oxidation of **9** (2.00 g, 5.26 mmol) with potassium permanganate (2.34 g, 14.8 mmol) in a manner analogous to the oxidation of **3** afforded 1.9 g of product mixture which was partitioned between chloroform (100 ml) and water (100 ml). The organic phase was separated and extracted with saturated Na_2CO_3 solution (2 × 50 ml). The organic phase was dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was recrystallized from ethanol to afford 0.90 g (58% yield) of α-(*p*-chlorophenylsulfonyl)acetophenone (**18**): mp 133–134° (lit.[20] mp 134.5°); ^{1}H NMR ($CDCl_3$) δ 4.73 (s, 2 H), 7.3–8.0 (m, 9 H); mass spectrum *m/e* 294, 296 (M^+).

Anal. Calcd for $C_{14}H_{11}ClO_3S$: C, 57.04; H, 3.76; Cl, 12.03; S, 10.88. Found: C, 57.33; H, 4.01; Cl, 11.96; S, 10.65.

Table III
Aminocyclopropyl Sulfides

Compd	Mp or bp (mm), °C	Recrystn solvent	^{1}H NMR, δ (CDCl$_3$)	Formula[a]
3	59–61	EtOH–H_2O	1.19 (s, 6 H), 1.69 (d, 1 H, J = 7 Hz), 1.96 (d, 1 H, J = 7 Hz), 2.27 (s, 6 H), 7.20 (s, 4 H)	$C_{13}H_{18}ClNS$
4	100–104 (0.09)		1.08 (s, 3 H), 1.33 (s, 3 H), 1.44 (d, 1 H, J = 3.5 Hz), 1.91 (d, 1 H, J = 3.5 Hz), 2.20 (s, 6 H)	$C_{13}H_{18}ClNS$
6	141.5–142.5	$CHCl_3$–Et_2O	2.90 (t, 1 H, J = 6.5 Hz), 3.0–3.25 (br, 7 H), 3.93 (d of d, 1 H, J = 5.0 and 6.5 Hz), 7.0–7.6 (br m, 9 H)	$C_{17}H_{19}Cl_2NS$
7	160–160.5	$CHCl_3$–Et_2O	2.75–3.10 (br, 6 H), 3.30–3.55 (br, 1 H), 3.55–3.90 (m, 2 H), 7.13 (s, 4 H), 7.22 (s, 5 H)	$C_{17}H_{19}Cl_2NS$
9	155.5–156 dec	$CHCl_3$–Et_2O	1.20–2.30 (br m, 7 H), 2.7–4.0 (br m, 7 H), 7.17 (s, 4 H), 7.25 (s, 5 H)	$C_{20}H_{23}Cl_2NS$
11	175.5–176	EtOH–Et_2O	0.9–3.7 (br, imposed d at 2.31, J = 5.5 Hz, 20 H), 7.30 (s, 4 H)	$C_{18}H_{25}Cl_2NS$
12	215.5–216	EtOH–Et_2O	1.1–3.6 (br, 19 H), 3.82 (d, 1 H, J = 10 Hz), 7.28 (s, 4 H)	$C_{18}H_{25}Cl_2NS$
14	65–68 (13)		1.08 (s, 3 H), 1.24 (s, 3 H), 1.44 (d, 1 H, J = 7.5 Hz), 1.59 (d, 1 H, J = 7.5 Hz), 2.09 (s, 3 H), 2.22 (s, 6 H)	$C_8H_{17}NS$
15	58–60 (13)		1.09 (s, 3 H), 1.22 (s, 3 H), 1.30 (d, 1 H, J = 3.5 Hz), 1.62 (d, 1 H, J = 3.5 Hz), 2.03 (s, 3 H), 2.21 (s, 6 H)	$C_8H_{17}NS$

[a] The compounds described in this table gave satisfactory analyses (within ± 0.4% of theoretical value) for C, H, N, and S (and Cl where applicable) except 7. Calcd for 7: S, 9.42. Found: S, 9.97.

The above sodium carbonate extracts were combined and acidified with 6 N hydrochloric acid. The resulting milky suspension was extracted with chloroform (2 × 50 ml) and the combined extracts were dried (Na_2SO_4). The solvent was removed in vacuo and the residue was recrystallized from benzene–petroleum ether to afford 0.30 g (18% yield) of 2-phenyl-3-(*p*-3-chlorophenylsulfonyl)propionic acid (**17**): mp 145–147°;[1b] ^{1}H NMR ($CDCl_3$) δ 3.2–4.2 (m, 3 H), 7.22 (s, 5 H), 7.55 (q, 4 H); mass spectrum *m/e* 324, 326 (M^+).

Anal. Calcd for $C_{15}H_{13}ClO_4S$: C, 55.47; H, 4.03; Cl, 10.92; S, 9.87. Found: C, 55.42; H, 3.98; Cl, 10.91; S, 9.98.

Oxidation of *endo*- and *exo*-1-[7-[(*p*-Chlorophenyl)thio]-6-norcaryl]piperidine Hydrochloride (11 and 12) with Potassium Permanganate in H_2O–HOAc. Oxidation of a mixture of **11** and **12**[19] (2.00 g, 5.6 mmol) with potassium permanganate (1.68 g, 10.6 mmol) in a manner analogous to the oxidation of **3** afforded 0.99 g (62% yield) of 2-[[(*p*-chlorophenyl)sulfonyl]methyl]cyclohexanone (**19**): mp 65–66° (hexane);[1b] ^{1}H NMR ($CDCl_3$)[21] δ 1.2–2.7 (br m, 8 H), 2.86 (d of d, J = −14 and 7 Hz, 1 H) 3.05 (m, 1 H), 3.91 (d of d, J = −14 and 3 Hz, 1 H), 7.70 (q, 4 H); mass spectrum *m/e* 286, 288 (M^+).

Anal. Calcd for $C_{13}H_{15}ClO_3S$: C, 54.45; H, 5.24; Cl, 12.39; S, 11.17. Found: C, 54.57; H, 5.42; Cl, 12.65; S, 11.41.

***cis*-*N,N,N*-Trimethyl-*N*-[[1,1-dimethyl-2-(*p*-chlorophenyl)thio]cyclopropyl]ammonium Iodide (20).** A mixture of **3** (10.0 g, 0.039 mol), methyl iodide (40 ml, 0.65 mol), and 2-butanone (100 ml) was heated at reflux for 45 hr. The reaction mixture was cooled slightly, ether was added to the cloud point, and the mixture was further cooled to afford 12.8 g (82% yield) of **20**: mp 96–98°; ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 3 H), 1.62 (s, 3 H), 2.73 (d, J = 8.5 Hz, 1 H), 3.65 (s, 9 H), 4.18 (d, J = 8.5 Hz, 1 H), 7.35 (s, 4 H).

Anal. Calcd for $C_{14}H_{21}ClINS$: C, 42.27; H, 5.32; N, 3.52; S, 8.06; I, 31.91. Found: C. 42.02; H, 5.55; N, 3.50; S, 8.14, I, 31.77.

***cis*-*N,N,N*-Trimethyl-*N*-[[1,1-dimethyl-2-(*p*-chlorophenyl)sulfonyl]cyclopropyl]ammonium Iodide (21).** A solution of potassium permanganate (23.9 g, 0.151 mol) in 50% aqueous acetic acid (500 ml) was added over a 15-min period to a stirred, cooled (20–25°) solution of **20** (10.0 g, 0.0251 mmol) in 50% aqueous acetic acid (200 ml). After stirring for an additional 2 hr at 20–25°, the reaction mixture was heated on a steam bath for 3 hr. The precipitate was removed by filtration through Celite and the filtrate was treated with sodium bisulfite solution until colorless and no longer gave a positive starch–iodide test. A solution of potassium iodide (4.16 g, 0.0251 mol) in water (25 ml) was added and the solvent was removed in vacuo to afford a white semisolid. Residual water and acetic acid were removed azeotropically with chloroform to afford a dry powder which was vigorously stirred with boiling chloroform (2 l.). The hot solution was filtered and the solvent of the filtrate was removed in vacuo. The residue was recrystallized from absolute ethanol to afford 6.82 g (63% yield) of **21**: mp 183–184° dec; ^{1}H NMR (Me_2SO-d_6) δ 1.02 (s, 3 H), 1.62 (s, 3 H), 3.21 (d, J = 9 Hz, 1 H), 3.40 (s, 9 H), 3.64 (d, J = 9 Hz, 1 H), 7.72 (q, 4 H).

Anal. Calcd for $C_{14}H_{21}ClINO_2S$: C, 39.12; H, 4.93; N, 3.26; Cl, 8.25; S, 7.46. Found: C, 39.35; H, 5.10; N, 3.00; Cl, 8.74; S, 7.73.

***trans*-2-[(*p*-Chlorophenyl)sulfonyl]-*N,N*,3,3-tetramethylcyclopropylamine *N*-Oxide Hydrochloride (22).** A solution of *m*-chloroperoxybenzoic acid (25.10 g, 0.123 mol) in methylene chloride (300 ml) was added dropwise to a stirred solution of **4** (7.00 g, 0.0274 mol) in methylene chloride (300 ml) maintained at −60 to −70°. The mixture was stirred for an additional 1 hr at −60 to −70° and then at ambient temperature for 18 hr. The mixture was poured onto a column of grade I basic alumina (1 kg) and eluted with 10% methanol in chloroform. Concentration of the appropriate fractions gave 7.92 g of oil which could not be made to crystallize. Treatment with anhydrous HCl in chloroform afforded 6.26 g (75% yield) of **22** (hygroscopic): mp 153.5–155.5°; ^{1}H NMR ($CDCl_3$) δ 1.48 and 1.53 (2 s, 6 H), 3.68 (d, J = 5.0 Hz, 1 H), 3.83 (s, 6 H), 4.44 (d, J = 5.0 Hz, 1 H), 7.72 (q, 4 H).

Anal. Calcd for $C_{13}H_{19}Cl_2NO_3S$: C, 45.88; H, 5.63; N, 4.12; Cl, 20.84. Found: C, 45.69; H, 5.58; N, 3.94; Cl, 21.01.

***trans*-2-[(*p*-Chlorophenyl)sulfonyl]-*N,N*,3,3-tetramethylcyclopropylamine (23).** A solution of triphenylborane[12] (3.35 g, 15.5 mmol) in chloroform (60 ml) was added dropwise to a stirred solution of **22** (4.72 g, 15.5 mmol) in chloroform (80 ml) under nitrogen, producing a slightly exothermic reaction. After stirring at ambient temperature for 4 hr the reaction mixture was washed briefly with cold 1 N sodium hydroxide solution and immediately dried (Na_2SO_4). The solvent was removed in vacuo and the residue was recrystallized from *n*-pentane to afford 2.52 g (57% yield) of **23** (hygroscopic): mp 81–85°; NMR ($CDCl_3$) δ 1.23 (s, 3 H), 1.42 (s, 3 H), 2.07 (d, J = 4.0 Hz, 1 H), 2.15 (s, 6 H), 2.35 (d, J = 4.0 Hz, 1 H), 7.67 (q, 4 H).

Anal. Calcd for $C_{13}H_{18}ClNO_2S$: C, 54.25; H, 6.30; N, 4.87; Cl, 12.32; S, 11.14. Found: C, 54.15; H, 6.27; N, 4.14; Cl, 12.59; S, 11.17.

Hydrolysis of 23. A mixture of **23** (0.10 g, 0.35 mmol), methanol (1 ml), and water (1 ml) was allowed to stand at 20–25° for 10 min. The reaction mixture was diluted with water (100 ml) and extracted with methylene chloride (4 × 75 ml). The combined extracts were washed with water (50 ml) and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was recrystallized from hexane to afford 0.76 g (84% yield) of 3-[(*p*-chlorophenyl)sulfonyl]-2,-2-dimethylpropionaldehyde (**24**), mp 68–70°. The ir and ^1H NMR spectra were identical with those of an authentic sample prepared below.

3-[(*p*-Chlorophenyl)thio]-2,2-dimethylpropionaldehyde. 3-[(*p*-Chlorophenyl)thio]-2,2-dimethylpropionic acid[1b] (28.3 g, 0.115 mol) was converted into the acid chloride with thionyl chloride (86% yield), bp 119–122° (0.2 mm). Lithium tri-*tert*-butoxyaluminum hydride (25.2 g, 0.0992 mol) in tetrahydrofuran (25 ml) was added dropwise to a stirred, cooled (−60 to − 70°) solution of the above acid chloride (26.1 g, 0.0992 mol) in THF (100 ml). The reaction mixture was stirred for an additional 1 hr at −60 to −70° and then allowed to warm to room temperature over a 1-hr period. The solvent was removed in vacuo. Water (500 ml) was added and the slurry was filtered. The solid was slurried with ethanol (1 l.) and filtered. The solvent of the filtrate was removed in vacuo and the residue was subjected to absorption chromatography on silica gel (eluted with methylene chloride). From the appropriate fractions there was obtained 12.0 g (53% yield) of 3-[(*p*-chlorophenyl)thio]-2,2-dimethylpropionaldehyde: bp 115–117° (2 mm); ^1H NMR ($CDCl_3$) δ 1.11 (s, 6 H), 3.02 (s, 2 H), 7.15 (s, 4 H) 9.67 (s, 1 H); mass spectrum *m/e* 228, 230 (M^+).

Anal. Calcd for $C_{11}H_{13}ClOS$: C, 57.76; H, 5.73; Cl, 15.50; S, 14.02. Found: C, 57.71; H, 5.59; Cl, 15.68; S, 13.68.

3-[(*p*-Chlorophenyl)sulfonyl]-2,2-dimethylpropionaldehyde (24). *m*-Chloroperoxybenzoic acid (17.75 g, 0.087 mol) in methylene chloride (400 ml) was added dropwise to a stirred solution of 3-[(*p*-chlorophenyl)thio]-2,2-dimethylpripionaldehyde (10.0 g, 0.0436 mol) in methylene chloride (350 ml) at ambient temperature. After stirring overnight, the reaction mixture was poured into a solution of saturated sodium carbonate (800 ml), containing sodium bisulfite (2 g), and shaken. The organic phase was separated and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was recrystallized from hexane to afford 7.0 g (61% yield) of **24:** mp 68–70°; ^1H NMR ($CDCl_3$) δ 1.33 (s, 6 H), 3.35 (s, 2 H), 7.71 (q, 4 H), 9.52 (s, 1 H); mass spectrum *m/e* 260, 262 (M^+).

Anal. Calcd for $C_{11}H_{13}ClO_3S$: C, 50.67; H, 5.02; Cl, 13.60; S, 12.30. Found: C, 50.83; H, 5.09; Cl, 13.83; S, 12.50.

***cis*-2-[(*p*-Chlorophenyl)sulfonyl]-*N,N*,3,3-tetramethylcyclopropylamine *N*-Oxide (25).** A solution of *m*-chloroperoxybenzoic acid (22.4 g, 0.11 mol) in chloroform (300 ml) was added dropwise to a stirred solution of **3** (10.0 g, 0.0367 mol) in chloroform (300 ml) maintained at −60 to −70°. After the addition was completed, the mixture was stirred at ambient temperature for 20 hr and poured onto a column of grade I basic alumina (1 kg) and eluted with 10% methanol in chloroform. Concentration of the appropriate fractions afforded crude **25** which was recrystallized from chloroform–hexane to afford 9.23 g (83% yield) of **25** (hygroscopic): mp 176° dec; ^1H NMR ($CDCl_3$) δ 1.14 (s, 3 H), 1.89 (s, 3 H), 2.44 (d, J = 8.0 Hz, 1 H), 3.18 (d, J = 8.0 Hz, 1 H), 3.30 (s, 3 H), 3.43 (s, 3 H), 7.70 (q, 4 H).

Anal. Calcd for $C_{13}H_{18}ClNO_3S$: C, 51.39; H, 5.97; N, 4.61; Cl, 11.67; S, 10.56. Found: C, 51.63; H, 5.94; N, 4.72; Cl, 11.85; S, 10.53.

Reaction of 25 with Triphenylborane. A. Aqueous Work-up. Reaction of triphenylborane (0.36 g, 1.64 mmol) with **25** (0.50 g, 1.64 mmol) under the same conditions used for the preparation of **23** afforded 0.37 g (86% yield) of **24**, mp 68–70°. The ir and ^1H NMR spectra were identical with those of an authentic sample prepared above.

B. Chromatographic Work-up. All of the operations were conducted under a nitrogen atmosphere. A solution of triphenylborane[12] (0.36 g, 1.64 mmol) in chloroform (20 ml) was added dropwise to a stirred solution of **25** (0.50 g, 1.64 mmol) in chloroform (20 ml). After stirring at ambient temperature for 6 hr the bulk of the solvent was removed and the residue was subjected to absorption chromatography. The absorbant was Woelm acetyl cellulose (40 g) which had been soaked in benzene for 20 hr, slurry pressure packed into a glass column, and washed thoroughly with *n*-hexane. The column was eluted with *n*-hexane. Concentration of the appropriate fractions gave 0.22 g (47% yield) of **23**, mp 82–84°. The ir and ^1H NMR spectra were identical with those of **23** prepared above.

***trans*-*N,N*,2,2-Tetramethyl-4-(*p*-tolylsulfonyl)cyclobutylamine (27).** A solution of *N,N*,2-trimethylpropenylamine (5.0 g, 0.050 mol) and **26** (9.1 g, 0.050 mol) in benzene (75 ml) was heated at reflux for 20 hr. The solvent was removed on a rotary evaporator and the residue was dissolved in ether (200 ml) and extracted with cold 10% HCl solution (3 × 100 ml). The combined extracts were washed with ether (2 × 50 ml) and then made basic with Na_2CO_3 solution. The oily suspension was extracted with ether (3 × 100 ml) and the combined extracts were dried (Na_2SO_4). The solvent was removed and the residue was recrystallized from hexane to afford 10 g (71% yield) of **27:** mp 73–74°; ^1H NMR ($CDCl_3$) δ 7.54 (q, 4 H), 3.58 (m, 1 H), 2.88 (d, J = 8 Hz, 1 H), 2.42 (s, 3 H), 2.21 (s, 6 H), 1.66 (m, 2 H), 1.15 (s, 3 H), 1.09 (s, 3 H); mass spectrum *m/e* 281 (M^+).

Anal. Calcd for $C_{15}H_{23}NO_2S$: C, 64.06; H, 8.19; N, 4.98; S, 11.39. Found: C, 63.81; H, 8.24; N, 4.87; S, 11.60.

***trans*-1-[2-(*p*-Tolylsulfonyl)spiro[3.5]non-1-yl]piperidine (28).** A solution of 1-(cyclohexylidenemethyl)piperidine[14] (8.9 g, 0.050 mol) and **26** (9.1 g, 0.050 mol) in benzene (100 ml) was heated at reflux for 18 hr. The solvent was removed and the residue was worked up as in the preparation of **27.** Recrystallization from hexane afforded 12 g (67% yield) of **28:** mp 119.5–121°; NMR ($CDCl_3$) δ 7.53 (q, 4 H), 3.60 (m, 1 H), 2.94 (d, J = 8 Hz, 1 H), 2.70–2.10 (broad m, 7 H), 1.87–0.90 (broad m, 18 H); mass spectrum *m/e* 361 (M^+).

Anal. Calcd for $C_{21}H_{31}NO_2S$: C, 69.77; H, 8.64; N, 3.88; S, 8.86. Found: C, 69.57; H, 8.70; N, 3.84; S, 8.98.

2,2-Dimethyl-4-(*p*-tolylsulfonyl)butyraldehyde (29). A solution of **27** (7.74 g, 0.027 mol) in water (100 ml) and dioxane (100 ml) was heated at reflux for 15 hr. The solvent was removed on a rotary evaporator and the residue was dissolved in methylene chloride (250 ml) and washed with water (50 ml). The solution was dried (Na_2SO_4) and the solvent was removed. The residue was recrystallized from hexane–cyclohexane to afford 5.71 g (83% yield) of **29:** mp 89–91°; NMR ($CDCl_3$) δ 9.06 (s, 1 H), 7.57 (q, 4 H), 3.20–2.84 (m, 2 H), 2.44 (s, 3 H), 2.03–1.66 (m, 2 H), 1.05 (s, 6 H); mass spectrum *m/e* 255 ($M^+ + 1$).

Anal. Calcd for $C_{13}H_{18}O_3S$: C, 61.42; H, 7.09; S, 12.60. Found: C, 61.36; H, 7.14; S, 12.82.

1-[2-(*p*-Tolylsulfonyl)ethyl]cyclohexanecarboxaldehyde (30). A solution of **28** (2.0 g, 0.0055 mol) in water (20 ml) and dioxane (20 ml) was heated at reflux for 17 hr. The reaction mixture was worked up as in the preparation of **29.** Recrystallization from hexane afforded 1.2 g (74% yield) of **30:** mp 58–59.5°; NMR ($CDCl_3$) δ 9.01 (s, 1 H), 7.50 (q, 4 H), 3.12–2.78 (m, 2 H), 2.42 (s, 3 H), 2.05–1.04 (broad m, 12 H); mass spectrum *m/e* 294 (M^+).

Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.26; H, 7.55. Found: C, 65.26; H, 7.53.

Registry No.—**1,** 6906-32-7; **2,** 7205-90-5; **3,** 37608-38-1; **4,** 37608-39-2; **5,** 14846-39-0: **6,** 51348-75-5; **7,** 51348-76-6; **8,** 55606-20-7; **9,** 51275-72-0; **10,** 2981-10-4; **11,** 37608-43-8; **12,** 37608-44-9; **13,** 2373-51-5; **14,** 37608-46-1; **15,** 37608-47-2; **16,** 36603-36-8; **17,** 36603-44-8; **18,** 36603-45-9; **19,** 55606-21-8; **20,** 51275-73-1; **21,** 55606-22-9; **22,** 55606-23-0; **23,** 55606-24-1; **24,** 55606-25-2; **25,** 55606-26-3; **26,** 5535-52-4; **27,** 55606-27-4; **28,** 55606-28-5; **29,** 55606-29-6; **30,** 55606-30-9; potassium permanganate, 7722-64-7; methyl iodide, 74-88-4; *m*-chloroperoxybenzoic acid, 937-14-4; triphenylborane, 960-71-4; 3-[(*p*-chlorophenyl)thio]-2,2-dimethylpropionyl chloride, 55606-31-0; 3-[(*p*-chlorophenyl)thio]-2,2-dimethylpropionaldehyde, 55606-32-1; 1-(cyclohexylidenemethyl)piperidine, 6604-81-5.

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(21) Data from 100-MHz spectrum performed and interpreted by S. A. Misak of The Upjohn Co.

Hydrogen and Alkyl Transfer in the Rearrangements of 2-Alkenyl-1,2-dihydroquinolines[1]

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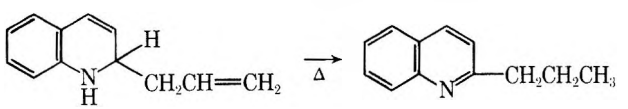
The addition of vinyl- or allylmagnesium chloride to quinoline yielded, at 25° and upon hydrolysis, the corresponding 2-alkenyl-1,2-dihydroquinoline. Heating the Grignard adduct with quinoline directly or heating the isolated dihydroquinoline caused isomerization to the corresponding 2-*n*-alkylquinoline or its magnesium salt, respectively. When the respective adducts were prepared from 2-deuterioquinoline and the subsequent isomerizations carried out, the resulting 2-*n*-alkylquinolines were found to be deuterated exclusively at the β position of the side chain. The coisomerization of 2-allyl-1,2-dihydroquinoline and 2-allyl-2,4-dideuterio-1,2-dihydroquinoline led to the production of much monodeuterated 2-*n*-propylquinoline, which indicates that such hydrogen transfer is largely, if not exclusively, intermolecular. 1,2-Dihydroquinolines and their N-metallic salts were found to undergo rather facile 1,2 elimination of RH or RM. In fact, 2-allyl-2-methyl-1,2-dihydroquinoline, as its *N*-magnesium chloride salt, was found to revert to quinaldine and allylmagnesium chloride. These components then recombined at higher temperatures to yield 4-allyl-2-methyl-1,4-dihydroquinoline as its *N*-magnesium salt. The foregoing findings point to two distinct pathways for intermolecular hydrogen transfer: (a) in the Grignard isomerization, a sequence involving MgHCl elimination, allyl–propenyl group isomerization, and 1,4 readdition of MgHCl; and (b) in the dihydro isomerization, elimination of RH in a free-radical initiation step, followed by concerted six-center hydrogen transfers and base-promoted allyl–propenyl group isomerization.

Hydrogen-transfer reactions of certain dihydropyridines have received much attention, since their conversion into pyridine derivatives is fundamental to the coenzymatic activity of dihydronicotinamide–adenine dinucleotide.[2] A special instance of this hydrogen transfer is that of isomerization, first observed in the rearrangement of 2-allyl-1,2-dihydroquinoline into 2-*n*-propylquinoline[3] (eq 1). Subsequently, isomerizing hydrogen transfers have been noted with similar derivatives, such as 4-allyl-1,4-dihydropyridines[4,5] and 2-phenylethynyl-1,2-dihydropyridine.[6]



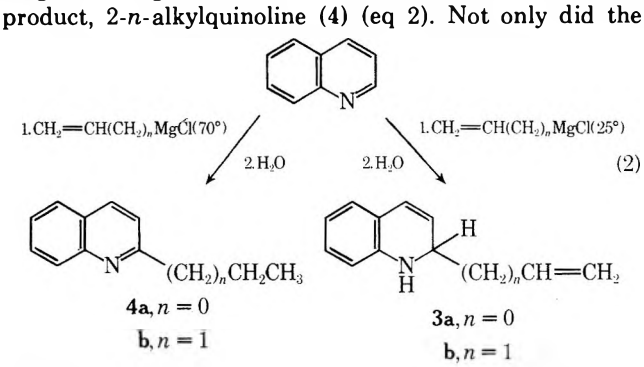
1 2 (1)

In these isomerizations the dihydropyridinoid derivative acts, in a formal sense, both as a hydrogen donor and acceptor. As a consequence, a detailed study of the nature and scope of these rearrangements appeared to offer a unique opportunity for gaining a better understanding of hydrogen-transfer processes in these heterocycles.

The present report describes the preparation and rearrangement behavior of certain 2-alkenyl-1,2-dihydroquinolines, that bear a deuterium atom or a methyl group at C_2 and in which the alkenyl group is vinyl, allyl, and phenyl. The thermal and photochemical reactivity of these derivatives was examined in order to obtain information on (a) the nature of any intermediates; (b) the fate of any deuterium undergoing transfer; (c) the inter- or intramolecularity of the rearrangement; and (d) the nature of the reaction mechanism.

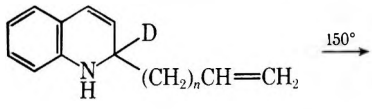
Results

The reaction of vinyl- or allylmagnesium chloride with quinoline yields the simple 1,2 adduct (**3**) at 25°, but prolonged heating favors the formation of the rearrangement product, 2-*n*-alkylquinoline (**4**) (eq 2). Not only did the Grignard adducts themselves, namely the 2-alkenyl-1,2-dihydro-1-quinolylmagnesium chlorides, undergo rearrangement, but also the isolated, pure dihydro compounds, **3a** and **3b**, were found to isomerize into **4a** and **4b**, respectively, in 50–80% yields when heated under a nitrogen atmosphere above 130°. In addition, the irradiation at 254 nm of **3b** dissolved in benzene also caused isomerization into 2-*n*-propylquinoline (**4b**, 20% after 24 hr), but much deallylation with the formation of quinoline (60%) accompanied this process.

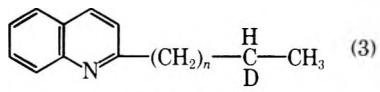


The fate of the NH and C_2H groups in **3** during the isomerization was studied by synthesizing C_2-deuterated analogs of **3a** and **3b** from 2-deuterioquinoline and the appropriate Grignard reagents (eq 2). Thermal rearrangement of

these compounds, **5a** and **5b**, yielded the respective 2-alkylquinolines, **6a** and **6b**, which by NMR spectroscopy were shown to be exclusively monodeuterated at the β carbon of the side chain (eq 3).



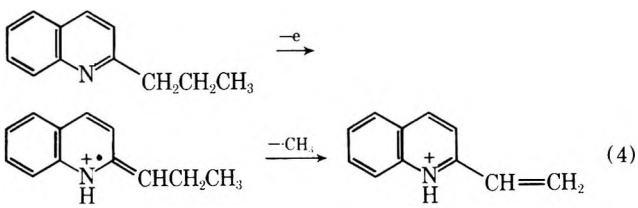
5a, $n = 0$
b, $n = 1$



(3)

6a, $n = 0$
b, $n = 1$

To test whether the hydrogen transfer takes place by an intramolecular or an intermolecular process, the thermal isomerization of a 1:1 mixture of 2-allyl-1,2-dihydroquinoline (**3b**) and 2-allyl-2,4-dideuterio-1,2-dihydroquinoline (**7**) was carried out at 150°. Mass spectral analysis of the crude reaction product, even at 20 eV, indicated the occurrence of much fragmentation and the presence of peaks corresponding to $C_{24}H_{22}N_2$ and $C_{24}H_{20}D_2N_2$ (338 and 340, respectively, presumably dimers of 2-propenylquinoline). Since fragmentation of the dimer contributed intensity to the P and P − 1 peaks of the 2-*n*-propylquinoline, the peaks in the mass range 170–173 could not be used for the detection of deuterium crossover. The P − 15 of **4b**, however, was found to be unchanged in intensity by the presence of such dimeric products (eq 4). The mass spectrum of



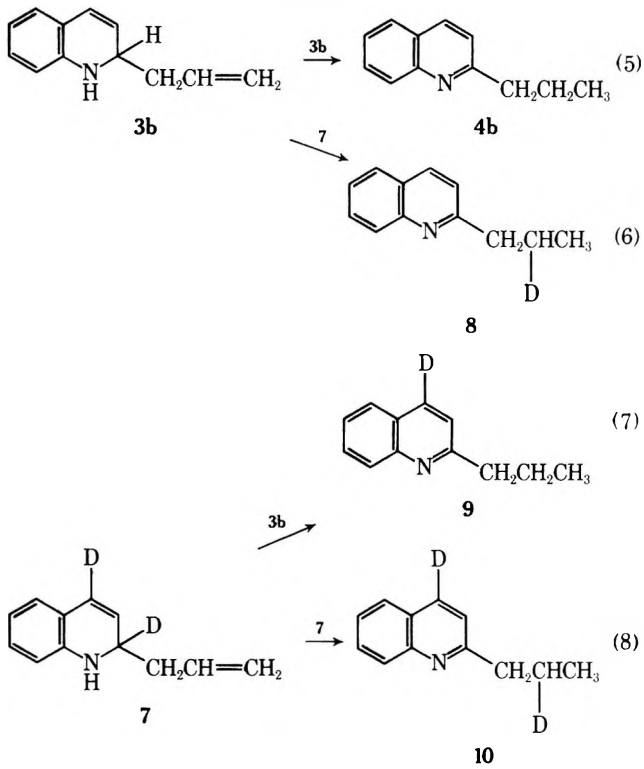
(4)

the crude 2-*n*-propylquinoline displayed peaks at *m/e* 158, 157, and 156 in a ratio of 1.2:1.2:1.0, respectively. The peak at *m/e* 157 can be ascribed to the presence of 2-*n*-(2-deuteriopropyl)- and 4-deuterio-2-*n*-propylquinolines (**8** and **9**), formed from the intermolecular hydrogen transfer between **3b** and **7** (Scheme I). Because a statistical intermolecular hydrogen transfer should result in the formation of **8** and **9** with the same probability as for **4b** and for **10**, the ratio of peaks at 158, 157, and 156 should be 1.0:2.0:1.0 for random exchange. On the other hand, exclusively intramolecular hydrogen transfer would lead to a ratio of 1.0:0:1.0. The observed ratio can mean either that both intramolecular and intermolecular hydrogen transfers are operative, or that a deuterium isotope ($k_H/k_D > 1.0$) favors the intermolecular reaction of 2-allyl-1,2-dihydroquinoline (**3b**) with itself. In this situation, as **3b** would be preferentially consumed in forming **4b**, the chances of **7** reacting with itself to form **10** would then increase.

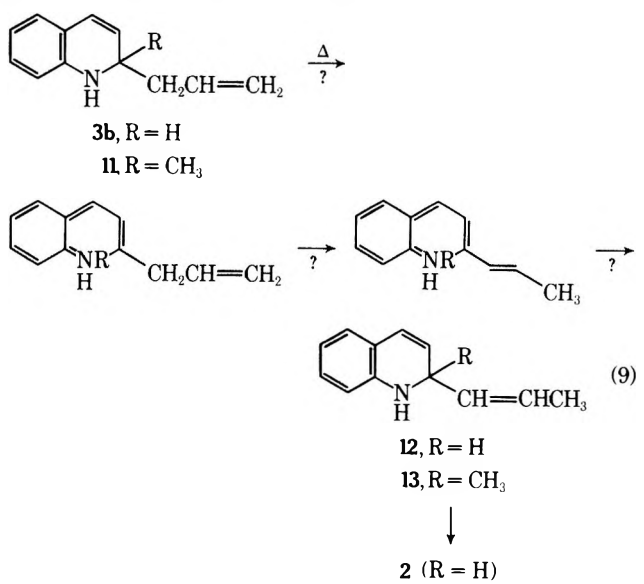
A mass spectral analysis of the 2-*n*-propylquinoline isolated by distillation from the coisomerization of **3b** and **7** showed the same ratio of peaks at *m/e* 158, 157, and 156.

Since 1,2-dihydroquinolines can be viewed as aza-substituted 1,3-cyclohexadienes, the question arose whether any part of the rearrangement involved an electrocyclic ring opening,[7] followed by an isomerization and an electrocyclic ring closure.[7] The final isomerization of the resulting 2-propenyl-1,2-dihydroquinoline (**12**) could be achieved by intermolecular hydrogen transfer (eq 9). If such electrocyclic processes were involved, then 2-allyl-2-methyl-1,2-dihydroquinoline (**11**), as the free base or the *N*-magnesium chloride salt (**14**), should be able to isomerize to **13**.

Scheme I

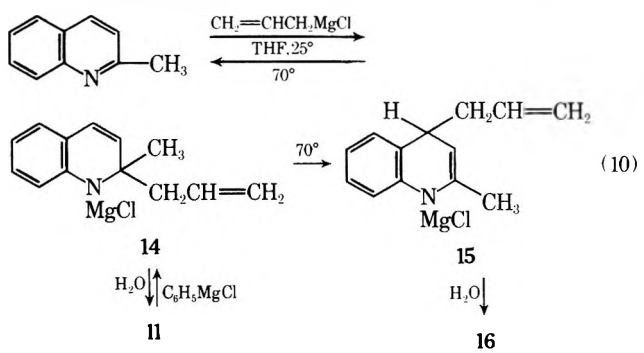


(5) (6) (7) (8)



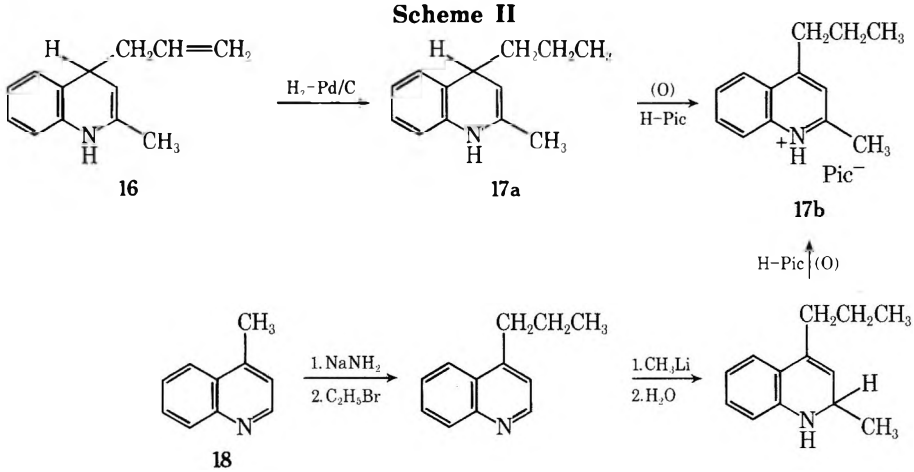
(9)

Therefore, **11** was prepared in high yield from the addition of allylmagnesium chloride in THF to 2-methylquinoline at 25°. Attempts to cause the isomerization envisaged



(10)

Scheme II

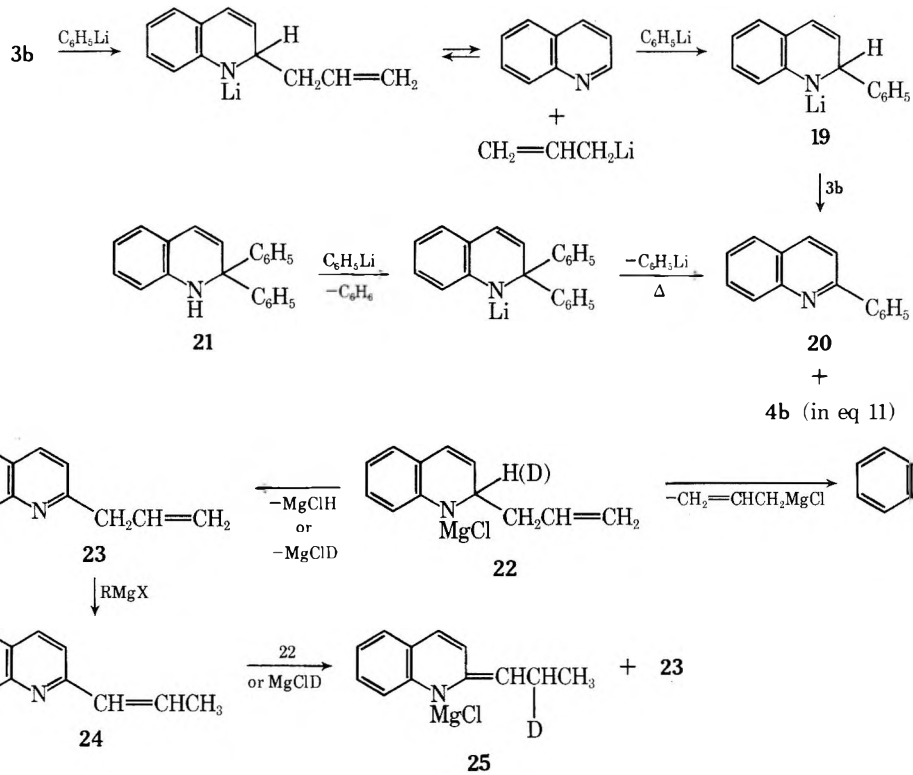


in eq 9, however, gave no discernible amount of **13**, but rather an allylic rearrangement. When the first-formed magnesium salt **14** was heated with an excess of Grignard reagent, the final principal product was the magnesium salt **15** of 4-allyl-2-methyl-1,4-dihydroquinoline (**16**) (eq 10). The proof of structure for **16** was achieved by means of spectroscopic data and by its catalytic hydrogenation to 2-methyl-4-*n*-propyl-1,4-dihydroquinoline (**17a**). The latter compound was oxidatively aromatized to 2-methyl-4-*n*-propylquinoline picrate (**17b**), which was identical in its spectral and physical properties with a sample synthesized unambiguously from lepidine (**18**)[8] (Scheme II).

Although the observed rearrangement of **14** into **15** effectively ruled out the occurrence of electrocyclic processes (eq 9) as part of the allyldihydro–propyl group isomerization (eq 10), the question as to the mechanism of the allyl group migration still remained. Either an intramolecular, [3,3] sigmatropic shift could be responsible[9] or the reelimination of allyl Grignard reagent from **14** to form quinaldine could occur, followed by the readdition of the Grignard reagent in a 1,4 manner. To test the tendency of **14** to undergo dissociation, **14** was prepared from pure, isolated **11** by treatment with phenylmagnesium chloride in THF. After 24 hr at room temperature such a solution was shown to contain 60% of quinaldine and 40% of **14**. Heating a solution of **14** at reflux led to 75% of quinaldine, 20% of **16**, and only 5% of **11**. From these results it is readily apparent that the dissociation of **14** is the dominant process in THF. Hence, **16** arises, most probably, from a thermodynamically controlled 1,4 Grignard addition to quinaldine.

This tendency of **14** to undergo elimination was found to be fairly general for such 2-substituted 1,2-dihydroquinolines. Thus, even treatment of **3b** with an excess of phenyllithium led to the isolation of 2-phenylquinoline (**20**), quinoline, and 2-*n*-propylquinoline. The products point to the dissociation of the lithium salt of **3b** into quinoline and allyllithium, the capture of some quinoline by phenyllithium, and the transfer of lithium hydride from **19** to **3b** yielding 2-phenylquinoline and 2-*n*-propylquinoline (eq 11). A phenyl group was found to be eliminated even from N-metallic salts of 2,2-diphenyl-1,2-dihydroquinoline (**21**), albeit such processes were slower (eq 12).

Not only did the metal salts of 1,2-dihydroquinolines tend to aromatize by loss of R–M, but the dihydro deriva-



tives themselves lost R–H at moderate temperatures or with photochemical activation. Heating 2-allyl-1,2-dihydroquinoline (**1**) under nitrogen gas above 130° always led to the formation of some quinoline and propylene, in addition to the usual isomerization to 2-*n*-propylquinoline (**2**) (eq 1). Indeed, direct heating of **1** at 285° gave almost equal parts of quinoline and **2**. Direct irradiation of **1** at 45° gave quinoline as the chief product. Likewise, the heating of **11** gave much quinaldine and propylene, together with complex rearrangement products.

These results on the thermal lability of dihydroquinolines and N-metallic salts show that during hydrogen-transfer (eq 1) and alkyl-transfer (eq 10) processes there are always varying amounts of the corresponding aza aromatic system present as a possible intermediate (quinoline in eq 1 and quinaldine in eq 10).

Discussion

The thermal rearrangements of 2-alkenyl-1,2-dihydroquinolines themselves (case I) and of their magnesium salts (case II) need not proceed by similar mechanisms. In fact, previous work on the interactions of organometallic reagents with the azomethine group would tend to support the operation of polar processes;[10] on the other hand, studies on the thermal decomposition of 1,2-dihydroquinolines have concluded that radical processes are involved.[11] Since kinetic studies on these rearrangements have not yet been made, the present discussion will consider what conclusions can be drawn from the foregoing product analyses. First of all, transfer of the C_2 H of 2-allyl-1,2-dihydroquinoline to yield 2-*n*-propylquinoline occurs largely, if not exclusively, intermolecularly. With the assumption of a modest isotope effect, $k_H/k_D \simeq 3$, and only one rate-limiting step, namely the formation of radical **31c**, the initial rate (ratio) of formation for **10**, **8** + **9**, and **4b** would be 1:4:3. A mixture of **3b** and **7** permitted to rearrange to completion should give a ratio of the peaks at *m/e* 158, 157, and 156 closer to 1:1:1, in general agreement with the observed ratio. However, more detailed work would be required to rule out any minor role for intramolecular transfer.

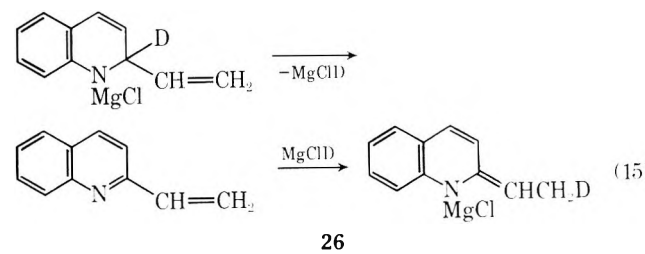
Secondly, the initiation of rearrangements in both cases would seem to occur by 1,2-elimination processes. For the N-metallic salts, it is well known that thermal elimination of metal hydrides leads to aromatization.[12] At higher temperatures metal alkyls have also been split out.[13] In this study the unusually ready elimination of allylmetallics and even the more difficult elimination of arylmetallics have been demonstrated. Likewise, for the 2-allyl-1,2-dihydroquinolines, **3b** and **11**, the facile elimination of propylene, presumably by a homolytic process, is remarkable. Quinoline is always produced in the isomerization of **3b**. From this known behavior, then, in the rearrangement of the magnesium salt **22**, it can be concluded that both quinoline and 2-allylquinoline (**22**) should be formed in small amounts (eq 13). The quinoline can be detected; the 2-allylquinoline has not been observed. However, it was previously established that Grignard reagents cause **23** to isomerize to **24**,[3a] and, in fact, small amounts of *trans*-2-propenylquinoline (**24**) have been detected in such Grignard isomerizations of **22**.

Thirdly, the actual isomerizations in both cases clearly involve intermolecular hydrogen transfers. In the Grignard process, such attack would seem to be the polar attack of MgClH (MgClD) or **22** on **24**, with formation of **25** and the generation of more **23** (when **22** is source of MgClH) (eq 14). A cyclic process

$$23 \longrightarrow 24 \xrightarrow{22} 25 + 23$$

could thus perpetuate the conversion to 2-*n*-propylquinoline. Whether **22** is the source of hydride by elimination (→ **23**) or direct transfer (**24** → **25**) is unclear; in any event, the C_2 D is correctly predicted to enter the β position of the propyl side chain (**25**).

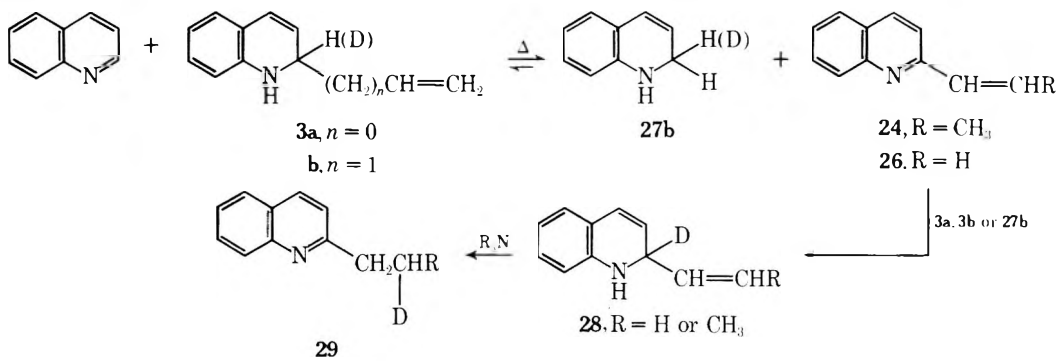
This mechanistic pathway can readily account for the Grignard isomerization of 2-vinyl-1,2-dihydroquinoline (**3a**), except that here no prototropic shift (**23** → **24**) is involved (eq 15).



(15)

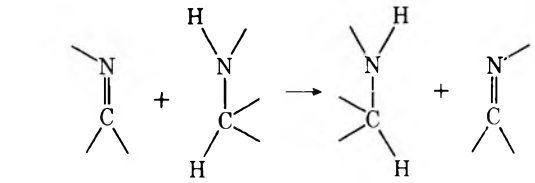
26

With the direct isomerization of 2-alkenyl-1,2-dihydroquinolines, thermal equilibration with the quinoline produced by 1,2 elimination could lead to the formation of 1,2-dihydroquinoline and 2-alkenylquinoline (**23**, **24**, or **26**). These alkenyl intermediates could then undergo reduction via hydrogen transfer from **3a** or **3b** (or **27b**), respectively (eq 16). The transfers of HD from **3a** or **3b** to quinoline to yield **27b** and from **3a**, **3b**, or **27b** to **24** or **26** to yield **28** may not be concerted, but such concerted double group transfers would be expected to be thermally allowed.[14] On the other hand, interaction of **24** or **26** with **3** or **27b** to yield **29** directly would not be a thermally allowed, concerted process (eq 17). Hence, thermally allowed transfers and a final base-catalyzed isomerization of **28** into **29** are proposed. Again, the position of C_2 D in **3** at the β position in **29** is consistent with these pathways.

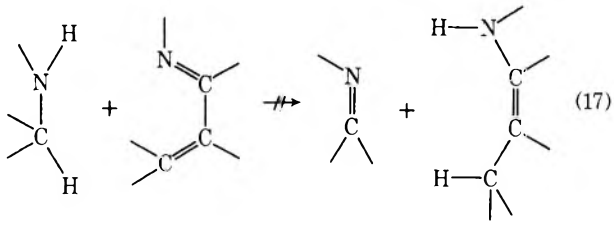


(16)

Finally, in the absence of kinetic results, the question of radical-induced initiation steps in these rearrangements must be left open. Just as there is evidence for single electron transfer in Grignard additions to carbonyl and azo-

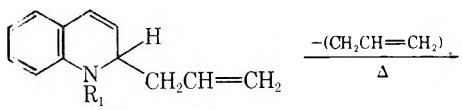


cf.

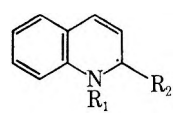


(17)

methine linkages,[15] so the reversal of these additions might involve homolysis (**30a** → **31a**). Such rupture may be related to the probable homolysis encountered with the 2-allyl-1,2-dihydroquinolines themselves (**30b** → **31b**). These stabilized 1-substituted dihydroquinolyl radicals might then initiate free-radical, hydrogen-transfer chains. The occurrence of a radical process in these isomerizations is consistent with the observed formation of dimeric and polymeric by-products. However, if radical chains were to be operative in the actual hydrogen-transfer steps, such chains would have to achieve the specific transfer of the C_2 D in **3** and 22 to the β position of the resulting alkylquinoline.



30a, R_1 = MgCl
b, R_1 = H



31a. R_1 = MgCl; R_2 = H
b, R_1, R_2 = H
c, R_1 = H; R_2 = $CH_2CH{=}CH_2$

Experimental Section

All melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (ir) were recorded on a Perkin-Elmer spectrometer, Model 137, equipped with sodium chloride optics. Proton magnetic resonance spectra (^{1}H NMR) were obtained with a Varian spectrometer, Model A-60, on neat samples or on 10% solutions in pure solvents. The values are reported on the δ scale in parts per million with reference to internal or external tetramethylsilane, followed by the relative proton intensities and the coupling constants (J) in hertz. Vapor phase chromatographic analysis (VPC) and isolations were carried out on an F & M chromatograph, Model 720, equipped with a 6 ft × 0.25 in. column of 10% SE-30 silicone gum rubber on Chromosorb P. Mass spectra of solids and liquids were obtained on a Varian MAT spectrometer, Model CH5, and those of gases on a Consolidated Electrodynamics instrument, Model CEC-21-620A. Elemental analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

All preparations and reactions involving air- and moisture-sensitive organometallic or heterocyclic intermediates were conducted under an atmosphere of dry, oxygen-free nitrogen, with adherence to published procedures.[16] Solvents of reagent grade were used in all reactions. The anhydrous ethyl ether (Fisher) was used directly; the tetrahydrofuran and benzene were dried just before use by distilling them from the sodium ketyl of benzophenone under a dry nitrogen atmosphere.

Photochemical reactions were run in a Rayonet apparatus, Model 100, equipped with low-pressure mercury (254 nm) lamps.

Preparation of Starting Materials. Allylmagnesium bromide in ethyl ether,[17] allylmagnesium chloride in tetrahydrofuran,[18] allyllithium in ethyl ether,[19] vinylmagnesium chloride in tetrahydrofuran,[20] and n-butyllithium in ethyl ether[21] were prepared according to published procedures. n-Butyllithium in hexane was from the Foote Mineral Co.

2-Bromoquinoline was prepared from carbostyril and $POBr_3$ to yield colorless crystals from 95% ethanol, mp 47.5–49° (lit.[22] mp 47–49°). 2-Phenylquinoline was obtained from quinoline and phenyllithium, mp 81–82.5° (lit.[23] mp 83–84°).

2-Deuterioquinoline was prepared from 2-chloroquinoline by reduction with powdered tin metal in the presence of deuterium oxide (99.8% D).[24] By mass spectrometric measurement of the m/e 130 peak and by the absence of the C_2 H peak in the NMR spectrum, the product was found to be >99% pure.

2,2-Diphenyl-1,2-dihydroquinoline was prepared from 2-phenylquinoline and phenyllithium, according to a published procedure.[25] Repeated recrystallizations of the crude distilled product from ethanol gave a colorless solid, mp 95–97°. Since this melting point was considerably higher than the reported value of 86–87°, spectral data were examined: ir (CCl_4) 3450 cm^{-1} (N–H); NMR (CCl_4) δ 4.0 (broad s, NH), 5.8–6.9 (m, 6 H), and 7.3 (broad s, 10 H); MS P m/e 283. Apparently, the previously reported product was contaminated with 2-phenylquinoline.

2,4-Dichloroquinoline. Admixture of 80.0 g (0.39 mol) of the disodium salt of 2,4-dihydroxyquinoline (Pfaltz and Bauer) with 250 g (1.2 mol) of phosphorus pentachloride was conducted slowly, while cooling in an ice bath, since the components reacted vigorously. After 15 min 290 g (1.9 mol) of phosphorus oxychloride were added dropwise to the aforementioned chilled and stirred mixture. The resulting brown mixture was stirred at 100° for 3 hr, then cooled in an ice bath and finally poured slowly into ice water (*caution*). The thawed, yellow solution was made slightly basic by the addition of concentrated, aqueous NaOH solution. Extraction of this solution with ether, drying of the extracts over anhydrous Na_2SO_4, removal of the solvent, and distillation gave 46.4 g (60%) of crude 2,4-dichloroquinoline, bp 112–114° (0.70 mm). Recrystallization of the solidified distillate from methanol provided a 50% yield of colorless crystals, mp 61–63° (lit.[26] mp 66–67°).

2,4-Dideuterioquinoline. A mixture of 15.0 g (0.076 mol) of 2,4-dichloroquinoline, 24.0 g (0.20 g-atom) of tin metal (powdered to pass 240 mesh screen), and 150 ml of deuterium oxide (99.8% D) was heated at 70° for 15 min under a nitrogen atmosphere. Then 48.0 g (0.313 mol) of phosphorus oxychloride was added dropwise to the vigorously stirred mixture, during which the grayish-brown mixture became a pinkish yellow. After 6 hr of stirring at 70–75° and 3 hr at 25° the mixture was cooled in an ice bath and slowly basified with aqueous NaOH solution. Ether extraction of the basic mixture, drying of the extracts over anhydrous Na_2SO_4, removal of the solvent, and distillation gave a 57% yield of 2,4-dideuterioquinoline bp 58–61° (0.35 mm). Spectral data: ir (neat) 3280 and 3070 (C–H stretch), 2275 (C–D stretch), 1640 and 1570 (C=C stretch), 1400, 1085, 918, 905, and 770 cm^{-1}; NMR (CCl_4) δ 7.17 (broad s, 1 H), 7.3–7.8 (m, 3 H), 8.05–8.30 (m, 1 H) and no traces of C_2 H or C_4 H; MS m/e (rel intensity) 132 (14), 131 (P, 100), 130 (18), 129 (11), 104 (18), 103 (21), and 76 (14). The compound was greater than 98% dideuterated.

4-*n*-Propylquinoline. Under a nitrogen atmosphere, a solution of 11.2 g (78 mmol) of 4-methylquinoline in 100 ml of anhydrous ethyl ether was cooled in a bath and then, with stirring, a slurry of sodium amide (10.0 g, 0.256 mol) in 100 ml of ethyl ether was gradually introduced. The greenish-blue solution was stirred at 25–30° for 4 hr and again cooled in an ice bath. A color change to a blue-brown was noted as an ethereal solution of ethyl bromide (9.0 g, 83 mmol) was added dropwise. After 2.5 hr at room temperature the cooled mixture was cautiously hydrolyzed with water. The ethereal layer was separated, washed with water until weakly basic, dried with anhydrous Na_2SO_4, and free of solvent. The residual yellow oil (11.2 g) was shown by NMR spectroscopy to consist of 4-n-propylquinoline (56%), 4-(3-pentyl)quinoline (31%), and 4-methylquinoline (13%). Fractional distillation through a 10 × 1 cm column filled with glass helices eventually gave pure 4-n-propylquinoline: bp 110–111° (1.35 mm); NMR (CCl_4) δ 0.83 (t, CH_3, J = 7.0 Hz), 1.55 (unsymmetrical sextet, CH_2), 2.78 (t, CH_3, J = 7.5 Hz), 6.9–8.3 (m, 5 H), and 8.66–8.9 (m, 1 H); picrate, yellow needles, mp 204–204.5° (lit.[8] mp 204°, 207°). The 4-(3-pentyl)quinoline gave a

picrate as yellow needles, mp 133–133.5°, and displayed NMR signals in CCl_4 at δ 0.72 (t, CH_3, J = 7.0 Hz), 1.71 (q, CH_2), and 2.75–3.3 (m, CH).

2-Methyl-4-*n*-propylquinoline. A solution of 2.5 g (15 mmol) of 4-*n*-propylquinoline in 100 ml of anhydrous ethyl ether was treated dropwise at 0° with 125 ml of an ethereal methyllithium solution (48 mmol). After 24 hr at 20–25° the resulting dark green solution was treated with water and the ethereal layer separated. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and freed of solvent. The residual oil was heated at reflux with 15 g of nitrobenzene for 3 hr. The cooled solution was made acidic by adding 150 ml of 10% aqueous hydrochloric acid and the insoluble nitrobenzene and other products were then extracted into ether. The aqueous layer was then basified with 20% potassium hydroxide solution and the liberated oil was taken up in ether. Usual work-up of the ether extract gave an 89% yield of the crude 2-methyl-4-*n*-propylquinoline. Purification through the picrate (mp 199–201° from ethanol) gave the pure product. Spectral data on the quinoline: ir (neat) 3075, 2985, 2880, 1615, 1575, 1370, 1195, 1025, 872, and 762 cm^{-1}; NMR (CCl_4) δ 0.75–1.15 (t, 3 H), 1.5–1.9 (broad m, 2 H), 2.65 (s, 3 H), 2.5–3.0 (broad m, 2 H), and 6.4–8.1 (m, 5 H); MS *m/e* (rel intensity) 185 (P, 100), 170 (39), 157 (72), 156 (78), 142 (12), 129 (21), 128 (25), and 115 (50). Spectral data on the picrate: MS *m/e* (rel intensity) 228 (22), 185 (100), 170 (39), 157 (69), 156 (69), 142 (7), 129 (19), 128 (22), and 115 (42).

Anal. Calcd. for $C_{19}H_{18}N_4O_7$: C, 55.07; H, 4.38; N, 13.52. Found: C, 55.09; H, 4.32; N, 13.46.

2-Allyl-1,2-dihydroquinoline (3b). With adherence to the published procedure,[3a] this compound was prepared from quinoline and allylmagnesium bromide in tetrahydrofuran solution. The highest yields of pure product, which contained very little 2-*n*-propylquinoline, were obtained when the hydrolytic work-up and distillative isolation were done promptly and under an atmosphere of nitrogen. Especially important was that the 10 × 1 cm, glass helices filled fractionating column was wrapped with an electrically heated tape, so that overheating of the distillate and a prolonged residence time in the column did not occur. Spectral data: ir (neat) 3390 (N–H stretch), 3030, 2860, 1645 (C=CH_2 stretch), 1480, 1315, 1120, 995, and 915 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 2.0 (t, 2 H, J = 6.5 Hz), 3.5 (broad s, 1 H), 3.9 broad m, 1 H), 4.6–5.8 (m, 4 H), and 6.0–6.8 (m, 5 H).

2-Allyl-2-deuterio-1,2-dihydroquinoline (5b). This compound was prepared in 67% yield from 0.12 mol of 2-deuterioquinoline by use of the published procedure. Its ir spectrum showed a band at 2105 cm^{-1} (C–D stretch) and its NMR spectrum lacked the broad multiplet centered at 3.9 ppm (C_2 H) and displayed only a doublet at 2.0 ppm (J = 6.5 Hz).

2-Allyl-2,4-dideuterio-1,2-dihydroquinoline (7). This compound was isolated pure in 60% yield by applying the foregoing alkylation procedure to 46 mmol of 2,4-dideuterioquinoline. Its ir spectrum showed a C–D stretch at 2250 cm^{-1} and its NMR spectrum (CCl_4) had a doublet at 2.0 ppm ($DCCH_2CH=CH_2$), but lacked the broad multiplet at 3.9 ppm (C_2 H) and had over four protons in the 6.0–6.8 ppm region.

Reaction of 2-Methylquinoline with Allylmagnesium Chloride at 25°. 2-Allyl-2-methyl-1,2-dihydroquinoline (11). A chilled solution of allylmagnesium chloride (0.375 mol) in 300 ml of tetrahydrofuran was added dropwise to a solution of 2-methylquinoline (18.0 g, 0.126 mol) in 180 ml of tetrahydrofuran, which was maintained at 0°. A yellow-green color developed immediately upon admixing the reagents and deepened to dark green during the 20-hr reaction period at 20–25°. The reaction mixture was cooled in an ice bath, hydrolyzed with saturated aqueous NH_4Cl solution, and treated with ethyl ether. (All work-up procedures were performed under a nitrogen atmosphere.) The organic layer was separated, washed with water, dried with anhydrous $CaSO_4$, and freed from solvent. By NMR spectroscopic comparison of the methyl signal intensities at 2.6 (2-methylquinoline) and 1.2 ppm (the 2-allyl-2-methyl-1,2-dihydro product), the reaction was found to have given a yield of ca. 95%.

Distillation through a 10 × 1 cm, glass helices filled column, which was wrapped and warmed with electrical heating tape, provided 2-allyl-2-methyl-1,2-dihydroquinoline as a yellow liquid: bp 82–83° (0.28 mm); ir (neat) 3425 (N–H stretch), 1655 (s, C=C), 1625 (s, aromatic stretch), 1590 (conjugated C=C), 915 and 995 cm^{-1} (C–H deformations of CH=CH_2); NMR (CCl_4) δ 1.17 (s, CH_3), 2.1–2.3 (d, 2 H, J = 7.0 Hz), 3.58 (br s, NH), 4.85–6.0 (m, 4 H, CH=CH_2 and C_3 H), and 6.1–7.1 (m, 5 H).

Anal. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.30; H, 8.16; N, 7.45.

Reactions of Quinoline with Vinylmagnesium Chloride. A solution of 46.6 g (0.361 mol) of quinoline in 130 ml of dry tetrahydrofuran was admixed at 0° with 0.481 mol of vinylmagnesium chloride in 200 ml of tetrahydrofuran, whereupon a dark yellow-brown color developed. After 24 hr at 20–25° the solution was hydrolyzed with aqueous NH_4Cl solution and then worked up under a nitrogen atmosphere, as in the foregoing procedure. Combined NMR and ir spectral analyses of the resulting oil (45 g) indicated the presence of <5% of quinoline [NMR (CCl_4) no discernible, characteristic q for C_2 H at 8.6–8.7 ppm, but ir (neat) weak bands at 830 and 805 cm^{-1}], 70% of 2-vinyl-1,2-dihydroquinoline [ir (neat) 3390 (N–H stretch) and 995 and 915 cm^{-1} (C–H deformations of CH=CH_2); NMR (CCl_4, external Me_4Si) δ 3.97 (br s, NH), 4.52 (br t, C_2 H), 4.68–5.08 (m, CH=CH_2), 5.26 (d of d, C_3 H, $J_{3,4}$ = 9.0, $J_{2,4}$ = 4.0 Hz), 5.81 (m, CH=CH), 6.1 (d, C_4 H, $J_{3,4}$ = 9.0 Hz), and 6.0–7.0 (m)], and 30% of 2-ethylquinoline [NMR (CCl_4) 1.32 (t, CH_3, J = 7.5 Hz), 2.91 (q, CH_3, J = 7.5 Hz), and 6.95–8.2 (m)]. Attempts to separate these major components by fractional distillation were unsuccessful. Prolonged heating led to polymerization, some cracking to quinoline [NMR (CCl_4) 8.6–8.7 ppm], some oxidation to 2-vinylquinoline [NMR (CCl_4) 6.1 (m, CH=CH_2) and 5.22 ppm [d of d, distinct from the 2-vinyl-1,2-dihydro derivative, CH=CH (trans)]], and gradual isomerization into 2-ethylquinoline: bp (51–52° (0.04 mm); ir (neat) 3080, 2990, 1615, 1520, 1435, 1305, 1125, 950, and 835 cm^{-1}; picrate mp 147–148° (lit.[27] mp 148°).

Reaction of 2-Deuterioquinoline with Vinylmagnesium Chloride. As in the foregoing procedure, 2-deuterioquinoline (13.0 g, 0.10 mol) was allowed to react with 0.102 mol of the Grignard reagent in tetrahydrofuran at 20–25° for 24 hr. The usual hydrolytic work-up under a nitrogen atmosphere and solvent removal gave a yellow oil whose NMR spectrum (CCl_4) showed only traces of quinoline and 2-ethylquinoline: δ 3.63 (br s, NH), 4.55–4.92 (m, CH=CH_2), 5.13 (d, CH=CH_2, $J_{3,4}$ = 9.0 Hz), 5.53 (d of d, CH=CH, J_{trans} = 15 and J_{cis} = 9 Hz), 5.95 (d, C_4 H, $J_{3,4}$ = 9.0 Hz), and 5.75–6.70 (m). Only weak triplets of the deuterated 2-ethylquinoline were observed at 1.3 and 2.85 ppm, and the C_2 H of 2-vinyl-1,2-dihydroquinoline at 4.5 ppm was absent. Thus, the product consisted of >90% 2-deuterio-2-vinyl-1,2-dihydroquinoline.

Since fractional distillation caused isomerization to the ethylquinoline, the whole product was heated at 148–150° under nitrogen for 48 hr. The NMR spectrum of the crude product (CCl_4) was principally that of 2-(2-deuterioethyl)quinoline. Fractional distillation gave the product contaminated with ca. 10% deuterated quinoline and other impurities: bp 58–59° (0.15 mm); NMR (CCl_4) δ 1.25 (t ot t, CH_2D, J = 7.5, J_{HD} = 1.2 Hz), 2.80 (t, CH_2), ratio of CH_2D/CH_2 1:1, 6.75–7.9 (m), with trace absorptions at δ 1.7, 2.5, 3.9, and 6.0–6.7.

Reaction of 2-Allyl-1,2-dihydroquinoline with Phenyllithium. To a solution of 3.75 g (0.023 mol) of freshly distilled 2-allyl-1,2-dihydroquinoline in 50 ml of benzene was added 40 ml (0.049 mol) of a 1.25 *N* ethereal phenyllithium solution. The solution became dark red and a yellow precipitate was formed during the addition. The solution was heated under reflux for 90 min, cooled, and then hydrolyzed with water. After the usual work-up and removal of solvent, the organic residue was distilled to yield two principal fractions: (1) bp 80–95° (0.4 mm), containing principally quinoline and 2-*n*-propylquinoline [ir (neat) 815 and 835 cm^{-1}]; and (2) bp 95–120° (0.4 mm), a waxy, pale yellow solid, 1.5 g. The latter solid was chromatographed on a 90 × 2.5 cm column of neutral alumina and the components were eluted with petroleum ether (bp 30–60°). The principal component was 2-phenylquinoline, mp 80–82° (lit.[23] mp 81–83°), picrate (EtOH) mp 190–191.5° (lit. mp 191°).

Reaction of 2,2-Diphenyl-1,2-dihydroquinoline with Phenyllithium. A solution of 2.0 g (7 mmol) of the diphenyl-1,2-dihydro compound in 100 ml of dry benzene was treated with 30 ml of a 0.65 *N* ethereal solution of phenyllithium (20 mmol). The resulting bright yellow solution was heated at reflux for 80 hr and then hydrolyzed. Work-up gave an organic oil that was chromatographed on a 64 × 3 cm column of silica gel and the components were eluted by a sequence of hexane, hexane–benzene, and benzene–ether. The principal component isolated was 2-phenylquinoline, as demonstrated by spectral and melting point comparisons.

Reaction of 2-Allyl-2-methyl-1,2-dihydroquinoline with Phenylmagnesium Chloride. To a solution of 4.5 g (24.4 mmol) of the freshly distilled and pure dihydroquinoline in 40 ml of dry tetrahydrofuran was added 100 ml of 0.48 *N* phenylmagnesium chloride in the same solvent. Gradually the resulting solution became yellow-green during 24 hr at 20–25°. One-half of the solution

was then withdrawn and hydrolyzed with an aqueous NH_4Cl solution. The organic layer was diluted with ethyl ether, separated, washed with water, dried over anhydrous Mg_2SO_4, and then freed of solvent in vacuo. The resulting oil (2.5 g) was shown by NMR spectroscopy to consist of 60% 2-methylquinoline and 40% 2-allyl-2-methyl-1,2-dihydroquinoline.

The remaining portion of the original reaction mixture was heated at reflux under a nitrogen atmosphere for 24 hr. The resulting brown solution was hydrolyzed and worked up as described above. The dark brown oil (2.3 g) was shown by NMR spectroscopy to consist of 75% 2-methylquinoline, 20% 4-allyl-2-methyl-1,4-dihydroquinoline (cf. infra), and only ca. 5% 2-allyl-2-methyl-1,2-dihydroquinoline.

Reaction of 2-Methylquinoline with Allylmagnesium Chloride at 70°. 4-Allyl-2-methyl-1,4-dihydroquinoline (16). A solution of 23.0 g (0.161 mol) of 2-methylquinoline in 120 ml of dry tetrahydrofuran was allowed to react with 270 ml (0.392 mol) of 1.45 *N* allylmagnesium chloride in tetrahydrofuran for a period of 20 hr at 20–25° and 25 hr at reflux. The usual hydrolytic work-up yielded a brown oil (29.8 g), whose NMR spectrum had only weak signals characteristic of 2-allyl-2-methyl-1,2-dihydroquinoline (especially at 1.17 ppm) and perhaps small amounts of 2-methylquinoline. The principal absorptions were multiplets of moderate intensity at 1.0–1.4, 2.4–2.8, and 3.2–3.7 ppm, as well as intense bands at 2.10 (s), 2.15–2.4 (m), 4.7–5.1 (m, CH_2=CH), 5.1–5.9 (m), and 6.2–7.2 ppm (m). Fractional distillation at 0.4 mmHg pressure yielded four fractions: (1) bp 86–90°; (2) bp 91–94°; (3) bp 95–99°; and (4) bp 102–130°. The NMR and ir spectra of fractions 1–3 were very similar: aside from minor differences in the region of 1.0–1.5 ppm, these spectra exhibited signals consistent with the presence of allylmethyldihydroquinoline derivatives [ir 3280 (N–H), 1630 (C=C), 995, and 915 cm^{-1}]. Although the NMR spectrum was complex, the presence of the following components seemed to be evident: (1) 4-allyl-2-methyl-1,4-dihydroquinoline as the principal component (ca. 75%) [2.07 (s, CH_3), 1.95–2.35 (m, CH_2CH=CH_2), 3.1–3.4 ppm (m, C_4 H)] (cf. infra for structure proof); (2) 4-allyl-2-methylquinoline [2.60 (s, CH_3), 3.68 ppm (d, CH_2)]; and (3) 4-allyl-2-methyl-1,2-dihydroquinoline [1.1 ppm (d, CH_3)].

Fraction 4 had quite different NMR and ir spectra, displaying as principal absorptions those signals found in the other fractions as minor bands. As will be seen, these bands were best attributable to tetrahydroquinoline derivatives.

In order to aid the identification of these components, a 6.0-g portion of fraction 3 dissolved in 125 ml of absolute ethanol was hydrogenated at 20–25° under 1 atm in the presence of 0.3 g of a catalyst of 10% palladium on charcoal. After 27 hr the amount of hydrogen necessary to reduce one C=C bond had been absorbed. The filtered ethanolic reaction solution was treated with picric acid: mp 198–200°; the mixture melting point with an authentic sample of 2-methyl-4-*n*-propylquinoline picrate was undepressed, and the NMR and ir spectra were superimposable.

The ethanolic filtrate from the picrate preparation was made basic with 10% aqueous KOH solution and the liberated oil was taken up in ether. Drying over anhydrous Na_2SO_4 and removal of solvent in vacuo gave a brown oil: ir (neat) 3380 cm^{-1} (N–H) but no C=C or CH=CH_2 bands; NMR (CCl_4) δ 0.8–2.1 (m, 15 H), 2.4–3.6 (m, 4 H), and 6.2–7.1 (4 H); mass spectrum *m/e* (rel intensity) 189 (P, 54), 185 (8), 174 (59), 146 (100), 144 (27), 132 (15), 130 (16), and 118 (10). These data permit the conclusion that this oil is a mixture of 2-methyl-4-*n*-propyl-1,2,3,4-tetrahydroquinolines.

Thermal Rearrangement of 2-Allyl-1,2-dihydroquinoline. A. General Procedure. A freshly distilled sample (4.0–8.0 g, 23–46 mmol) that had been purified under nitrogen and analyzed by NMR spectroscopy was placed in a 25-ml, pear-shaped flask connected to an air-reflux condenser. The top of the condenser was connected both to the nitrogen line and to a vacuum line by means of a three-way stopcock. By chilling the sample flask in a solid CO_2–acetone bath and by the alternate application of reduced pressure and nitrogen, all traces of moisture and oxygen were minimized. The system was then opened to a gas manifold at atmosphere pressure, which manifold led through a trap at −78° to a closed, evacuated gas collection bulb. After the heating period had ended, the liquid in the cold trap was allowed to evaporate into the gas collection bulb, by lowering the cooling bath from the trap and opening the stopcock on the collection bulb. The gas was analyzed by mass spectrometry and the liquid residue in the pyrolysis flask separated by distillation and examined by ir and NMR spectroscopy, as well as mass spectroscopy.

From the results of 15 different pyrolyses conducted variously at temperatures between 130 and 300° and at times of 1–72 hr, with samples of different purity, the following conclusion can be drawn. First of all, the purest samples yield 2-*n*-propylquinoline, quinoline, propylene, and small amounts of *trans*-2-propenylquinoline and its dimer. The propylene was identified as the principal volatile component by its MS (70 eV) prominent peaks at *m/e* 42, 41, 27, and 15. Fractional distillation of the liquid product permitted the ready isolation of quinoline; even in the crude liquid, its presence was easily discerned by its NMR quartet at 8.6–8.7 ppm for its C_2 H and its ir bands at 805 and 830 cm^{-1}. The 2-*n*-propylquinoline was essentially pure after distillation: bp 85–87° (0.1 mm); ir (neat) prominent bands at 3030, 2945, 1600, 1505, 1565, 1420, 1305, 1115, 1045, and 828 cm^{-1}; NMR CCl_4) δ 0.97 (t, CH_3, J = 7.2 Hz), 1.83 (br sextet, CH_2), 2.88 (br t, CH_2, J = 7.0 Hz), 7.04 (d, C_3 H, J = 8.5 Hz), 7.25–8.1 (m, 5 H); picrate, yellow needles from EtOH, mp 162.5–163.5° (lit.[3a] mp 163–164°); mixture melting point undepressed. Traces of *trans*-2-propenylquinoline in such distillates were detected by the presence of a characteristic ir band at 970 cm^{-1}. In the mass spectrum of the distillation residue distillation residue peaks were observed at *m/e* (rel intensity) 340 (8), 339 (12), 338 (25), 324 (8), 323 (21), 200 (8), 199 (17), 198 (100), and 196 (27). These data are consistent with the presence of a dimer (or higher oligomer) of 2-propenylquinoline (mol wt 340) and its principal cracking by loss of the quinaldinyl group (P − 142).

The second conclusion on these pyrolysis is that higher temperatures favor the formation of propylene and quinoline (temperature and percent of quinoline): 130–140°, trace; 160–170°, 2%; and 285°, 52%.

Thirdly, starting material that was stored under nitrogen for several weeks before pyrolysis gave a significantly higher proportion of *trans*-2-propenylquinoline and gummy products (25–35%).

Fourthly, the cleanest isomerization was achieved by heating a 4.0-g sample of pure 2-allyl-1,2-dihydroquinoline in a Wood's metal bath for 10–20 hr at 150–165°. Only about 2% of quinoline was formed; the distillate was pure 2-*n*-propylquinoline.

B. Pyrolysis of 2-Allyl-2-deuterio-1,2-dihydroquinoline. A 5.4-g sample (31 mmol) was heated at 150–155° for 24 hr under a nitrogen atmosphere. Since an NMR spectrum showed the presence of some starting material, the liquid was heated for an additional 24 hr. Fractional distillation of the product gave essentially pure 2-(2-deuterio-*n*-propyl)quinoline containing traces of quinoline: bp 80–82° (0.1 mm); ir (neat) 3040, 2900, 2155 (C–D stretch), 1600, 1505, 1425, 1305, 1115, and 828 cm^{-1}; NMR (CCl_4) δ 0.97 (d, 3 H), 1.5–1.9 (complex m, 1 H), 2.88 (d, 2 H), and 6.8–7.9 (m, 6 H).

When a sample of the starting material was heated at 150° for 24 hr, the gas evolved was shown by MS to be essentially, if not all, undeuterated propylene.

C. Crossover Experiment between 2-Allyl-1,2-dihydroquinoline and 2-Allyl-2,4-dideuterio-1,2-dihydroquinoline. In three different sample tubes were placed, respectively, 3.0 g (16 mmol) of 2-allyl-2,4-dideuterio-1,2-dihydroquinoline (sample A), 3.0 g (16 mmol) of its undeuterated counterpart (sample B), and finallly a mixture of 1.5 g each of these two components (sample C). All three sample flasks were heated, under nitrogen, in the same oil bath for 40 hr at 148–150°. Then each sample was submitted directly to spectral and mass spectrometric analyses.

Sample A: by ir and NMR analyses the principal product was shown to be 2-(2-deuterio-*n*-propyl)-4-deuterioquinoline (ca. 96%), with only 4% of starting allyldihydro compound remaining: ir (neat) 3490 (weak N–H stretch), 2275 and 2178 (C–D stretches); NMR (CCl_4) δ 0.98 (d, 3 H), 1.5–1.9 (complex m, 1 H), 2.88 (d, 2 H), and 7.0–8.1 (m, 5 H). Any 2-deuterioquinoline present would not have been observable.

Sample B: by the spectral criteria given above, this product was found to contain 91% 2-*n*-propylquinoline, 6% quinoline, and 3% starting allyldihydro compound.

Sample C: this contained 88% 2-*n*-propylquinoline (in deuterated and undeuterated forms), 4% quinoline (deuterated not included), and the balance as allyldihydro compounds.

The mass spectra of these crude samples, even at a low ionization voltage of 20 eV, proved to be somewhat less suitable for detection of crossover, because of the presence of considerable amounts of components of higher molecular weight, such as the 2-propenylquinoline dimers mentioned above. Cracking of these dimers contributed to the parent and P − 1 peaks of deuterated and undeuterated 2-*n*-propylquinolines, *m/e* 173, 172, 171, and 170, thus vitiating any conclusions about crossover that might be based

on the *m/e* 172 peak. However, the P − 15 peak of 2-*n*-propylquinoline was found not to be changed in intensity due to the presence of such dimeric products.

Sample A: *m/e* (rel intensity) 346 (5), 343 (5), 341 (3), 340 (7), 326 (4), 325 (8), 202 (8), 201 (26), 200 (84), 175 (8), 174 (29), 173 (100), 172 (32), 171 (71), 159 (8), 158 (24), 157 (0), 156 (0), 145 (16), 144 (47), and 131 (3).

Sample B: *m/e* (rel intensity) 340 (6), 339 (0), 338 (19), 324 (6), 323 (16), 200 (6), 199 (13), 198 (75), 196 (19), 172 (19), 171 (100), 170 (82), 159 (0), 158 (0), 157 (0), 156 (28), 143 (81), 132 (22), and 129 (6).

Thus, it is noteworthy that sample C shows peaks <171 at *m/e* (rel intensity) 170 (35), 158 (13), 157 (13), 156 (11), 145 (11), 144 (41), 143 (24), 131 (2), 130 (2), and 129 (0).

All three samples were then individually subjected to fractional distillation and the MS analyses repeated at 15 eV on the isolated 2-*n*-propylquinolines.

Sample A: *m/e* (rel intensity) 173 (7), 172 (4), 171 (4), 158 (9), 157 (2), 156 (2), 145 (22), 144 (100), 143 (35).

Sample B: *m/e* (rel intensity) 171 (12), 170 (2), 169 (2), 157 (2), 156 (8), 144 (18), 143 (100), 142 (4).

Sample C: *m/e* (rel intensity) 173 (4), 172 (5), 171 (5), 170 (2), 158 (10), 157 (10), 156 (10), 145 (18), 144 (80), 143 (100), 142 (8).

Photochemical Reaction of 2-Allyl-1,2-dihydroquinoline. A 4.2-g sample (25 mmol) in 200 ml of freshly distilled and deoxygenated benzene was irradiated in a photochemical reactor equipped with low-pressure mercury vapor lamps (254 nm) for a period of 24 hr. After removal of the solvent, a NMR analysis showed the presence of 60% quinoline, 20% 2-*n*-propylquinoline, and 20% starting material.

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Registry No.—**3a**, 55570-22-4; **3b**, 55570-23-5; **4a**, 1613-34-9; **4b**, 1613-32-7; **5b**, 55570-24-6; **6b**, 55570-25-7; **7**, 55570-26-8; **10**, 55570-27-9; **11**, 38178-76-6; **16**, 38178-79-9; **17b**, 38178-81-3; **17b** free base, 33538-26-0; **18**, 491-35-0; **21**, 55570-28-0; 2,4-dichloroquinoline, 703-61-7; 4-*n*-propylquinoline, 20668-44-4; 2-methylquinoline, 91-63-4; allyl chloride, 107-05-1; quinoline, 91-22-5; vinyl chloride, 75-01-4; 2-vinylquinoline, 772-03-2; 2-deuterioquinoline, 15793-81-4; 2-(2-deuterioethyl)quinoline, 55570-29-1; phenyllithuim, 591-51-5; 2,4-dideuterioquinoline, 55570-30-4; phenyl chloride, 108-09-7; 4-allyl-2-methylquinoline, 38178-77-7; 4-allyl-2-methyl-1,2-dihydroquinoline, 38178-78-8; *cis*-2-methyl-4-*n*-propyl-1,2,3,4-tetrahydroquinoline, 55570-31-5; *trans*-2-methyl-4-*n*-propyl-1,2,3,4-tetrahydroquinoline, 55570-32-6; *trans*-2-propenylquinoline, 55570-33-7.

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Diquinocyclopropanones, Diquinoethylenes, and the Anion-Radical and Free-Radical Intermediates in Their Formation[1]

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Reaction of trichlorocyclopropenium tetrachloroaluminate with 2 equiv of hindered phenols followed by hydrolysis leads to bis(hydroxyaryl)cyclopropenones (**1**). These are converted upon oxidation to diquinocyclopropanones (**2**), which lose carbon monoxide spontaneously, forming diquinoethylenes (**4**). When photolyzed, compounds **1** lose carbon monoxide, giving bis(hydroxyaryl)acetylenes (**3**), which can be oxidized reversibly to **4**. The free-radical and anion-radical intermediates in the oxidation of **1c** to **2c** and **3c** to **4c** have been studied by electron spin resonance spectroscopy. The hyperfine splitting constants for the anion radicals of **2c**, **4c**, and related quinonoid compounds are rationalized by molecular orbital calculations.

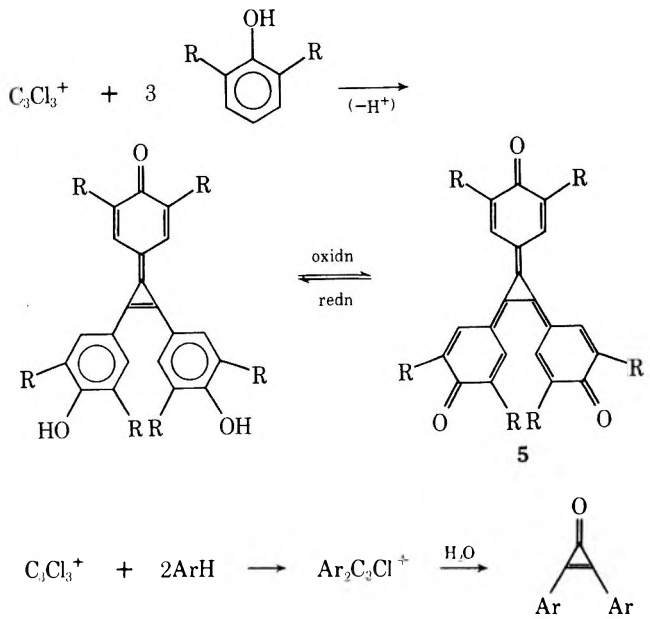
The triquinocyclopropanes (**5**), brilliant blue dye-like compounds, are obtained by reaction of trichlorocyclopropenium tetrachloroaluminate with 2,6-disubstituted phenols followed by deprotonation and oxidation.[2] The reaction of $C_3Cl_3^+$ with aromatic hydrocarbons can also be controlled so that only two of the three chlorine atoms are replaced. The product of this reaction, after hydrolysis, is a diarylcyclopropenone.[3]

This paper reports the reaction of 2,6-dialkylphenols with $C_3Cl_3^+$, leading to bis(hydroxyaryl)cyclopropenones **1a–c**. These compounds undergo oxidation to bright purple diquinocyclopropanones, **2**. The latter can be reduced back to **1** if the reduction is carried out immediately, but if **2a–c** are allowed to stand in solution they spontaneously lose carbon monoxide to give the cumulene derivatives **4a–c**. These are magenta-colored solids (λ_{max} 486 nm), which we term diquinoethylenes.

The stability of diquinoethylenes depends on the alkyl groups: **4c** (R = *tert*-butyl) is stable and unreactive, **4b** (R = isopropyl) is isolable but reacts with water, and **4a** (R =

Table I
Calculated Odd-Electron Spin Densities at the Hydrogen-Bearing Carbon of the Anion Radical of 4c

	h					
k	0.4	0.5	0.6	0.8	1.0	1.2
0.8		+0.001		+0.031		+0.059
1.0	−0.009		+0.005		+0.034	
1.1		−0.004			+0.028	
1.2			0.000	+0.012		
1.3	−0.012		−0.002		+0.018	
1.4			−0.005			



methyl) was so reactive that it could not be isolated and was detected only by its uv spectrum in solution.

Diquinoethylenes can also be obtained from **1a–c** by a second pathway. A known reaction of cyclopropenones is photolytic decarbonylation to acetylenes.[4] Photolysis of **1a–c** yields bis(hydroxyaryl)acetylenes, **3a–c**. These can be converted to the corresponding diquinoethylenes by a reversible oxidation.

Within this series of compounds one observes two separate oxidation–reduction systems differing by the loss of carbon monoxide from the three-membered ring. For both systems oxidation and reduction involves transfer of two

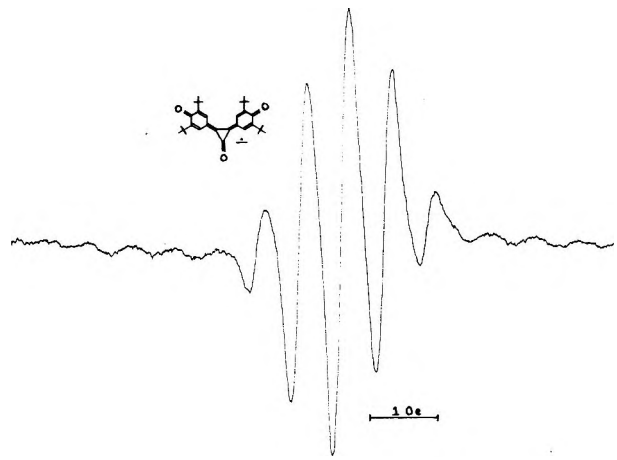


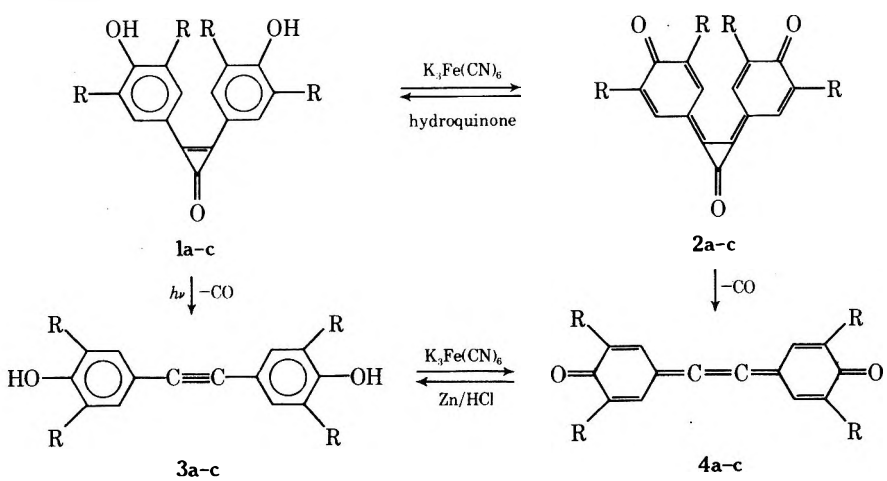
Figure 1. Electron spin resonance spectrum of anion radical of diquinocyclopropanone **2c**.

electrons between diamagnetic products. However, as with the triquinocyclopropanes,[5] paramagnetic one-electron intermediates in the redox reactions can be detected and studied by electron spin resonance spectroscopy. Because the compounds with R = *tert*-butyl were the most stable, the intermediates were studied mostly for the **1c–2c** and **3c–4c** systems.

Anion Radicals. Under basic conditions, intermediate anion radicals might be formed either by reduction of **2c** and **4c** or oxidation of the dianions of **1c** and **3c**, respectively.

Treatment of the diquinocyclopropanone **2c** with Na–K alloy in 1,2 dimethoxyethane at −60° produced an anion radical which gave the ESR spectrum shown in Figure 1, a five-line pattern with relative intensities 1:4:6:4:1 indicating hyperfine splitting by four equivalent protons, with a splitting constant of 0.63 G. The same anion radical showing an identical ESR spectrum was also generated by oxidation of the diarylcyclopropenone **1c** with PbO_2 in the presence of base.

Treatment of the diquinoethylene **4c** with Na–K alloy gave a single strong line with no detectable hyperfine splitting. The same ESR signal was obtained when **4c** was reduced electrolytically in THF. A single line was observed at all temperatures from −80 to 30° indicating that the hyperfine splitting constant for the ring protons must be <0.04 G. This very small value is surprising because all related species show sizable hyperfine splitting for the protons on carbon atoms meta to oxygen.[5–7]

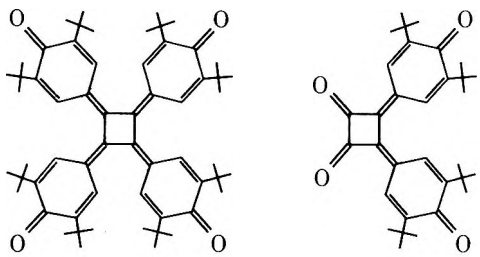


a, R = CH_3
b, R = $CH(CH_3)_2$
c, R = $C(CH_3)_3$

Table II
Calculated and Observed Hyperfine Splitting Constants (Gauss) for Anion Radicals

Registry no.	Anion radical	ρ calcd	a_H calcd, $Q = -24$	a_H calcd, $Q = -28$	a_H obsd	Ref
55281-77-1	4c·⁻	0.000	0.00	0.00	<0.04	This work
34470-38-1	5·⁻	−0.014	0.34	0.39	0.43	5
55255-32-8	6·⁻	−0.012	0.29	0.34	0.33	6
55255-33-9	2c·⁻	−0.024	0.58	0.67	0.63	This work
55255-34-0	7·⁻	−0.025	0.60	0.70	0.71	7

In order to see if this result could be rationalized theoretically, molecular orbital calculations were carried out first for the anion radical from **4c** and then for all of the related species whose ESR spectra have been determined. These include the anion radicals of diquinocyclopropanone **2c**, hexa-*tert*-butyltriquinocyclopropane (**5**, R = *t*-Bu),[5] octa-*tert*-butyltetraquinocyclobutane (**6**),[6] and tetra-*tert*-butyl-1,2-diquinocyclobutanedione (**7**).[7] Odd electron spin



6 **7**

densities (ρ) at the hydrogen-bearing carbons were calculated by the method of McLachlan[8] using Hückel molecular orbitals and a value of 1.0 for λ. Spin densities were converted to coupling constants by McConnell's equation,[9] $a_H = Q\rho$, using McLachlan's value of −24 G for Q.

In the Hückel calculations, the coulomb and resonance integrals, α_c and β_{cc}, were assumed to be identical for all carbon atoms and carbon–carbon π bonds. The coulomb integrals for oxygen atoms, α_O, and the resonance integrals for the carbon–oxygen π-bonds, β_{CO}, were related to α_c and β_{cc} in the usual way (eq 1 and 2). Frequently h and k for

$$\alpha_O = \alpha_C + h\beta_{CC} \quad (1)$$

$$\beta_{CO} = k\beta_{CC} \quad (2)$$

carbon–oxygen double bonds are taken to be 1.0, but other values have been used.[10] The odd-electron spin densities at the hydrogen-bearing carbons of the anion radical of **4c** were calculated for values of h from 0.4 to 1.2 and of k from 0.8 to 1.4, as shown in Table I. The values $h = 0.6$ and $k = 1.2$ gave a very low spin density consistent with the experimental result.

These latter values were then used to calculate the spin densities at the appropriate carbons of the other compounds. The calculated coupling constants agreed with the observed values for the anion radicals of **5** and **6** but not for **2c** and **7**. However, if the values $h = 1.0$ and $k = 1.0$ were used for the cyclopropanone and cyclobutanedione oxygens of **2c** and **7** along with the values $h = 0.6$ and $k = 1.2$ for the quinonoid oxygens, good agreement with the experimental data was obtained. The calculated and observed coupling constants are shown in Table II. Even better agreement between calculated and observed data is obtained if a value of $Q = -28$ G is used. This value is within the range of −20 to −30 G suggested by McLachlan.[8]

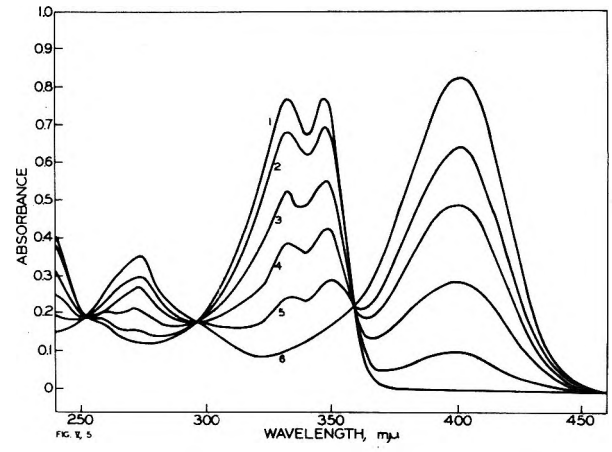
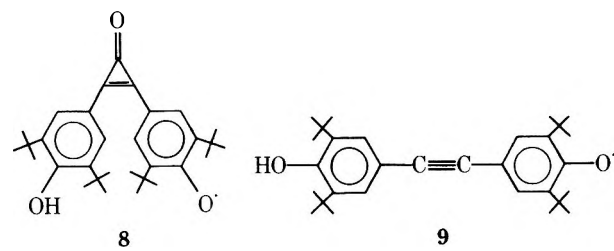


Figure 2. Spectrophotometric titration of dihydroxydiarylcyclopropenone **1c** with aqueous NaOH in methanol. Curve 1 is **1c** alone, 0.00120 *M* in methanol. Curve 6 the same concentration of **1c** in the presence of 0.00240 *M* NaOH.

Dianions. To obtain the dianion of the dihydroxydiarylcyclopropenone **1c**, a methanolic solution of **1c** was titrated with aqueous NaOH and titration was followed by ultraviolet–visible spectroscopy (Figure 2). Only one set of isosbestic points was observed, indicating that the cyclopropenone was converted directly to the corresponding dianion.

The diarylacetylene **3c** reacted very slowly with NaOH, so a spectroscopic titration similar to that described above for **1** was not performed. However, addition of excess base to **3c** in methanol gave a solution which showed a new electronic absorption maximum at 455 nm, probably due to the corresponding dianion.

Monoradicals. Neutral oxidation of cyclopropenone **1c** (or neutral reduction of **2c**) should proceed through the radical **8** (note that **8** is the protonated form of the anion radical). Similarly, neutral oxidation of **3c** or reduction of **4c** should proceed through the radical **9.** To generate these



8 **9**

radicals the diarylcyclopropenone **1c** and the diarylacetylene **3c** were treated with traces of Ag_2O or PbO_2 and the ESR spectra were recorded (Figure 3). The nine-line pattern observed for **8** is in good agreement with that predicted for splitting by two sets of two equivalent protons, with coupling constants of 0.72 and 1.86 G. Likewise the seven-line pattern observed for **9**, with relative intensities of 1:2:3:4:3:2:1, is attributable to two sets of two equivalent protons having coupling constants of 0.93 and 1.86 G. The two spectra are therefore consistent with those expected for the monoradicals **8** and **9**, respectively. In both cases, it is assumed that the larger splitting is caused by the aromatic protons of the phenoxyl ring, while the smaller splitting is due to the two aromatic protons of the ring bearing the hydroxyl group.

The principal splittings of 1.86 G observed for **8** and **9** are almost twice those observed for the corresponding monoradical **10** in the triquinocyclopropane series, which shows $a_H = 1.00$ G. This is consistent with delocalization of the unpaired electron over two equivalent rings in the triquinocyclopropane radical **10**, and restriction of the un-

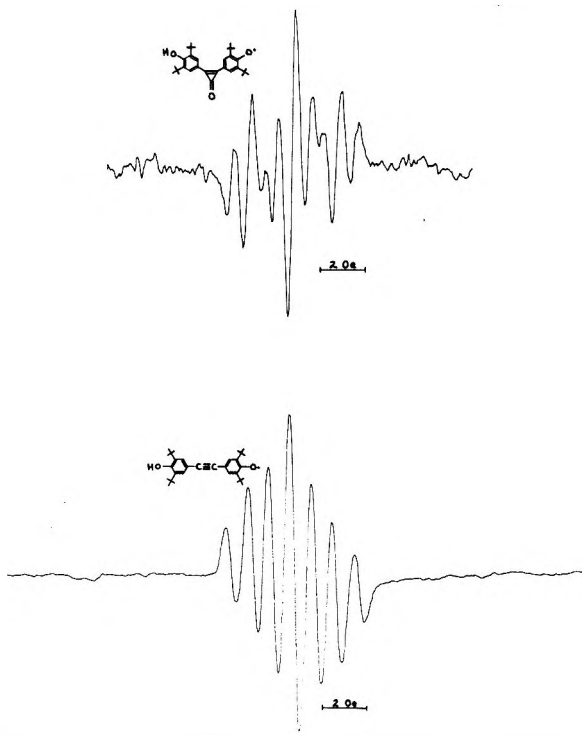
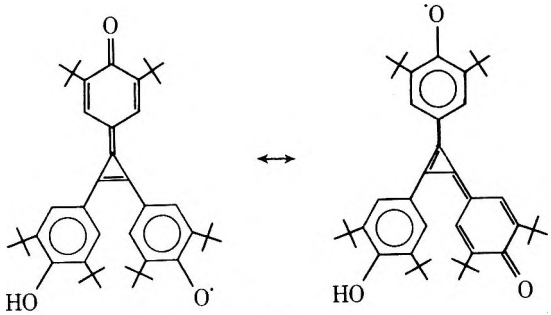


Figure 3. ESR spectra of monoradicals 8 (above) and 9 (below).

paired electron mainly to one six-membered ring in 8 and 9.



10

Experimental Section

General Procedures. All syntheses were carried out using purified grades of commercially available starting materials. Combustion analyses were performed by Alfred Bernhardt Laboratories, Mülheim, Germany, and Galbraith Laboratories, Knoxville, Tenn. Spectra were recorded by means of the following instruments: infrared, Perkin-Elmer-237; proton NMR, Varian A-60 or A-60A; ultraviolet–visible, Cary 14; mass spectra, CEC Type 21-103C; ESR, Varian 4502-13. Infrared spectra reported are Fluorolube–Nujol mull composites unless otherwise specified.

Bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)cyclopropenone (1c). Aluminum chloride (10 g, 0.075 mol) was added to 13.4 g (0.075 mol) of tetrachlorocyclopropene in 10 ml of dichloromethane under nitrogen. The slurry was stirred and heated at reflux until pronounced thickening indicated the formation of the $C_3Cl_3^+AlCl_4^-$ salt. The reaction mixture was cooled to −15° and another 10 ml of dichloromethane was added followed by dropwise addition of 30.9 g (0.15 mol) of 2,6-di-*tert*-butylphenol in 75 ml of dichloromethane, while the temperature of the reaction was maintained at −10 to −5°. The mixture was stirred for 1 hr at −5° and then 100 ml of water was added. The organic layer was separated, dried, filtered, and evaporated. Addition of 100 ml of diethyl ether induced cystallization and 22.2 g (64%) of white **1c** was collected: mp 215° dec; ir 1840 (s), 1590 (s), 1415 (m), 1345 (s), 1295 (w), 1255 (m), 1230 (m, sh), 1195 (w), 1085 (br, m), 1020 (w, sh), 920 (w), 890 (w, sh), 885 (m), 775 (w), 720 cm^{-1} (w); ^1H NMR (CF_3COOH) δ 1.60 (36 H), 4.10 (2 H), 8.07 (4 H); uv-visible λ_{max} (CH_3CN) 236 nm (log ε 4.26), 326 (4.40), 344 (4.36).

Anal. Calcd for $C_{31}H_{42}O_3$: C, 80.51; H, 9.09; O, 10.40. Found: C, 80.32; H, 9.30; O, 10.24.

Compounds **1a** (R = methyl) and **1b** (R = isopropyl) were prepared by similar procedures using 2,6-dimethylphenol and 2,6-diisopropylphenol in 100 and 82% yield, respectively.

Bis(3,5-dimethyl-4-hydroxyphenyl)cyclopropenone (1a): mp 268° dec; ir 1840 (s), 1600 (s), 1560 (s), 1495 (m), 1375 (vs), 1335 (vs), 1265 (s), 1210 (vs), 1120 (m), 1105 (m), 1025 (m), 990 (w), 950 (vs), 935 (vw), 890 (m), 875 (sh, w), 860 cm^{-1} (sh, w); ^1H NMR (CF_3COOH) δ 2.42 (12 H), 4.07 (2 H), 7.78 (4 H); uv-visible λ_{max} (CH_3OH) 237 nm (log ε 4.33), 332 (4.57), 347 (4.58).

Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.55; H, 6.12. Found: C, 77.42; H, 6.21.

Bis(3,5-diisopropyl-4-hydroxyphenyl)cyclopropenone (1b): mp 209–211° dec; ir 3200 (m, v br), 2960 (m), 2920 (m, sh), 2870 (m), 1850 (s, sh), 1835 (vs), 1705 (w), 1595 (vs), 1560 (vs), 1460 (s), 1430 (s), 1370 (vs), 1335 (s), 1305 (vs, br), 1260 (s), 1200 (vs, br), 1145 (s), 1105 (m), 1045 (m), 1025 (w), 955 (vw), 935 (m), 885 (m), 820 (vs), 775 (w), 745 cm^{-1} (w); ^1H NMR (CF_3COOH) δ 1.44 (d, 24 H, J = 7 Hz), 3.38 (septet, 4 H, J = 7 Hz), 4.10 (s, 2 H), 7.97 (s, 4 H); uv-visible λ_{max} (CH_3OH) 239 nm (log ε 4.35), 333 (4.57), 348 (4.58).

Anal. Calcd for $C_{27}H_{34}O_3$: C, 79.80; H, 8.38. Found: C, 79.33; H, 8.51.

Bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetylene (3c). A solution of bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)cyclopropenone (**1c**, 131 mg, 0.283 mmol) in 10 ml of benzene was irradiated for 2 hr in a quartz vessel using a Hanovia mercury arc source. The benzene was removed by rotary evaporation, leaving 120 mg (98%) of crude light brown **3c**. A portion of this material was recrystallized twice from cyclohexane and sublimed at 220° (0.5 Torr) to give colorless solid **3c**: mp 256–259° dec; ir 3625 (w), 2950–2850 (s), 1440 (vs), 1390 (m), 1360 (m), 1300 (w), 1240 (s), 1195 (m), 1150 (m), 1120 (w), 1025 (w), 985 (w), 920 (vw), 880 (s), 790 (m), 760 cm^{-1} (m); uv-visible λ_{max} (CH_3CN) 295 nm (log ε 4.65), 302 sh (4.48), 314 (4.53).

Anal. Calcd for $C_{30}H_{42}O_2$: C, 82.94; H, 9.69. Found: C, 82.98; H, 9.68.

The syntheses of acetylenes **3a,b** from cyclopropenones **1a,b** were carried out in similar fashion except that methanol and 2-propanol were used as solvents, respectively. Acetylene **3a** was isolated in 24% yield after purification and **3b** in 5.4% yield.

Bis(3,5-dimethyl-4-hydroxyphenyl)acetylene (3a): mp 209–210° dec; ir 3425 (s, br), 2960–2860 (m), 1595 (w), 1485 (s), 1440 (m), 1320 (s), 1260 (w), 1235 (m), 1205 (s), 1170 (s), 1040 (m), 1025 (m), 970 (w), 945 (m), 880 (m), 870 (s), 770 (w), 725 cm^{-1} (w); uv-visible λ_{max} (CH_3CN) 294 nm (log ε 4.58), 302 sh (4.49), 312 (4.51).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.20; H, 6.77. Found: C, 81.04; H, 6.93.

Bis(3,5-diisopropyl-4-hydroxyphenyl)acetylene (3b): mp 148–152° dec; ir 1465 (vs), 1375 (m), 1360 (m), 1335 (m), 1305 (s), 1285 (s), 1250 (m), 1235 (m), 1200 (s), 1180 (m), 1150 (s), 1125 (w), 1105 (w), 1070 (w), 980 (w), 935 (w), 880 (s), 815 (vw), 785 (m), 760 cm^{-1} (m); uv-visible λ_{max} (CH_3CN) 294 nm (log ε 4.55), 302 sh (4.47), 313 (4.50).

Anal. Calcd for $C_{26}H_{34}O_2$: C, 82.54; H, 9.00. Found: C, 81.90; H, 8.79.

Bis(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)-cyclopropanone (2c) and Bis(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)ethylene (4c). A solution of 11.6 g (0.025 mol) of **1c** in 1 l. of benzene was added to 1 l. of 0.1 *M* aqueous KOH containing 21.4 g (0.065 mol) of $K_3Fe(CN)_6$. The organic layer was immediately separated, washed with water to remove excess oxidizing agent, dried, filtered, and evaporated as quickly as possible to give a purple solid, whose infrared spectrum indicated the presence of **2c** contaminated with 15–20% **4c**: ir (Nujol mull) 1810 (m), 1590 cm^{-1} (vs); uv-visible λ_{max} (benzene) 542 nm.

Anal. Calcd for $C_{31}H_{40}O_3$: C, 80.86; H, 8.70; O, 10.44. Found: C, 80.12; H. 8.86; O, 10.14 (corrected for 1.9% residue).

No attempt was made to recrystallize this solid because of its instability in solution, although once isolated **2c** appeared to be stable. If work-up of the reaction mixture was delayed for 45 min and the benzene solution was allowed to stand over drying agent for several hours the product isolated was **4c** in a yield of 9.06 g (84%), after washing with acetonitrile to remove most impurities: ir (Nujol mull) 1620 (w), 1595 cm^{-1} (vs); ^1H NMR (CCl_4) δ 1.33 (s, 36 H), 7.00 (s, 4 H); uv-visible λ_{max} (benzene) 486 nm (log ε 5.08).

Anal Calcd for $C_{30}H_{40}O_2$: C, 83.33; H, 9.26. Found: C, 83.17; H, 9.34.

During oxidation of **1a** and **1b** in benzene solution, intense absorptions were observed due to **2a** and **2b** at 514 and 543 nm, respectively. However, these products were not isolated. After a short time these absorptions were replaced by those of **4a** and **4b**

at λ_{max} 476 and 486 nm. Compound **4a** could not be isolated but oxidation of **1b** under aprotic conditions allowed isolation of **4b**.

Preparation of Bis(3,5-diisopropyl-4-oxo-2,5-cyclohexadien-1-ylidene)ethylene (4b). To a solution of 5.0 g (0.0123 mol) of **1b** in 600 ml of dry benzene was added 10 g of $MgSO_4$ and approximately 5 g of PbO_2. The mixture was stirred under nitrogen for 2 days. Filtration under nitrogen followed by removal of solvent by vacuum distillation (0°, 1 Torr) left a quantitative yield of **4b** by ^1H NMR. Recrystallization from dichloromethane–acetonitrile gave red-purple crystals: ir 2970–2860, 1630 (m), 1585 (vs), 1520 (w), 1365 (m), 1285 (m), 1260 (w), 1220 (m), 1105 (w), 1075 (m), 960 (vw), 945 (m), 935 (w), 915 (m), 865 (vw), 815 (m), 805 (sh), 790 cm^{-1} (w); ^1H NMR (CCl_4) δ 1.17 (d, J = 6.5 Hz, 12 H), 3.10 (septet, J = 6.5 Hz, 2 H), 6.78 (s, 4 H); uv–visible λ_{max} (benzene) 486 nm (log ϵ 5.02).

Anal. Calcd for $C_{26}H_{32}O_2$: C, 82.95; H, 8.51. Found: C, 83.07; H, 8.53.

Oxidation of Bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetylene (3c). A solution of **3c** (0.190 g, 0.440 mmol) in 50 ml of benzene was swirled for 15 min with an aqueous solution containing 1.00 g (3.00 mmol) of $K_3Fe(CN)_6$ and 1.0 g of KOH. The red-brown benzene layer was separated, washed with water, dried ($MgSO_4$), filtered, and evaporated, leaving 0.17 g (91%) of crude maroon solid which was recrystallized from dichloromethane–acetonitrile to give **4c**.

The same procedure applied to acetylenes **3a,b** gave solutions whose uv–visible maxima at 476 and 486 nm, respectively, indicated the presence of the desired diquinoethylenes **4a,b**, but work-up resulted in decomposition.

Reduction of the Diquinoethylene 4c. A solution of 0.3 g (0.7 mmol) of diquinoethylene **4c** in 200 ml of benzene was treated with excess powdered zinc and acetic acid. The solution was stirred vigorously until it had changed from red-brown to light yellow, then filtered free of excess zinc and washed with water to extract the excess acetic acid. The benzene layer was separated, dried ($CaCl_2$), filtered, and stripped of solvent by rotary evaporation. The residue was crystallized from cyclohexane to give 0.20 g (0.46 mmol, 66%) of a white solid, identified as bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetylene (**3c**) by comparison of its physical properties with those given above for **3c**.

Reduction of the Diquinocyclopropanone (2c). A benzene solution of the diquinocyclopropanone **2c**, showing maxima at 486 and 542 nm (the 486-nm band due to decomposition to the diquinoethylene **4c**), was treated with excess hydroquinone. The new electronic spectrum showed maxima at 327, 346, and 486 nm, indicating that diquinocyclopropanone **2c** had been reduced to diarylcyclopropenone **1c** (327, 346 nm) while the diquinoethylene **4c** remained unaffected.

Base Titration of 1c. To a solution of **1c** (110 mg, 0.24 mmol) in 200 ml of methanol was added 0.08 M aqueous NaOH in 1-ml aliquots. The uv–visible spectrum was determined (Figure 2) and the spectrum sample was returned to the titration mixture after each addition of base. Isosbestic points were observed at 251, 295, and 359 nm throughout the titration, indicating that the cyclopropenone was converted directly to the dianion, which has λ_{max} 400 nm (log ϵ 4.61).

Preparation of Anion Radicals and Monoradicals for ESR Studies. Anion Radical of 2c. The anion radical of the diquinocyclopropanone **2c** was prepared both by reduction of **2c** with Na–K alloy in vacuo at −60° in 1,2-dimethoxyethane and by oxidation of **1c** with PbO_2 in the presence of base. A mixture of **1c** and PbO_2 was prepared, 3:1 by weight. About 1.5 mg of the mixture was placed in an ESR sample tube and 1 ml of 1,2-dimethoxyethane, containing ca. 10% freshly prepared methanol–sodium methoxide solution, was added. The solution was quickly deoxygenated by flushing with nitrogen, then sealed and immediately placed in the ESR spectrometer at −60°.

Either method of generation gave the same ESR spectrum (Figure 1), consisting of five lines with relative intensities 1:4:6:4:1 with a_H = 0.63 G and g = 2.0046.

Anion Radical of 4c. The chemical reduction of **4c** was carried out as described for the reduction of **2c**. For electrolytic reduction, about 1 mg of **4c** with a few milligrams of $(n\text{-}Bu)_4N^+ClO_4^-$ was placed in an electrolytic cell. A small piece of glass wool was placed between the electrodes to slow diffusion. The cell was evacuated and tetrahydrofuran (distilled from $LiAlH_4$, stored over Na–K anthracene) was distilled into the cell. The solution was degassed twice and the cell was placed in the ESR cavity at −80°. A minimal current was passed through the cell and scanning was begun. A single strong line was soon observed, whose sharpness and apparent stability did not vary from −80° to room temperature, g = 2.0056. The same spectrum was obtained by chemical reduction of **4c**.

Monoradical of 1c. About 1.5 mg of a 3:1 mixture (by weight) of the cyclopropenone **1c** and PbO_2 was placed in an ESR sample tube, and 1 ml of p-xylene was added. The tube was flushed with nitrogen, sealed, agitated to dissolve and oxidize the sample, and examined in the ESR spectrometer. The spectrum (Figure 3) consists of nine lines with a_H (2 H) = 0.72 G, a_H (2 H) = 1.86 G.

Monoradical of 3c. Six milligrams of a 3:1 mixture of **3c** and silver(I) oxide was ground with 2 g of naphthalene in a mortar. About 500 mg of this mixture was then placed in an ESR sample tube which was heated to 90° to melt the naphthalene. The ESR spectrum of the monoradical, shown in Figure 3, consists of seven lines with ratio of intensities 1:2:3:4:3:2:1 with a_H (2 H) = 0.93 G and a_H (2 H) = 1.86 G.

Acknowledgment. This work was supported by Grant GP32081 from the National Science Foundation.

Registry No.—**1a,** 25361-96-0; **1b,** 25361-97-1; **1c,** 14106-41-3; **1c** free radical, 55255-27-1; **2c,** 15331-04-1; **3a,** 55255-28-2; **3b,** 55255-29-3; **3c,** 14106-39-9; **3c** free radical, 55255-30-6; **4b,** 55255-31-7; **4c,** 14106-40-2; tetrachlorocyclopropene, 6262-42-6; 2,6-di-*tert*-butylphenol, 128-39-2.

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Synthesis and Reactions of a Tetraquinocyclobutane

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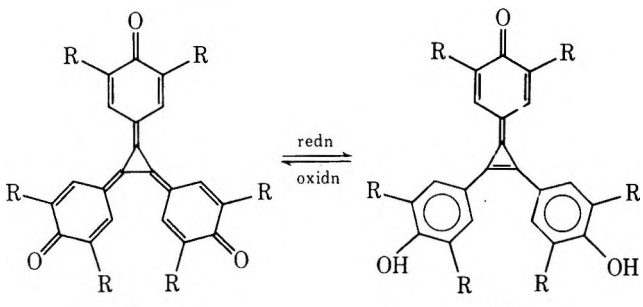
Thermal dimerization of the cumulene **5** yields the bright purple tetraquinocyclobutane **3**, which is reduced by benzopinacol to the diaryldiquinocyclobutene **4**. Reduction of **3** electrolytically or by the dianion of **4** gives a stable anion radical whose electron spin resonance spectrum indicates that the unpaired electron is fully delocalized over the five-ring system. Direct oxidation of **4** proceeds through a neutral monoradical intermediate **9**. The ESR spectrum of **9** indicates odd-electron delocalization over three aromatic rings.

The properties of triquinocyclopropanes **1** and their reduction products, diarylquinocyclopropenes (**2**), have been reported earlier.[1] This paper describes the synthesis and chemistry of four-membered ring analogs to these compounds: the tetraquinocyclobutane **3** [tetrakis(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)cyclobutane] and the diaryldiquinocyclobutene **4**.



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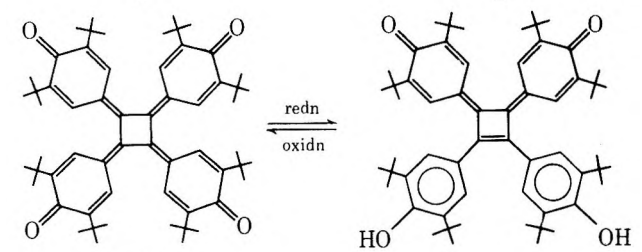
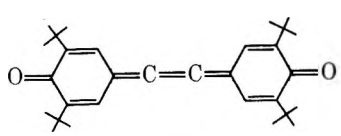


3 4

Compound **3** is obtained by thermal dimerization of the diquinoethylene **5**.[2] When heated in cyclooctane for 3–4 hr,



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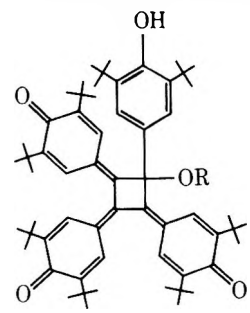
5 disappears completely and work-up of the reaction mixture yields 25% of **3** as sparkling purple crystals.[3] The tetraquinocyclobutane structure is related to those of 4-radialenes, many of which can similarly by synthesized by dimerization of cumulenes.[4,5]

In organic solvents **3** gives brilliant purple solutions which show complex electronic spectra in the visible and ultraviolet region (Figure 1). The spectrum of **3** is rather similar to that of the triquinocyclopropanes **1**,[1] but the visible absorptions occur at higher energy for **3**.

Molecular models indicate that a planar conformation is possible for **1** but not for **3**, and X-ray crystal structure determinations on both compounds confirm this deduction.[6,7] Compound **1** (R = *tert*-butyl) is almost planar with an average angle of twist of the six-membered rings of 5.5°. In contrast **3** exists in a propeller-like conformation with an average twist angle of 36°. The central four-membered ring is also distorted from planarity.

As would be expected from the high symmetry of the molecule, the infrared spectrum of **3** is quite simple, showing only ten medium and intense bands, and the ^{1}H NMR spectrum shows only two singlets in the expected 9:1 ratio.

Although it is stable indefinitely as a solid and in hydrocarbon solutions, **3** reacts with nucleophiles. Solution in methanol results in the addition of 1 mol of methanol to **3**. Similarly, if **3** is dissolved in wet *N*,*N*-dimethylformamide a water adduct is isolated. Based on ^{1}H NMR evidence the most likely structures for these adducts are **6a, b**. The ex-



6a, R = CH_3
b, R = H

pected 1:1:1:1 ratio of *tert*-butyl resonances is observed in the ^{1}H NMR of the methanol adduct in deuteriobenzene, while the water adduct shows a 2:1:1 pattern.

Although triquinocyclopropanes are reduced to diarylquinocyclopropenes by hydroquinone,[1] **3** does not react at all with hydroquinone. Other conventional reduction techniques (e.g., Zn–HCl, Zn–HOAc) fail because of the reactivity of **3** and **4** with nucleophiles. However, when **3** is refluxed with a slight excess of benzopinacol in cyclooctane the desired diaryldiquinocyclobutene **4** is formed as a bright orange solid. The ^{1}H NMR of **4** (C_6D_6) shows three types of *tert*-butyl protons in a 2:1:1 ratio (Figure 2) consistent with the assigned structure. The ^{1}H NMR spectrum also rules out the possibility of reduction diagonally across the ring to give a bicyclobutane structure, since this would be expected to give two resonances of equal intensity in the *tert*-butyl region. Although quite stable in the solid state, **4** is oxidized back to **3** by atmospheric oxygen if left in solution for a few hours. This diaryldiquinocyclobutene also exhibits the sensitivity to nucleophiles observed for **3**. A gradual change in the electronic spectrum occurs when **4** is dissolved in methanol, the final spectrum showing λ_{max} 460 nm (ϵ 3.87 × 10^4). No attempt was made to determine the exact structure of the methanol adduct(s).

The diarylquinocyclopropene analogous to **4**, compound **2** (R = *tert*-butyl), has its electronic absorption at 413 nm in benzene but shows a blue shift to 406 in acetonitrile. This suggests that the ground state of **2** is more polar than

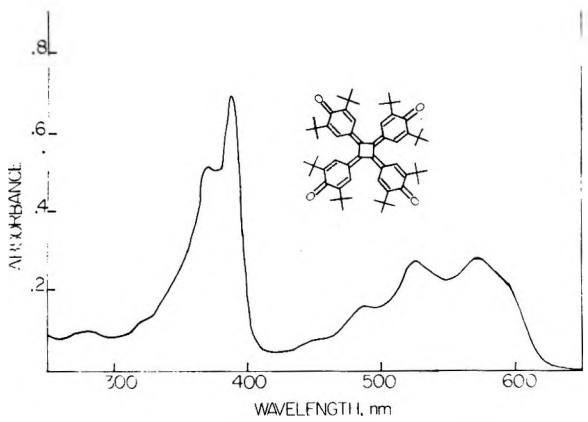


Figure 1. Electronic spectrum of tetraquinocyclobutane **3**, 0.1 m*M* in cyclohexane.

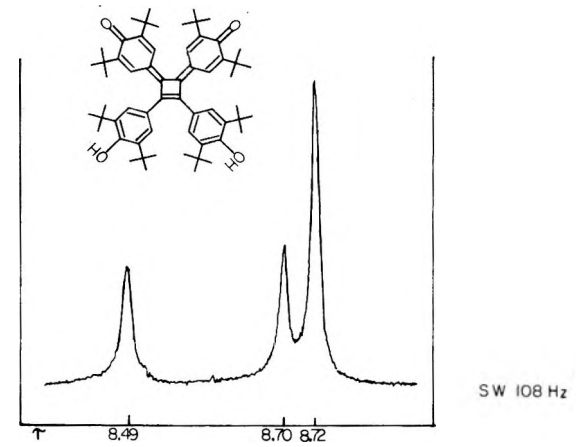
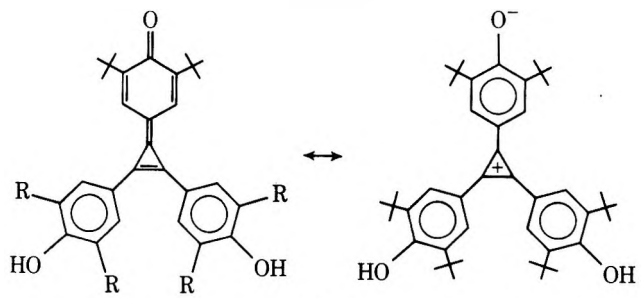


Figure 2. Proton magnetic resonance spectrum of **4** in C_6D_6.

the excited state and is evidence for the importance of the resonance contribution of the cyclopropenium cation in the ground state, as pictured below. The absence of a similar



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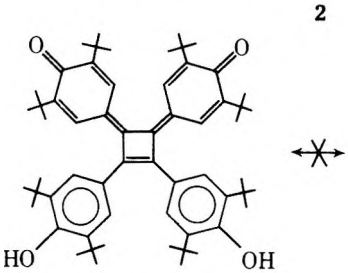

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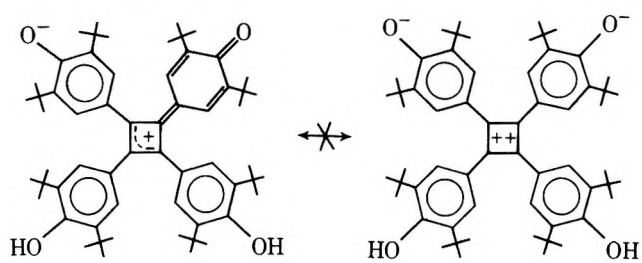
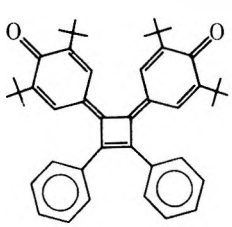


solvent shift in the spectrum of **4** is evidence that the cyclobutenyl cation or cyclobutadienyl dication does not contribute significantly to the ground state of **4**, or anyway no more than to the excited state.

The diaryldiquinocyclobutene **7** was reported[8] while our work with diaryldiquinocyclobutene **4** was in progress. Compound **7** was synthesized by oxidative dimerization of



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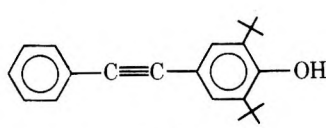

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acetylene **8** and appears to have properties similar to those of **4**. Compound **7** also reacts with alcohols to form "asymmetric adducts in which alcohol molecules seem to have reacted at one of the double bonds of the molecule".[8]

Deprotonation of 4 to Its Dianion. Spectrophotometric titrations with various bases were attempted in order to convert **4** to its dianion. In acetonitrile with aqueous sodium hydroxide as base, the isosbestic point was lost after about 1 equiv had been added, indicating that reaction was occurring rather than simple deprotonation. Titration with potassium *tert*-butoxide was similarly unsuccessful. However, when the hindered bicyclic amine, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), was used as the base in dry tetrahydrofuran, simple deprotonation was observed to give the turquoise-colored dianion (Figure 3). All intermediate curves pass through two isosbestic points at 522 and 300 nm, implying that the monoanion is not stable with respect to the dianion under the conditions used. To complete the deprotonation an amount of DBN in excess of the theoretical 2 equiv was required, showing qualitatively that **4** is not a very strong acid.

The Anion Radical of 3. Electrolytic reduction of **3** to its anion radical was carried out in tetrahydrofuran (THF). The reduced solution gave an ESR spectrum shown in Figure 4. The nine-line pattern indicates splitting by eight equivalent quinonoid protons, showing that the odd electron is completely delocalized over the four six-membered rings. Delocalization was similarly observed for the analogous triquinocyclopropane anion radical[9] as well as for the anion radicals of the related diquinoethylene and diquinocyclopropanone.[10] The proton hyperfine splitting constant, 0.43 G, is accounted for by molecular orbital calculations discussed in the accompanying paper.[10] The anion radical of **3** is stable for several days and can be exposed at least briefly to air without decomposition. If degassing is carried out after such exposure, the original nine-line pattern is observed.

To confirm that the species observed by electrolytic reduction of **3** was the anion radical, a solution of **3** plus the same volume of an equimolar solution of the dianion of **4** (prepared by DBN deprotonation) were mixed. The resulting solution showed exactly the same nine-line ESR pattern. The electronic spectrum showed no absorptions due to **3** or the dianion of **4** but gave a new maximum at 615 nm which can be assigned to the anion radical.

The Monoradical of 4. While the anion radical of **3** and the dianion of **4** should be redox intermediates in the tetraquinocyclobutane system under basic conditions, the expected intermediate under neutral conditions would be the monoradical **9** (the protonated anion radical). Two methods were employed to generate **9** in the ESR cavity, both

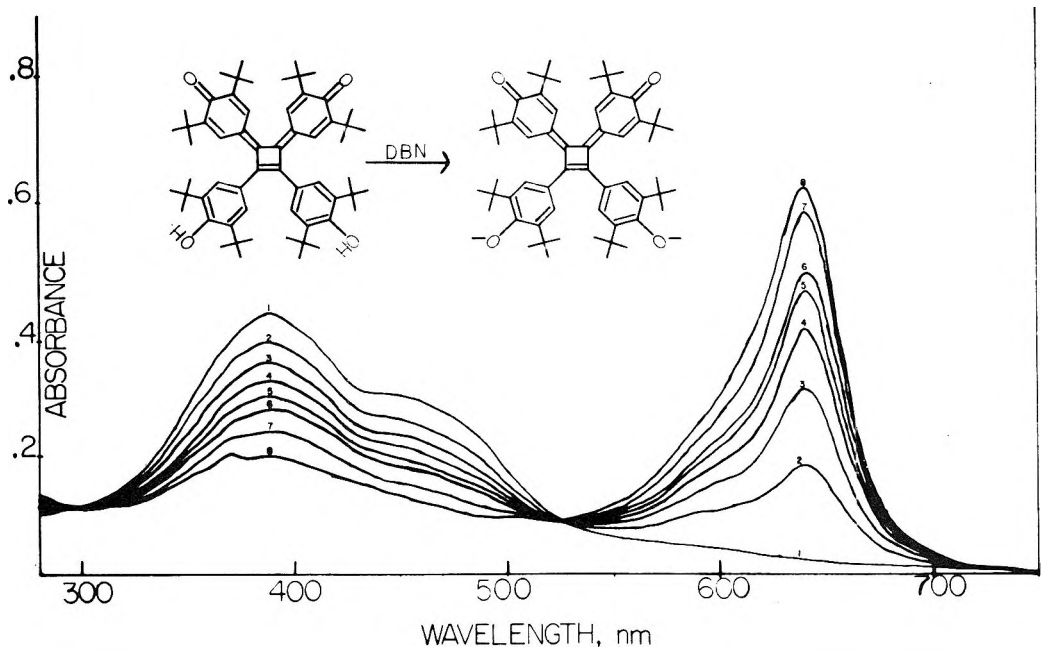


Figure 3. Spectrophotometric titration of **4** with DBN in THF solvent. Curve 1 shows the spectrum of pure **4**. Curve 8 shows the spectrum of **4** in the presence of excess DBN sufficient to convert **4** almost completely to the dianion.

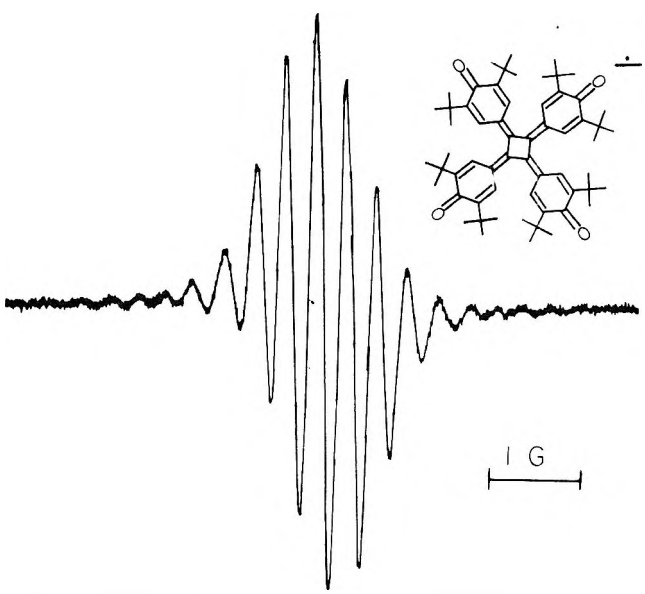
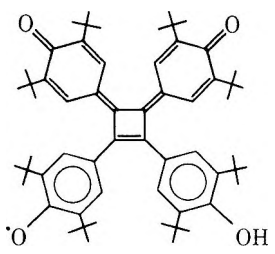


Figure 4. ESR spectrum of the anion radical of **3**, showing splitting by eight equivalent protons.

involving partial oxidation of **4**. When **4** was treated with PbO_2 in xylene, no signal was observed below 90°, when a weak multiplet appeared. The signal intensity increased as the temperature was raised to 135°, and decreased to the previously observed level when the temperature was lowered. Radical **9** was also generated from **4** in melted naphthalene using an equivalent amount of **3** as oxidant. The same pattern and reversible temperature effect was observed up to 180° (Figure 5). These results indicate that **3** and **4** undergo reversible comproportionation to **9** as shown below. The weakness of the signal shows that the equilibrium lies very far toward **3** and **4** at moderate temperatures.



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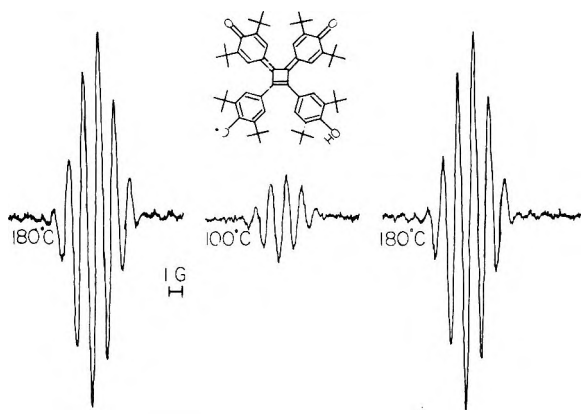
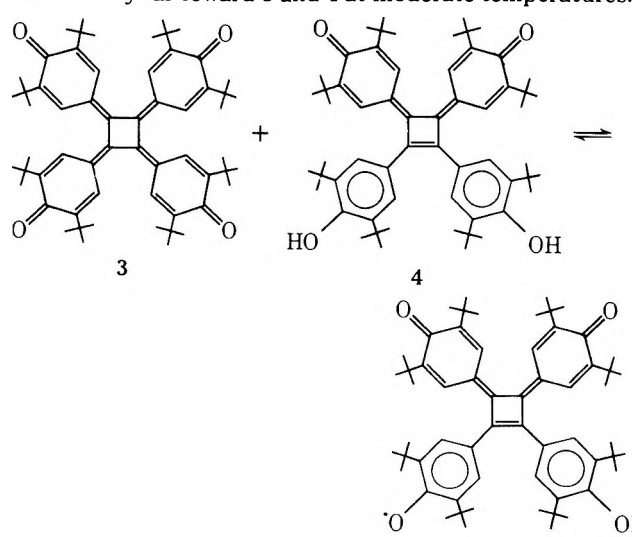
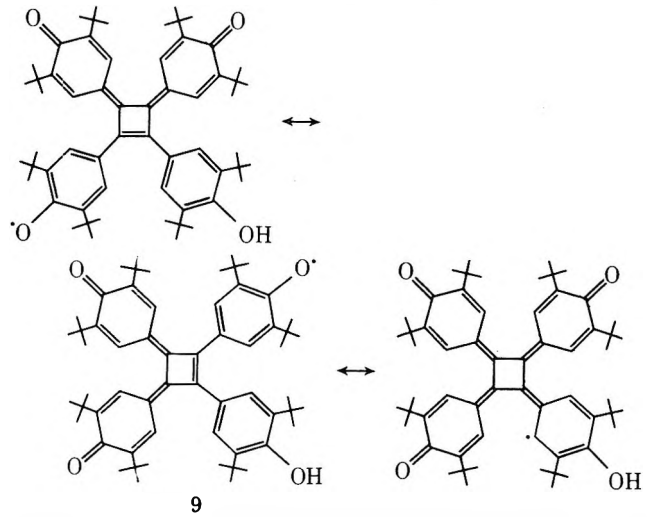


Figure 5. ESR spectrum of monoradical **9** formed by comproportionation of **3** and **4**, at 100 and 180° in melted naphthalene.



The ESR spectrum of **9** is a seven-line pattern, with the two outermost lines partially obscured by noise (Figure 5). This indicates hyperfine splitting by six equivalent pro-

tons, i.e., delocalization over three of the benzenoid rings. Resonance structures can be drawn (see below) consistent



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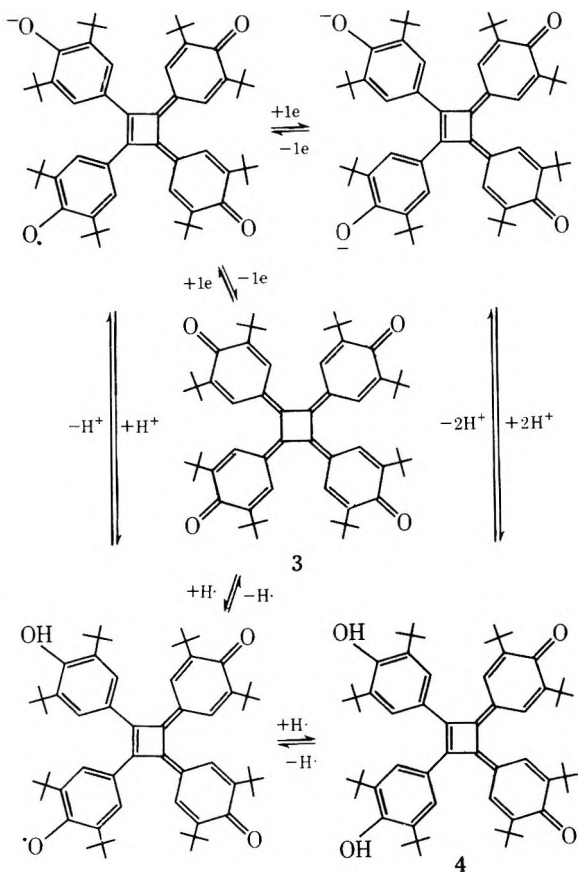
with delocalization of the odd electron over three (and not four) rings, but only two of the rings are equivalent. Evidently accidental equivalence accounts for the equal splitting by six protons and the odd-electron density is too small in the fourth ring to cause observable splitting.

Scheme I summarizes the intermediates in the **3** ⇌ **4** redox systems and the relationships between them.

Scheme I



Experimental Section

General Procedures. Hydrocarbon and ether solvents were freshly distilled from Na–K alloy or $LiAlH_4$, respectively, before use. Combustion analyses were performed by Alfred Bernhardt, Engelskirchen, West Germany. All melting points are uncorrected.

Spectra were recorded by means of the following instruments: infrared, Perkin-Elmer 457 or Beckman IR-33; proton NMR, Varian A-60A or Jeol JNM-MH-100; mass spectra, AEI-MS 902 at 70 eV; ultraviolet–visible, Cary 14; ESR, Varian 4502-13.

ESR electrolysis experiments were carried out using a 300-V battery source with the current kept at <0.1 μA. The *g* values of all observed radicals were measured using double-cavity technique and potassium nitrosyldisulfonate (Fremy's salt) as a standard.

Synthesis of Tetraquinocyclobutane 3. Compound **5** (0.30 g, 0.70 mmol) in 20 ml of cyclooctane was heated to boiling under nitrogen for 3.5 hr. The cyclooctane was vacuum distilled to a volume of 1–2 ml, 10–15 ml of dry hexane was added, and the solution was filtered through a sintered glass funnel and washed with 5–10 ml of hexane. This solution was concentrated to about 10 ml and cooled. Two crops of crystals were collected in good purity, totaling 51 mg (17%). Mother liquors from several such syntheses were combined and chromatographed on Florisil eluting with hexane and hexane–ether mixtures to yield further product after recrystallization (to about 25% total yield): mp 267°; ^1H NMR ($CDCl_3$) δ 1.33 (72 H), 7.45 (8 H); ir ($CHCl_3$) 2950 (s), 2850 (s), 1630 (m, br), 1450 (s), 1357 (m, doublet), 1260 (m), 1110 (m), 1018 (m), 915 (w, sh), 910 (m), 865 cm^{-1} (m); uv–visible λ_{max} (cyclohexane) 240 nm (log ε 4.07), 280 (4.03), 325 sh (4.18), 371 sh (4.82), 389 (4.87), 455 (4.03), 485 (4.28), 535 (4.48), 570 (4.50), 595 (4.35). Calcd for $C_{60}H_{80}O_4$: *m/e* 864.6056. Found: 864.6056.

Anal. Calcd for $C_{60}H_{80}O_4$: C, 83.28; H, 9.33; 0, 7.40. Found: C, 83.13; H, 9.30; O, 7.42.

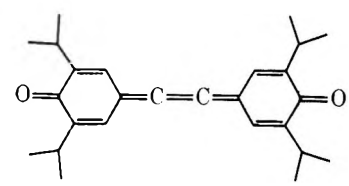
Methanol Adduct of 3 (6a). **3** (100 mg) was dissolved in 100 ml of anhydrous methanol and refluxed for 3 hr. Evaporation of methanol followed by ^1H NMR of the crude solid in deuteriobenzene showed essentially quantitative conversion. Recrystallization from dry hexane gave red-purple crystals: mp 175°; ^1H NMR (C_6D_6) δ 1.25 (18 H), 1.31 (18 H), 1.35 (18 H), 1.41 (18 H), 3.05 (3 H), 4.91 (1 H), 7.70–7.78 (8 H); ir ($CHCl_3$) 3618 (w) and 1600 cm^{-1} (vs); uv–visible λ_{max} ($CHCl_3$) 227 nm (log ε 4.26), 285 (4.23), 303 sh (4.04), 352 sh (4.29), 370 sh (4.56), 389 (4.71), 538 (very broad, 4.47).

Anal. Calcd for $C_{61}H_{84}O_5$: C, 81.63; H, 9.45; O, 8.92. Found: C, 81.48; H, 9.54; O, 8.98 (diff).

H_2O Adduct of 3 (6b). A solution of 54 mg of **3** in 35 ml of *N,N*-dimethylformamide and 0.5 ml of H_2O was heated to 120° for 0.5 hr, then stirred at room temperature for several days. TLC showed essentially quantitative conversion of **3** to the deep blue-purple **6b**. Ether was added and the solution was washed with water several times, dried ($MgSO_4$), filtered, and evaporated. Recrystallization from hexane–ether gave sparkling irridescent purple crystals: ^1H NMR (C_6D_6) δ 1.26 (36 H), 1.28 (18 H), 1.63 (18 H), 6.92 (8 H), 7.25 (1 H), 8.07 (1 H); ir ($CHCl_3$) 3618 (w), 1582 cm^{-1} (vs); uv–visible λ_{max} ($CHCl_3$) 300 nm (log ε 4.11), 335 (4.33), 563 sh (4.76), 587 (4.82).

Anal. Calcd for $C_{60}H_{82}O_5$: C, 81.58; H, 9.36; O, 9.06. Found: C, 81.45: H, 9.26; O, 8.93.

Attempted Dimerization of 10. At present **3** is the only tetraquinocyclobutane known. Repeated attempts were made to dimerize diquinoethylene **10**,[11] but decomposition invariably occurred



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without formation of the desired tetraquinocyclobutane. Reactions were monitored by TLC and were allowed to proceed until complete decomposition was observed. Except for the melting point tube experiment, the reactions were carried out in red-tinted glassware to minimize contact with light. None of the following methods gave any indication of tetraquinocyclobutane formation: (1) melting solid **10**; (2) thermolysis of **10** in a sealed melting point capillary in dry decalin; (3) thermolysis of **10** in refluxing benzene in the presence of a small amount of PbO_2; (4) thermolysis of **10** in refluxing cyclooctane in the presence of a small amount of hydroquinone; and (5) thermolysis of **10** in refluxing cyclooctane in the presence of a catalytic amount of $AlCl_3$.

Reduction of 3 to 4. Compound **3** (365 mg, 0.42 mmol) and 157 mg (0.46 mmol) of benzopinacol were refluxed in 80 ml of dry cyclooctane under nitrogen for 45 min. About half the solvent was distilled off just above room temperature under vacuum. The reaction was allowed to cool and settle overnight. After the addition of 10–15 ml of dry hexane, the orange precipitate (257 mg, 70%) was collected under nitrogen, washed with 15 ml of dry hexane, and al-

lowed to dry overnight. The product gave the following spectral data: ^{1}H NMR (C_6D_6) δ 1.28 (36 H), 1.30 (18 H), 1.51 (18 H), 5.16 (2 H), 7.37 (4 H), 7.67 (2 H), 7.86 (2 H); ir (CCl_4) 3600, 3550, 1600, 1580 cm^{-1}; mass spectrum *m/e* 866 (M^+), 851, 824, 809, also minor peaks at 884 ($M + H_2O$), 890 ($3 + 2H_2O$); uv-visible λ_{max} (CCl_4) 265 nm (log ϵ 3.51), 387 (4.63), 404 sh (4.56), 440 sh (4.41). Calcd for $C_{60}H_{82}O_4$: *m/e* 866.6213. Found: 866.6206.

Electron Spin Resonance Experiments. Anion Radical of 3. A few milligrams of **3** with a small amount of $(n\text{-Bu})_4N^+ClO_4^-$ was placed in an electrolytic cell. A small piece of glass wool was placed between the electrodes to slow diffusion. The cell was evacuated and THF (distilled from $LiAlH_4$, stored over Na–K anthracene) was distilled into the cell. The solution was degassed twice and the cell was placed in the ESR cavity. A minimal current was passed through the cell and scanning was begun.

The best spectrum was obtained by electrolytic reduction at room temperature of a sample which had been reduced several times before, and observation at 0° using the line-sharpening technique devised by Glarum.[12] The spectrum showed a_H = 0.33 G and g = 2.0054, with a ratio of line intensities 70:55.6:28.3:9.1 (calcd for nine lines 70:56:29:8).

Monoradical of 4 (9). 3 as Oxidizing Agent. **3** (8.2 mg), 8.7 mg of **4** (1:1 molar ratios), and 2 g of naphthalene were ground together in a mortar and pestle and a small amount of this mixture was placed in an ESR cell. The cell was twice alternately evacuated and flushed with nitrogen, leaving 1 atm of nitrogen in the cell. (A previous experiment showed this technique was necessary to prevent loss of resolution and signal level.) No signal from this solid mixture was evident at room temperature or until it melted at about 90°. A weak five- or seven-line pattern was then observed and better resolved with the line-sharpening technique devised by Glarum.[12] The signal level increased (reversibly) with temperature up through 180°. The sample was opened to the air momentarily at 140 and 170° (with no loss of signal) to prevent undue build-up of pressure.

PbO_2 as Oxidizing Agent. **4** (6 mg) and 2 mg of PbO_2 were weighed together and manually mixed with a spatula. Approximately ⅓ of this mixture was placed in an ESR cell with about 1 ml of dry xylene. The cell was degassed twice and then nitrogen was added. A weak signal (like the signal observed with **3** as oxidizing agent) was observed at 90°. As the temperature was increased, the signal level increased reversibly up to 135° (bp of xylene 137–140°).

In both this experiment and the previous one, a_H = 1.17 G, g = 2.0051, with a ratio of line intensities 20:14.5:5.7:1.2 (calcd for seven lines, 20:15:6:1).

Base Titrations of 4. NaOH–CH_3CN Titration. A 0.04 *N* NaOH solution and a 300-ml solution of 52 mg of **4** in CH_3CN were used; 0.5-ml aliquots of base were added to the CH_3CN solution of **4**, and samples were withdrawn for uv-visible spectrum and returned after each addition. After the addition of about 1 equiv, the isosbestic point was lost and the spectrum changed, indicating that reaction had taken place.

Potassium *tert*-Butoxide–THF Titration. A solution of 20.3 mg of **4** in 300 ml of dry THF was titrated with a solution of 122.2 mg of potassium *tert*-butoxide in 100 ml of dry THF, as previously described. After addition of about 1 equiv of base the isosbestic was again lost. Evidently **4** also reacts with *tert*-butyl alcohol.

DBN–THF Titration. A solution of 22.7 mg of **4** in 300 ml of dry THF was titrated with 21.6 mg of DBN in 100 ml of THF using the same procedure. This time the isosbestic points at 522 and 300 nm persisted throughout the titration. After 2 equiv of base had been added, the new dianion peak stopped growing appreciably but the absorption due to **4** continued to diminish slightly after each addition even after five times the theoretical amount was added. The dianion has λ_{max} 640 nm (log ϵ 4.80), 393 (3.41), 370 (3.43). After standing overnight, the solution gave an altered spectrum, e.g., the main band was weaker and appeared at 630 nm instead of 640 nm indicating that the DBN–H^+ salt of the dianion is not indefinitely stable.

Acknowledgment. This work was supported by Grant GP32081 from the National Science Foundation.

Registry No.—**3**, 34879-70-4; **3** radical ion, 55255-32-8; **4**, 55255-35-1; **5**, 14106-40-2; **6a**, 55281-78-2; **6b**, 55255-36-2; **9**, 55255-37-3; **10**, 55255-31-7.

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Synthesis of Heterofulvenes—Derivatives of 9-Alkylenexanthenes by the Friedel–Crafts Reaction, Accompanied by Halide Exchange

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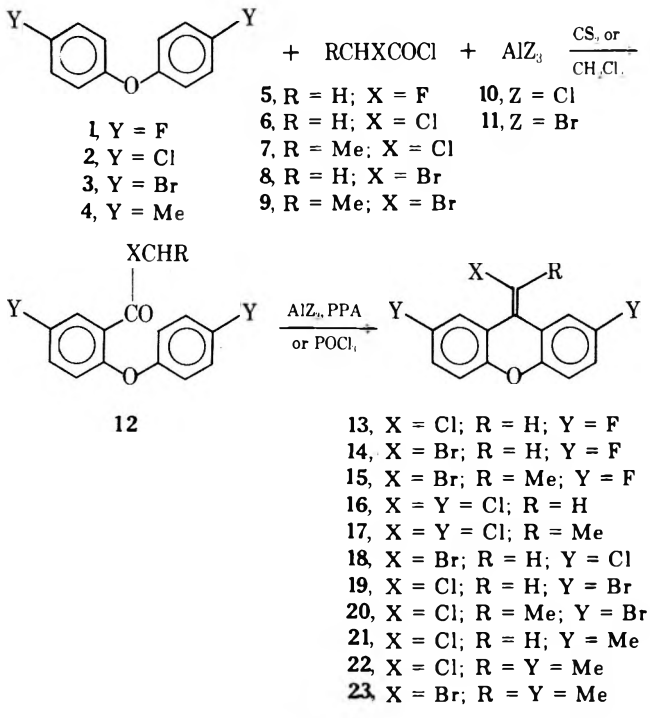
11-Chloro- and 11-bromo-9-alkylenexanthenes can be prepared from aromatic ethers and 2-haloacyl chlorides in the presence of aluminum halides. In some cases, halide exchange occurs between the haloacyl compounds and the aluminum halides. Occasionally, intermediate ketones are obtained and can be transformed to the final products by heating with phosphorus oxychloride or polyphosphoric acid. 9-Methylenexanthenes can be similarly synthesized.

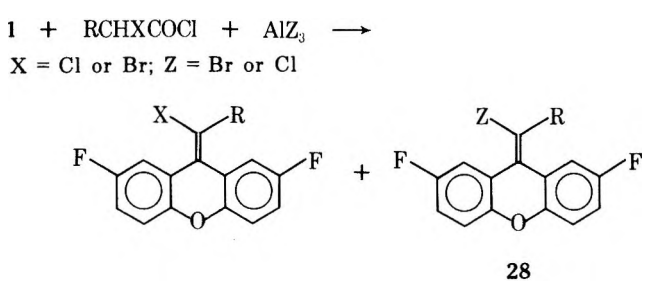
9-Alkylenexanthenes, such as **13**, are π-isoelectronic with the corresponding thioxanthenes and dibenzoheptafulvenes,[1,2] and consequently are of both biological and theoretical interest. In fact, it has been suggested that the 9-alkylenexanthenes are more "heptafulvenic" in nature than the dibenzoheptafulvenes.[3,4] Only one general approach to the synthesis of these olefins exists to date, namely, the reaction of xanthen-9-one with Grignard reagents, followed by dehydration.[5] However, this and the Wittig reaction[6] were found unsatisfactory for the preparation of 9-methylenexanthene.

We would like to report a convenient procedure for the synthesis of 9-alkylenexanthenes, such as **13** or **25**, using the aluminum halide catalyzed condensation of aromatic ethers **1–4** and acyl chlorides[7] illustrated in Scheme I. This approach is especially suited for the preparation of 11-chloro- and 11-bromo-9-alkylenexanthenes **13–23**. Halide exchange between the 2-haloacyl compounds **5–9** or **12** and

Scheme I



Scheme II



the aluminum halides **10** and **11** occurs when X ≠ Z. (See Scheme II.)

The intermediate ketones **12** (R = H) were usually not isolated, as they cyclized in situ, giving the final products. Occasionally, these ketones were obtained and converted to the product olefins by brief boiling with phosphorus oxychloride. The same treatment, or alternatively heating with polyphosphoric acid (PPA), completed the cyclization of **12** (R = Me), in which case **10** is usually ineffective for the cyclization. Aluminum bromide (**11**) is superior for this latter step. It appears that the halide X in **12** facilitates the aluminum halide induced cyclization of these ketones, possibly by enhancing the enolization of **12** as compared with **24**. Thus, acetyl chloride yields mainly (80–98%) the ketones **24** when employed according to Scheme I. The latter ketones are best transformed to the appropriate 9-methylenexanthenes **25–27** by heating them for 1 hr with freshly prepared PPA at 100–110° under N_2. The lack of an 11 substituent in these heterofulvenes[8] renders them highly sensitive to air oxidation,[9] yielding eventually the corresponding xanthen-9-ones.

Surprisingly, the 11-fluoro analog of **13** could not be obtained. Whenever fluoroacetyl chloride (**5**) was used according to Scheme I, total fluoride exchange with **10** or **11** took place, leading finally to **13** and **14**, respectively. This phenomenon is independent of the solvent. Partial chlorination during Friedel–Crafts fluoroacetylation of benzene in the presence of aluminum chloride has been recorded.[10] However, this has been a side reaction which could be eliminated[10] by use of dichloromethane as the solvent. The halide exchange observed in all the other reactions studied, i.e., where X ≠ F or Z, was incomplete, giving a mixture of 11-halo-9-alkylenexanthenes, as shown in Scheme II.

Generally, bromination by **11** proceeds to a greater extent than chlorination by **10** (see Table I). In two reactions, those of **1** and **2** with **8** in the presence of **10**, the chlorination is negligible. The halide exchange involves **5–9** or possibly **12**, but not the final products, since prolonged heating of the reaction mixture does not increase the halide exchange degree. In conclusion, pure **13–23** must be prepared from 2-haloacyl chlorides and aluminum halides containing the same halogens. Halide exchange degrees during the Friedel–Crafts haloacylations of **1** are given in Table I.

Table I
Halide Exchange Degrees during Haloacylations of 1

Starting materials		
RCHXCOCl	AlZ_3	Exchange degree, %
5	10	100
5	11	100
6	11	37
8	10	0
9	10	25
7	11	50

The relatively facile fluoride exchange with the aluminum halides could be due to the Lewis acid induced polarization of the carbon–fluorine bond.[11] Alternatively, simple metathesis reaction could have occurred between the aluminum halides and the haloacyl compounds, competing with the Friedel–Crafts acylation. This is in accord with the soft–hard acid–base concept,[12] since the harder the base (the smaller the halide), the greater its affinity to the hard Lewis acid **10** or **11**. Consequently, the observed relative reactivities of the halides in the haloacyl groups studies (F > Cl > Br) could be expected.

The 9-halomethylenexanthenes, e.g., **14**, are partly decomposed by light or heating at ca. 150° into intense red products which have not been identified. The homologs, such as **15**, are more stable. All these exocyclic olefins are oxidized by potassium permanganate, yielding the corresponding xanthen-9-ones.[7]

Product mixtures (Scheme II) were identified by NMR spectroscopy, using the different chemical shifts of H-8 and H-11 in the 11-chloro- and 11-bromo-9-alkylenexanthenes. The deshielding of H-8, arising from the long-range electrical effect[13] of the vinylic halide, is greater for Br than for Cl. Consequently, H-8 in **14**, e.g., resonates at a lower field than H-8 in **13**. (See Experimental Section.) A similar effect is observed for R = H (H-11) or Me in **13–23**. The differences in the corresponding chemical shifts of the latter protons, which are influenced directly by the vinylic halides, are greater than those associated with H-8.

All the new compounds obtained in this study were also characterized by mass spectrometry. The molecular ions

are always observed as the typical isotope peak patterns. In some of the mass spectra they are not the most intense peaks.

Experimental Section

Melting points were taken with a Thomas-Hoover Unimelt apparatus and are uncorrected. Uv spectra were recorded for solutions in 96% ethanol with a Bausch and Lomb Spectronic 505 instrument. NMR spectra were run for solutions in $CDCl_3$ with Me_4Si as internal standard with a Jeol C-60 HL high resolution spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU 6 spectrometer at 70 eV, using the direct insertion probe and a source temperature of 120–180°. The aromatic ethers and haloacyl chlorides used in this study were either commercially available or prepared as described elsewhere.[14,15]

General Procedure for the Condensation of Aromatic Ethers with Haloacyl Chlorides. The haloacyl chloride **5–9** (0.11 mol) was added rapidly to a mechanically stirred mixture of carbon disulfide (or dichloromethane) (250 ml), the aromatic ether (**1–4**) (0.1 mol), and the aluminum halide (**10** or **11**) (0.13 mol). The mixture was refluxed for 5 hr, cooled, and decomposed with ice–water. The organic layer and a $CHCl_3$ extract (if needed) yielded, after evaporation, a crude product which was examined by NMR. The mixture obtained upon incomplete cyclization was heated for 1 hr with phosphorus oxychloride (150 ml) (R = H; X = Cl or Br) or PPA (200 ml) at 100–110°. Finally, decomposition of the reaction mixture with ice–water and extraction with $CHCl_3$ afforded the appropriate 9-alkylenexanthene **13–23.**

2,7-Difluoro-9-chloromethylenexanthene[7] **(13)** was prepared from **1, 5,** and **10** (60%): mp and mmp 147°; NMR δ 6.48 (1 H, s, H-11), 7.05 (5 H, m, HAr), 8.09 (1 H, m, H-8).

Anal. Calcd for $C_{14}H_7ClF_2O$: C, 63.5; H, 2.6; Cl, 13.4. Found: C, 63.6; H, 2.6; Cl, 13.5.

2,7-Difluoro-9-bromomethylenexanthene (14) was prepared from **1, 8,** and **10** (40%) and also from **1, 5,** and **11** (45%): mp 142° (EtOH); NMR δ 6.61 (1 H, s, H-11), 7.10 (5 H, m, HAr), 8.17 (1 H, m, H-8); λ_{max} 240 nm (sh, ε 11,300), 263 (5600), 290 (sh, 3300), 338 (9500).

Anal. Calcd for $C_{14}H_7BrF_2O$: C, 54.4; H, 2.3; Br, 25.9; F, 12.3. Found: C, 54.6; H, 2.5; Br, 25.4; F, 12.6.

11-Bromo-2,7-difluoro-9-ethylidenexanthene (15) was prepared from **1, 9,** and **11** (45%): mp 163° (EtOAc); NMR δ 2.8 (3 H, s, Me), 7.37 (5 H, m, HAr), 8.09 (1 H, m, H-8); λ_{max} 254 nm (sh, ε 7100), 286 (2580), 321 (7750).

Anal. Calcd for $C_{15}H_9BrF_2O$: C, 55.7; H, 2.8; Br, 24.8; F, 11.8. Found: C, 55.5; H, 2.7; Br, 24.6; F, 12.0.

2,7,11-Trichloro-9-methylenexanthene (16) was prepared from **2, 6,** and **10** (42%): mp 105° (EtOH); NMR δ 6.55 (1 H, s, H-11), 7.32 (5 H, m, HAr), 8.34 (1 H, d, H-8).

Anal. Calcd for $C_{14}H_7Cl_3O$: C, 56.5; H, 2.4; Cl, 35.8. Found: C, 56.4; H, 2.4; Cl, 35.5.

2,7,11-Trichloro-9-ethylidenexanthene (17) was prepared from **2, 7,** and **10** (40%): mp 173° (EtOAc); NMR δ 2.49 (3 H, s, Me), 7.15 (5 H, m, HAr), 7.90 (1 H, d, H-8); mass spectrum *m/e* (rel intensity) 310 (87, M^+), 275 (44), 250 (60), 239 (100), 205 (53).

Anal. Calcd for $C_{15}H_9Cl_3O$: C, 57.8; H, 2.9; Cl, 34.1. Found: C, 57.8; H, 3.0; Cl, 34.1.

2,7-Dichloro-9-bromomethylenexanthene (18) was prepared from **2, 8,** and **10** (52%): mp 113° (EtOH); NMR δ 6.61 (1 H, s, H-11), 7.20 (5 H, m, HAr), 8.49 (1 H, d, H-8); mass spectrum *m/e* (rel intensity) 340 (64, M^+), 233 (13), 226 (26), 197 (10), 164 (13).

Anal. Calcd for $C_{14}H_7BrCl_2O$: C, 49.1; H, 2.1. Found: C, 49.2; H, 2.3.

2,7-Dibromo-9-chloromethylenexanthene (19) was prepared from **3, 6,** and **10** (45%) mp 128° (EtOAc); NMR δ 6.52 (1 H, s, H-11), 7.27 (5 H, m, HAr), 8.55 (1 H, d, H-8); λ_{max} 250 nm (sh, ε 11,200), 264 (sh, 7760), 294 (sh, 3100), 339 (6900); mass spectrum *m/e* (rel intensity) 384 (45, M^+), 270 (16), 163 (47), 162 (14), 113 (16).

Anal. Calcd for $C_{14}H_7Br_2ClO$: C, 43.5; H, 1.8. Found: C, 43.4; H, 1.8.

11-Chloro-2,7-dibromo-9-ethylidenexanthene (20) was prepared from **3, 7,** and **10** (35%): mp 163° (EtOH–EtOAc); NMR δ 2.50 (3 H, s, Me), 7.30 (5 H, m, HAr), 8.16 (1 H, d, H-8); λ_{max} 255 nm (ε 12,050), 290 (2720), 323 (6220); mass spectrum *m/e* (rel intensity) 398 (33 M^+), 284 (30), 283 (48), 205 (100). 176 (32).

Anal. Calcd for $C_{15}H_9Br_2ClO$: C, 44.9; H, 2.3. Found: C, 44.7; H, 2.3.

2,7-Dimethyl-9-chloromethylenexanthene (21) was prepared from **4, 6,** and **10** (70%): oil; NMR δ 2.14 (3 H, s, Me-2), 2.20 (3 H, s, Me-7); 6.07 (1 H, s, H-11), 6.72 (5 H, m, HAr), 7.85 (1 H, m, H-8).

This compound was further characterized by oxidation[7] with $KMnO_4$ to 2,7-dimethylxanthen-9-one, which was identical with an authentic sample,[16] mp and mmp 140°.

11-Chloro-2,7-dimethyl-9-ethylidenexanthene (22) was prepared from **4, 7,** and **10** (40%): mp 94° (EtOH); NMR δ 2.38 (6 H, s, MeAr), 2.52 (3 H, s, Me-11), 7.16 (5 H, m, HAr), 7.88 (1 H, m, H-8); mass spectrum *m/e* (rel intensity) 270 (100, M^+), 255 (31), 235 (45), 220 (24), 219 (54).

Anal. Calcd for $C_{17}H_{15}ClO$: C, 75.4; H, 5.5; Cl, 13.1. Found: C, 75.4; H, 5.7; Cl, 13.1.

11-Bromo-2,7-dimethyl-9-ethylidenexanthene (23) was prepared from **4, 9,** and **11** (45%): mp 93° (EtOH); NMR δ 2.37 (3 H, s, Me-2), 2.38 (3 H, s, Me-7), 2.73 (3 H, s, Me-11), 7.10 (5 H, m, HAr), 7.93 (1 H, m, H-8); mass spectrum *m/e* (rel intensity) 314 (80, M^+), 235 (79), 234 (40), 220 (52), 219 (100).

Anal. Calcd for $C_{17}H_{15}BrO$: C, 64.8; H, 4.8; Br, 25.4. Found: C, 64.9; H, 4.8; Br, 25.4.

Preparation of Substituted 9-Methylenexanthenes (25–27). These olefins were prepared as described above for the 11-halogenated derivatives, using aluminum chloride and acetyl chloride instead of the haloacyl chloride. However, the primary products were mixtures of the ketones **24** (80–98%) and the desired olefins (20–2%). These ketones were characterized by ^1H NMR, and then heated for 1 hr with a freshly prepared solution of P_2O_5 (160 g) and H_3PO_4 (200 ml) at 100–110° under N_2. Hydrolysis with ice–water (600 ml) followed by filtration yielded the appropriate **25–27.** When the cyclization reaction was conducted without an inert atmosphere, the 9-methylenexanthenes were heavily contaminated with the corresponding xanthen-9-ones. These olefins could not be recrystallized without partial oxidation, excluding the 2,7-dibromo derivative. Consequently, only the latter gave satisfactory combustion analysis. The other derivatives were characterized by their NMR and mass spectra, and by oxidation to the corresponding xanthen-9-ones by $KMnO_4$.[7]

2,7-Difluoro-9-methylenexanthene (25). The ketone **24** (Y = F) contained 20% of the desired **25,** when prepared from **1** and AcCl: NMR δ 2.65 (3 H, s, Me), 7.20 (7 H, m, HAr). Cyclization of this mixture afforded **25** (Y = F) (60%): mp 84–86°; NMR δ 5.50 (2 H, s, H-11), 7.10 (4 H, m, HAr), 7.40 (2 H, m, H-1 and 8). Oxidation of this olefin with $KMnO_4$[7] yielded 2,7-difluoroxanthen-9-one, mp and mmp[7] 170° (EtOH).

2,7-Dimethyl-9-methylenexanthene (27). The ketone **24** (Y = Me) had NMR δ 2.30 (6 H, s, MeAr), 2.64 (3 H, s, MeCO), 7.22 (7 H, m, HAr).

This ketone was transformed to the olefin (50%): mp 85° (EtOH); NMR δ 2.31 (6 H, s, Me), 5.48 (2 H, s, H-11), 7.05 (4 H, m, HAr), 7.50 (2 H, m, H-1 and -8). $KMnO_4$ oxidation[7] of this compound gave 2,7-dimethylxanthen-9-one, mp and mmp 140° (EtOH).[15]

2,7-Dibromo-9-methylenexanthene (26). The ketone **24** (Y = Br) was prepared from **3** and AcCl. The NMR spectrum showed peaks at δ 2.65 and 2.68 (3 H, two s, Me), 7.70 (7 H, m, HAr).

The desired olefin was obtained after the polyphosphoric acid treatment (50%): mp 150° (EtOAc); NMR δ 5.68 (2 H, s, H-11), 7.22 (2 H, d, H-4 and -5), 7.68 (2 H, dd, H-3 and -6), 8.10 (2 H, d, H-1 and -8); mass spectrum *m/e* (rel intensity) 350 (50, M^+), 192 (46), 164 (29), 163 (69), 162 (12). Anal. Calcd for $C_{14}H_8Br_2O$: C, 47.7; H, 2.3; Br, 45.5. Found: C, 47.5; H, 2.4; Br, 45.7.

Registry No.—**1,** 330-93-8; **2,** 2444-89-5; **3,** 2050-47-7; **4,** 1579-40-4; **5,** 359-06-8; **6,** 79-04-9; **7,** 7623-09-8; **8,** 22118-09-8; **9,** 7148-74-5; **10,** 7446-70-0; **11,** 7727-15-3; **13,** 37611-30-6; **14,** 55517-16-3; **15,** 55517-17-4; **16,** 55517-18-5; **17,** 55517-19-6; **18,** 55517-20-9; **19,** 55517-21-0; **20,** 55517-22-1; **21,** 55517-23-2; **22,** 55517-24-3; **23,** 55517-25-4; **24** (Y = F), 55517-26-5; **24** (Y = Me), 55517-27-6; **24** (Y = Br), 55517-28-7; **25,** 55164-23-3; **26,** 55164-25-5; **27,** 55164-24-4.

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Synthesis of Diepoxides and Diphenol Ethers of Pyrene and Dibenz[*a,h*]anthracene

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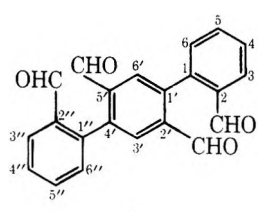
The diepoxides, 4,5,9,10-diepoxytetrahydropyrene and 5,6,12,13-diepoxytetrahydrodibenz[*a,h*]anthracene, were synthesized from the parent hydrocarbons via their respective diozonides and tetraaldehydes. Both epoxides were converted to diphenols; because of the instability of the diphenols they were converted to and characterized as phenol ethers. The two diphenol ethers derived from diepoxydibenz[*a,h*]anthracene were characterized as 5,12-dimethoxydibenz[*a,h*]anthracene and 6,13-dimethoxydibenz[*a,h*]anthracene. All of these compounds are new with the exception of 5,12-dimethoxydibenz[*a,h*]anthracene. These epoxides and their diphenols are important in chemical carcinogenesis studies.

Naphthalene epoxide is the first aromatic hydrocarbon epoxide to be synthesized and shown to be a metabolite in a biological system.[1] Since then a number of monoepoxides of carcinogenic hydrocarbons have been synthesized;[2] recently the synthesis of the monoepoxide of the noncarcinogenic hydrocarbon, pyrene, was also reported.[3] The metabolism of both pyrene and the carcinogen dibenz[*a,h*]anthracene has been studied in detail[4] and several phenolic metabolites of both hydrocarbons have been reported.[4] The definitive isolation of their mono- or diepoxides from in vivo or in vitro biological systems has, however, not been accomplished.[5] It has been shown, however, that 5,6-epoxydibenz[*a,h*]anthracene has weak tumor-inducing activity.[6]

The continued interest in mechanism of action and metabolism of aromatic hydrocarbons[7] prompted the synthesis of diepoxides of pyrene and of the carcinogen dibenz[*a,h*]anthracene, since these diepoxides are expected to play a role in the biologic activity of the hydrocarbons. In the present work, the phenol ethers formed from the diepoxides upon acid-catalyzed rearrangement and methylation are described and compared with the known metabolic products.

The general procedure of Newman and Blum[8] was used to convert the dialdehydes to the epoxides using Mark's reagent,[9] i.e., tris(dimethylamino)phosphine. The required precursor for the synthesis of 5,6,12,13-diepoxytetrahydrodibenz[*a,h*]anthracene is *p*-terphenyl-2,2′,5′,2″-tetracarboxaldehyde (**1**), which has been reported.[10] However, the reported product was not identical with the completely characterized product obtained in this work. Ozonization of a dilute solution of dibenz[*a,h*]anthracene in anhydrous CH_2Cl_2 at −70° with 2 molar equiv of ozone gave predominantly the 5,6,12,13-diozonide of the parent hydrocarbon. This was shown by the alkaline hydrogen peroxide oxidation of the diozonide to the known 2,2′,5′2″-tetracarboxy-*p*-terphenyl.[10] The diozonide on reduction with sodium iodide in acetic acid afforded an aldehyde, mp 234–236°, in good yield. The product reported earlier[10] had mp >360°. Based on its uv absorption at 296 and 233 nm, ir bands at 3.46, 3.61, and 5.93 μ, mass spectrum and C, H analysis it was characterized as the tetraaldehyde **1**. When refluxed with tris(dimethylamino)phosphine in dry benzene, the tetraaldehyde was converted to the diepoxide **2**, the structure of which was confirmed by spectral and combustion analyses. Additional support for its structure was provided by the comparison of its ultraviolet spectrum with that of 5,6,12,13-tetrahydrodibenz[*a,h*]anthracene.[11] In both compounds there is restricted rotation of the benzene rings and therefore they have similar uv absorption spectra which are, however, quite different from that of *p*-terphenyl.

The acid-catalyzed rearrangement of the diepoxide **2** could lead to three isomeric diphenols, i.e., 6,13-dihydroxy, 5,13-dihydroxy-, and 5,12-dihydroxydibenz[*a,h*]anthracene. Two of the methyl ethers derived from these phe-



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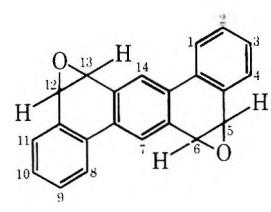

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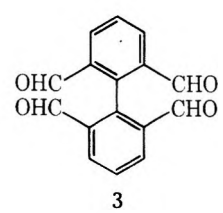

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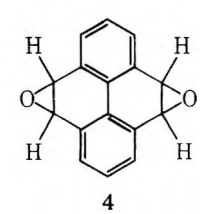

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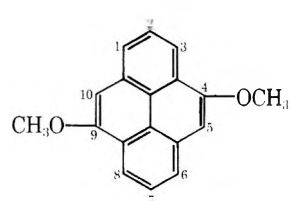

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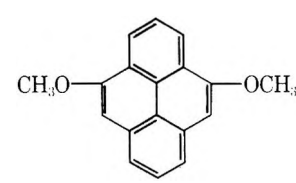

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nols have been described earlier.[12] They are the 5,12 and 5,13 isomers; the reported melting points of the two methyl ethers are 304–305 and 285–287°, respectively. The diepoxide was refluxed in HCl–acetone followed by methylation with dimethyl sulfate and potassium carbonate. The phenol ethers were separated by silica gel column chromatography followed by fractional crystallization. Two phenol ethers were obtained: the previously unknown 6,13-dimethoxy isomer, mp 271–273°, was obtained in good yield along with the previously characterized 5,12-dimethoxy isomer,[12] mp 303–305°, as the minor product. The new 6,13-dimethyl ether was characterized by its C, H analysis, ir, uv, and mass spectrum. None of the diphenols mentioned above have been detected as metabolites of dibenz[*a,h*]anthracene, although the presence of 6,13-dihydroxydibenz[*a,h*]anthracene as a possible metabolite has been suggested.[12,13]

Pyrene diepoxide **4** was synthesized by the same series of reactions as that described above for dibenz[*a,h*]anthracene. Biphenyl-2,2′,6,6′-tetracarboxaldehyde (**3**) was obtained in good yield by ozonolysis of pyrene followed by sodium iodide–acetic acid reduction of the intermediate ozonide. Its structure was confirmed by elemental and spectral analyses. The tetraaldehyde was cyclized to **4** in 19.3% yield. A mass spectral parent ion, *m/e* 234, and the absence of hydroxyl and carbonyl infrared absorptions as well as its uv absorption pattern, confirmed its structure as 4,5,9,10-diepoxytetrahydropyrene. The uv absorption spectrum was very similar to that of 9,10-epoxyphenanthrene synthesized in this laboratory using the previously described method.[8] An analytically pure sample of **4** could be obtained only when freshly redistilled Mark's reagent was used for this reaction. Acid-catalyzed rearrangement of **4** and subsequent methylation gave two isomeric methyl ethers, **5** and **6**, mp 250–252 and 153–155°, respectively; these two isomers were separated by fractional crystallization. The higher melting isomer has a uv spectrum very similar to that of pyrene. The positions of the methoxy groups in the two isomers has yet to be determined. The synthesis of 4,9-dihydroxypyrene has been reported;[14] however, the characterization of the compound was incomplete. Neither of the diphenols of pyrene has been identified as metabolites of the hydrocarbon in laboratory animals.[4]

As a part of this work, the fluorescence excitation and emission spectra of all fluorescent compounds were obtained (Table II), as additional information in the spectroscopic characterization of new compounds. In the course of these measurements it was observed that the diepoxides readily undergo photochemical rearrangement, presumably to the corresponding oxepins, as was observed earlier in the case of the monoepoxide of pyrene.[3a] These oxepins are, to our knowledge, unknown compounds and they were not investigated further in the course of this work.

With the renewed interest in aromatic hydrocarbon metabolism and improved analytical methods now available for the isolation of metabolites of aromatic hydrocarbons in vivo and/or in vitro, it is expected that the compounds described in this report will be of great interest to workers in chemical carcinogenesis. Furthermore, as bifunctional alkylating agents these epoxides are of particular interest because it is known that among aliphatic epoxides the bifunctional epoxides are frequently carcinogenic, whereas their monofunctional analogs are inactive.[6]

Experimental Section

Melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were determined in KBr pellets, using a Perkin-Elmer Model 421 spectrophotometer, and ultraviolet spectra (Table I) were obtained with a Cary Model 14. Proton magnetic resonance spectra were recorded only of those compounds which were sufficiently soluble in the commonly available NMR solvents using a Varian Model A-60A spectrometer. A custom-designed multipurpose luminescence spectrophotometer[15] was used to record the fluorescence excitation and emission spectra (Table II). Corrected emission spectra were recorded in quantum units and corrected excitation spectra in energy units. All fluorescence measurements were made by use of 5-nm slits on the excitation and emission monochromators. The mass spectra were obtained from the Morgan Schaffer Corp., Montreal, Canada. The samples were introduced through a direct inlet in most cases. The ozonizer used was a Welsbach Corp. Model T-408. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. TLC was carried out on precoated silica gel G plates; spots were visualized with short- and long-wavelength uv lamps. Most of the compounds reported are sensitive to photooxidation and precautions were taken to prevent such degradation.

***p*-Terphenyl-2,2′,5′,2″-tetracarboxaldehyde (1).** Dibenz[*a,h*]anthracene (1.13 g), dissolved in dry CH_2Cl_2 (350 ml), was cooled to −70° and treated with ozonized oxygen until approximately 2 molar equiv of ozone had been added. The crude ozonide precipitated during the addition of the second molar equivalent of ozone. The reaction mixture was immediately flushed with nitrogen, allowed to warm to room temperature, and concentrated to ~100 ml in a rotary evaporator under reduced pressure. Powdered sodium iodide (8 g) and glacial acetic acid (60 ml) were added to the white slurry with stirring. The clear reddish-brown solution was kept at 4° for 24 hr in a N_2 atmosphere. The liberated iodine was reduced with aqueous sodium thiosulfate (10%). The mixture was extracted with an excess of CH_2Cl_2, and the extract was washed with aqueous sodium carbonate (10%) and then with water. The extract was dried over anhydrous $MgSO_4$ and evaporated to dryness to yield a white residue which crystallized from CH_2Cl_2–hexane as creamy-white needles (0.820 g, 59%): mp 234–236° (lit.[10] mp >360°); ir 3.46, 3.61 (C–H stretch), 5.93 μm (C=O stretch); mass spectrum *m/e* 342 (parent ion). Anal. Calcd for $C_{22}H_{14}O_4$: C, 77.18; H, 4.12. Found: C, 76.69; H, 4.22. TLC, R_f 0.66 in CH_2Cl_2–acetone (9.75:0.25).

A part of the ozonide was oxidized by heating its suspension in ethanol with H_2O_2 (30%) and sodium hydroxide solution.[10] The solution was acidified and extracted with ether. The ether extract on concentration yielded colorless crystals, mp 310–314° dec. It was identified as 2,2′,5′,2″-tetracarboxy-*p*-terphenyl by direct comparison with an authentic sample (mixture melting point, ir, uv).

5,6,12,13-Diepoxy-5,6,12,13-tetrahydrodibenz[*a,h*]anthracene (2). The tetraaldehyde, structure **1** (0.5 g), was dissolved in heated dry benzene (100 ml) and freshly distilled tris(dimethylamino)phosphine (0.6 ml) was added to the solution. The mixture was refluxed in a N_2 atmosphere for 25 min and then evaporated to near dryness in a rotary evaporator under reduced pressure. Filtration and washing of the residue with benzene–hexane (1:1) left colorless needles of the diepoxide (0.36 g, 80%): mp 192–193° dec; ir 6.71, 6.98, 8.36, 9.81, 11.85, 13.5 μ; mass spectrum *m/e* 310 (parent ion). Anal. Calcd for $C_{22}H_{14}O_2$: C, 85.14; H, 4.55. Found: C, 84.85; H, 4.57. TLC, R_f 0.84 in cyclohexane–dioxane (6:4). This compound was sparingly soluble in most organic solvents. The diepoxide was stable at −10° and could be stored unchanged at −10° in the dark for several months but it is sensitive to light.

5,12-Dimethoxy- and 6,13-Dimethoxydibenz[*a,h*]anthracene. Concentrated HCl (1.0 ml) was added to the above diepoxide (0.650 g) in acetone (400 ml) and the solution was refluxed for 0.5 hr in a N_2 atmosphere. The reaction mixture was concentrated to a small volume (~5 ml). Acetone (100 ml, dried over K_2CO_3), dimethyl sulfate (1.0 ml), and anhydrous K_2CO_3 (5.0 g) were added immediately and the mixture was refluxed for 18 hr. The reaction mixture was filtered and washed with an excess of dry acetone and the solvent was removed by distillation under reduced pressure. The pale yellow residue was chromatographed on a Florisil column and eluted with hexane–benzene (8:2 v/v). The fractions having R_f 0.54 in hexane–CH_2Cl_2 (6:4) were combined and evaporated to dryness. Fractional crystallization of the pale yellow residue (0.380 g) from CH_2Cl_2 yielded two crops of product. The first crop (70 mg) was crystallized several times from benzene, colorless plates (30 mg): mp 303–305° (lit.[12] for 5,12-dimethoxydibenz[*a,h*]anthracene, mp 304–305°); ir 6.16, 6.24, 6.68, 6.83, 6.95, 7.16, 7.35 μm; mass spectrum *m/e* 338 (parent ion). Anal. Calcd for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 85.04; H, 5.39.

The second crop on rechromatography on silica gel using CH_2Cl_2–hexane (2:8) and recrystallization from a CH_2Cl_2–hexane mixture gave pale yellow plates (100 mg): mp 268–270°; ir 6.19,

Table I
Ultraviolet Absorption Spectra

Compd	λ_{max}, nm (EtOH)
p-Terphenyl-2,2′,5′,2″-tetracarboxaldehyde (1)[a]	233, 296 (sh)
5,6,12,13-Diepoxy-5,6,12,13-tetrahydrodibenz-[a,h]anthracene (2)[a]	215, 231 (sh), 247, 256, 291 (sh), 304, 318, 334
5,6,12,13-Tetrahydrodibenz[a,h]anthracene[b]	241, 250, 278 (sh), 290, 302, 320, 332
5,12-Dimethoxydibenz[a,h]anthracene[c] (cf. uv of dibenz[a,h]anthracene[16])	224, 257, 278 (sh), 291, 302, 325, 336, 352 (ε 46, 644, 18,590, 43,940, 82,810, 107,822, 16,731, 11,830, 8619)
6,13-Dimethoxydibenz[a,h]anthracene[d]	225, 273, 296, 302, 322, 333, 350 (40,560, 36,504, 77,064, 76,557, 20,111, 15,210, 13,182)
Biphenyl-2,2′,6,6′-tetracarboxaldehyde (3)[a]	233 (sh), 254 (sh), 298
4,5,9,10-Diepoxy-4,5,9,10-tetrahydropyrene (4)[a]	264 (sh), 276, 287, 300
Phenanthrene epoxide[e]	266, 277, 287, 300 (sh)
Dimethoxypyrene, mp 250–252°	234, 243, 255, 265, 276, 298 (sh), 311, 325, 341, 357, 376 (41,134, 73,797, 14,060, 27,248, 46,286, 5240, 11,091, 23,405, 30,304, 5414, 6200)
Dimethoxypyrene, mp 153–155°	220, 230 (sh), 240, 255, 266 (sh), 275, 298 (sh), 305, 319, 330, 350, 376 (27,335, 34,060, 52,400, 20,174, 18,340, 25,152, 10,480, 8733, 11,440, 19,300, 18,602, 1746)

[a] Because of insolubility in many organic solvents, ε values could not be calculated. [b] Registry no., 153-31-1. [c] Registry no., 55400-91-4. [d] Registry no., 55400-92-5. [e] Registry no., 585-08-0.

Table II
Fluorescence Excitation and Emission Spectra

Compd	Solvent and concn	Excitation maxima, nm	Emission wavelength, nm	Emission maxima, nm	Excitation wavelength, nm
5,6,12,13-Diepoxy-5,6,12,13-tetrahydrodibenz[a,h]-anthracene (2)	Cyclohexane, satd soln,[a] deoxygenated	232 (sh), 244 (sh), 253, 290 (sh), 302, 318, 336	355	338, 355, 372, 390 (sh)	334
5,12-Dimethoxydibenz[a,h]-anthracene	Ethanol, 0.04 μg/ml, deoxygenated	253, 281 (sh), 290, 302, 326 (sh), 337 (sh), 357, 375 (sh)	400	400, 423, 449, 480 (sh)	300
6,13-Dimethoxydibenz[a,h]-anthracene	Ethanol, 0.04 μg/ml, deoxygenated	272, 295, 302, 319 (sh), 418, 332, 349, 388	418	408 (sh), 419, 437 (sh)	295
Dimethoxypyrene, mp 250–252°	Ethanol, 0.03 μg/ml, deoxygenated	243, 264, 275, 310 (sh), 324, 339, 353 (sh)	396	377, 396, 417, 440 (sh)	275
Dimethoxypyrene, mp 153–155°	Ethanol, 0.03 μg/ml, deoxygenated	240, 255, 274, 303 (sh), 320 (sh), 355, 348	376	378, 399, 419, 445 (sh)	274

[a] Concentration not determined.

6.24, 6.44, 6.66, 6.85, 6.95, 7.14, 7.26 μm; mass spectrum *m/e* 338 (parent ion). Anal. Calcd for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 85.16; H, 5.30.

Biphenyl-2,2′,6,6′-tetracarboxaldehyde (3). Pyrene (2.02 g) in dry CH_2Cl_2 (400 ml) was ozonized using 2 molar equiv of ozone. Powdered sodium iodide (16 g) and glacial acetic acid (120 ml) were added after concentrating the solution. The reaction mixture was worked up as described for 1 and this gave a pale-yellow product which was purified by silica gel column chromatography with CH_2Cl_2 as eluent. The eluate on concentration and addition of hexane yielded colorless flakes (1.04 g, 39.4%): mp 154–156° (lit.[17] mp 162–163°); ir 3.48, 3.52, 3.62, 3.66 (C–H stretch), 5.95 μm (C=O stretch); NMR ($CDCl_3$) δ 8.2 (m, 6 H, aromatic), 9.86 (s, 4 H, –CHO). Anal. Calcd for $C_{16}H_{10}O_4$: C, 72.18; H, 3.78. Found: C, 72.24; H, 3.89. TLC, R_f 0.75 in CH_2Cl_2–CH_3OH (19.5:0.5).

4,5,9,10-Diepoxy-4,5,9,10-tetrahydropyrene (4). The tetraaldehyde (3, 0.5 g) in dry benzene (30 ml) was refluxed with tris(dimethylamino)phosphine (0.5 ml) for 0.5 hr. On cooling, light-brown needles (0.085 g, 19.3%), mp 206–208° dec, were obtained. The product was recrystallized from dioxane as colorless needles, without change in melting point. It was sparingly soluble in most organic solvents, TLC, R_F 0.64 in cyclohexane–dioxane (1:1). It showed ir 6.93, 8.1, 9.5, 12.2, 12.8 μm; mass spectrum *m/e* 234 (parent ion). Anal. Calcd for $C_{16}H_{10}O_2$: C, 82.04; H, 4.30. Found: C, 81.89; H, 4.40. The diepoxide rearranged to a mixture of phenols when subjected to vacuum sublimation at 175° (0.2 mm).

Acid-Catalyzed Rearrangement of Pyrene Diepoxide to Phenols and Their Subsequent Methylation (5, 6). Pyrene diepoxide (0.4 g) in dry acetone (300 ml) was refluxed with concentrated HCl (0.5 ml) for 0.25 hr. The reaction mixture was worked up and methylated with dimethyl sulfate as described above. The pale-yellow residue [R_f 0.58, CH_2Cl_2–hexane (4:6)] obtained after eluting the silica gel column with CH_2Cl_2–hexane (4:6 v/v) mixture gave two crops on fractional crystallization from CH_2Cl_2–hexane. The first crop crystallized from CH_2Cl_2 as colorless plates (0.09 g): mp 250–252°; ir 6.26, 6.32, 6.66, 6.84, 7.00, 7.14, 8.0, 8.84 μm; mass spectrum *m/e* 262 (parent ion). Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.38; H, 5.38.

The second crop was rechromatographed on silica gel and recrystallized from CH_2Cl_2–hexane as white flakes (0.123 g): mp 153–155°; ir 6.16, 6.26, 6.30, 6.45, 6.68, 7.25, 7.30, 7.95, 9.25 μm; mass spectrum *m/e* 262 (parent ion); NMR ($CDCl_3$) δ 4.12 (s, 6 H, 2-OCH_3), 7.2, 8.0, 8.6 (s, 2 H, m, 4 H, d, 2 H, aromatic). Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.49; H, 5.37.

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Registry No.—1, 55400-86-7; 2, 55400-87-8; 3, 4371-26-0; 4, 55400-88-9; 5, 55400-89-0; 6, 55400-90-3; dibenz[*a,h*]anthracene, 53-70-3; dimethyl sulfate, 77-78-1.

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Synthetic Studies on Phosphorylating Reagent. II.[1] 2-(*N,N*-Dialkylamino)-4-nitrophenyl Phosphate and Its Use in the Synthesis of Phosphate Esters

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2-(*N,N*-Dimethylamino)-4-nitrophenyl phosphate (**6a**) and 2-(*N,N*-diethylamino)-4-nitrophenyl phosphate (**6b**) were prepared from 2-amino-4-nitrophenol (**4**) via three steps. These compounds were activatable in situ by the addition of an acidic catalyst and showed moderate phosphorylating ability toward various alcohols. By the comparison of their reactivities in the reaction with benzyl alcohol, **6a** was shown to be a better phosphorylating agent than **6b**. It reacted readily with an alcohol having an unprotected amino group to give the aminoalkyl phosphate without unfavorable formation of the phosphoroamidate. Reaction with a mercapto alcohol under the same condition gave the *S*-hydroxyalkylphosphorothioate as the main product.

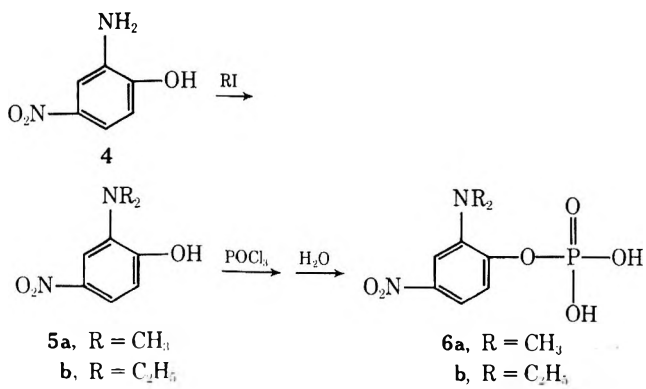
In previous papers,[1-6] we have reported the synthesis of a new phosphorylating reagent, 2-chloromethyl-4-nitrophenyl phosphorodichloridate (**1**), having an activatable protecting group and its use in the preparation of alkyl phosphates. It was shown that the reagent is very useful for the preparation of the valuable alkyl dihydrogen phosphates and dialkyl hydrogen phosphates from the corresponding alcohols. However, it could not be utilized in the phosphorylation of amino alcohols because of reaction with the amino group.

Recently, with a view to developing a milder reagent which could be used in the phosphorylation of amino alcohols, the reactivity of the inner salt of 1-(2-dihydrogenphosphoroxy-5-nitrobenzyl)pyridinium hydroxide (**3**) was investigated.[1] This reagent derived from **1** showed reduced activity and reacted satisfactorily with a *tert*-amino substituted alcohol to afford the *tert*-aminoalkyl phosphate. However, phosphorylation of alcohols which have secondary and primary amino groups resulted in the unfavorable formation of the phosphoroamidate. Another disadvantage of the reagent is its low reactivity and necessity of an excess of alcohol for completion of the reaction.

In the present study, with an aim to develop a more versatile reagent, 2-(*N,N*-dialkylamino)-4-nitrophenyl phosphate (**6**) was designed as a new phosphorylating agent on the following assumptions. The 2-(*N,N*-dialkylamino)-4-nitrophenyl group would function as a protecting group at the first stage, because the strong electron-withdrawing power of the nitro group, which exerts phosphorylating ability, is compensated by the electron-releasing effect of the dialkylamino group. However, upon addition of acidic catalyst the dialkylamino group would be converted into the positively charged ammonium group, which would enhance the electrophilicity of the phosphoryl group. Thus the reaction with a nucleophile such as alcohol and thiol would proceed smoothly. At the same time, it was expected that selective phosphorylation of the hydroxy group in an amino alcohol would be possible because of protonation of the amino group of the reactant under the conditions used.

While Amery and Corbett[7] obtained 2-(*N,N*-dimethylamino)-4-nitrophenol (**5a**) from 2-aminoanisole via three steps, we have attempted the preparation of 2-(*N,N*-dialkylamino)-4-nitrophenol by the selective dialkylation of 2-amino-4-nitrophenol (**4**). Alkylation of **4** with 2.5 molar quantities of methyl or ethyl iodide in the presence of triethylamine proceeded successfully to give the corresponding 2-(*N,N*-dialkylamino)-4-nitrophenol hydrochlorides **5a,b** in 58 and 19% yield, respectively (Chart I). In these al-

Chart I



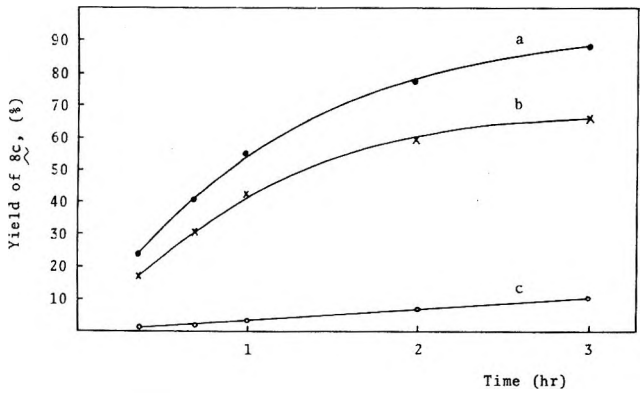


Figure 1. The yield of benzyl dihydrogen phosphate with time, in the reaction of benzyl alcohol (equimolar quantity) with phosphorylating reagents: a, 2-(*N,N*-dimethylamino)-4-nitrophenyl phosphate (**6a**); b, 2-(*N,N*-diethylamino)-4-nitrophenyl phosphate (**6b**); c, inner salt of *N*-(2-dihydrogen phosphoroxy-5-nitrobenzyl)pyridinium hydroxide (**3**).

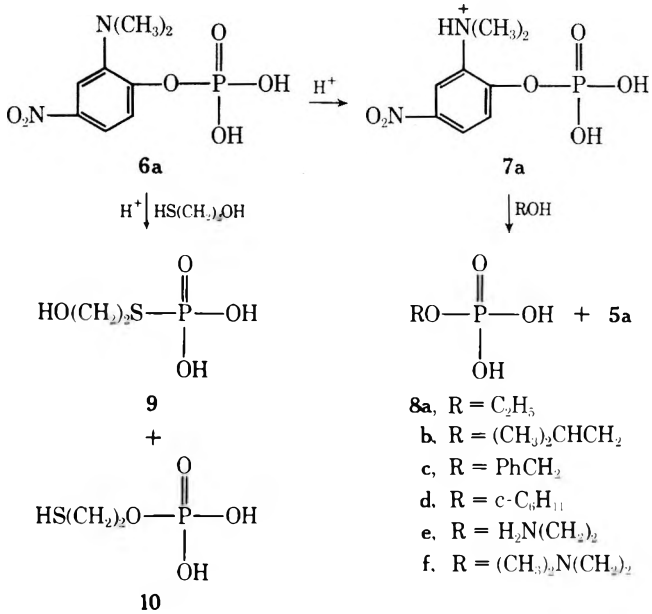
kylations, formation of other alkylated products were observed on TLC; however, their isolation was not attempted. The structure of **5a** was confirmed by NMR spectroscopy. A six-proton singlet assignable to the *N*-methyl protons appeared at 3.29 ppm and no signal attributable to the *O*-methyl protons was observed around 4.20 ppm. The phosphorylating agents **6** were readily prepared by refluxing **5** and 10 mol of phosphoryl chloride for 24 hr followed by mild hydrolysis with ice–water. Both reagents could be isolated as their crystalline ammonium salts, which could be stored in a desiccator for longer than several months without any deterioration.

Initial studies on these reagents were carried out with benzyl alcohol because the formation of product can be followed by its ultraviolet light absorption. A solution of 1 molar amount of the reagent **6**, which was converted into the triethylammonium salt before use, in anhydrous pyridine was allowed to react with an equimolar amount of benzyl alcohol in the presence of acetic acid (3 mol) and triethylamine (1 mol) under reflux for 3 hr. Aliquots were removed from the reaction mixture at various time intervals and worked up as described in the Experimental Section. The products were then chromatographed on Toyo Roshi No. 51A paper in solvent A. The ultraviolet-absorbing spot corresponding to benzyl dihydrogen phosphate[2] was eluted quantitatively and the amount of each was determined spectrophotometrically at 206 nm. The reactivity of **3** under similar reaction conditions was also traced in the same way for comparison. The results recorded in Figure 1 show that the reaction rate of **6a** is moderately faster than that of **6b** and much faster than that of **3**. The increasing reactivity would be in accord with the increasing electronegativities of the positively charged dialkylammonium and the pyridiniummethyl moieties, because they are protonated or quaternized in the reaction media. It was shown experimentally that other acidic catalysts such as H_2SO_4, CF_3CO_2H, and BF_3-Et_2O were also effective. In the absence of the acidic catalyst, the reaction was slower and reached 59% conversion under the same conditions.

Next, a series of experiments was carried out with **6a** to examine the chemical properties of the reagent and the limitations of application. The reactions with primary and secondary alcohols under similar conditions afforded the corresponding alkyl dihydrogen phosphates as monoanilinium salts in good yields. The products were identified with authentic samples prepared by known methods.[2,8] The compound **5a** formed concomitantly was easily recovered from the reaction by extraction with ethyl acetate.

Since phosphorylation of amino alcohols was our main object in this study, the reaction was attempted with 2-aminoethyl alcohols. Treatment of 2-amino- and 2-dimethylaminoethyl alcohol with **6a** in the same way gave 2-amino- (**8e**) and 2-dimethylaminoethyl dihydrogen phosphate (**8f**) in 79 and 73% yield, respectively. The use of equimolar quantities of the reagent **6a** and the reactant, and the fairly good yields, showed that no phosphoroamidate formation occurred in this case. The phosphorylation of 2-mercaptoethyl alcohol afforded a mixture of *S*-(2-hydroxyethyl) dihydrogen phosphorothioate (**9**) and 2-mercaptoethyl dihydrogen phosphate (**10**) in the ratio of 9:1 (Chart II).

Chart II



After the isolation of the mixture as the barium salt, each component was quantitatively determined according to Åkerfeldt's method.[11] It should be noted that predominant formation of the phosphorothioate **9** would be expected, owing to the strong nucleophilicity of the mercapto group.

The new reagent described here seems to have moderate phosphorylating ability toward the alcohol function of unprotected amino alcohols. Since no phosphorylating agent has been reported which does not react with primary amino groups, this procedure should provide a convenient method for the phosphorylation of compounds of biological interest such as nucleosides and aminoglycosides.

Experimental Section

Reagents. Alcohols, amines, and solvents were purified and dried by ordinary procedures. Phosphoryl chloride was freshly distilled before use.

Paper chromatography was carried out by descending technique using Toyo Roshi No. 51A paper. Solvent systems used were: A, isopropyl alcohol–concentrated ammonium hydroxide–water (7:1:2, v/v); B, 1-propanol–concentrated ammonium hydroxide–water (6:3:1, v/v). An uv lamp (254 nm) and Hanes–Isherwood reagent[12] were used for the detection of spots on paper chromatograms.

Melting points are uncorrected and were determined on a Yamato apparatus, Mp-21. The NMR spectra were determined on a Hitachi Perkin-Elmer R-20A instrument (Me_4Si). Ir spectra were determined on a Shimadzu IR-27G spectrometer, and uv spectra on a Hitachi EPS-3T spectrometer.

2-(*N,N*-Dimethylamino)-4-nitrophenol Hydrochloride (5a). To a solution of 2-amino-4-nitrophenol (**4**, 15.4 g, 0.1 mol) and triethylamine (15.1 g, 0.15 mol) in acetone (100 ml) was added drop-

wise methyl iodide (35.6 g, 0.25 mol) with stirring at room temperature for 30 min. The stirring was continued for 4 hr under reflux. Then the reaction mixture was evaporated to dryness under reduced pressure and the resulting syrup was dissolved in 2 *N* sodium acetate (100 ml). The solution was extracted with three 50-ml portions of ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was dissolved in 1 *N* hydrochloric acid and the solution was filtered with charcoal (2 g). The filtrate was evaporated to dryness and the residue was crystallized with ethanol (50 ml).

Recrystallization from methanol–ethyl ether gave **5a** (12.6 g, 58%) as colorless needles: mp 215–216° dec; ν_{max} (Nujol) 2720–2300 ($-^+NH$), 1602, 1497 (Ph), 1520, 1340 cm^{-1} (NO_2); NMR (D_2O) 3.29 (s, 6, 2 CH_3), 7.36 (d, 1, C_6H), 8.28 (q, 1, C_5H), 8.63 ppm (d, 1, C_3H); λ_{max} (H_2O) (pH 6.85) 225.5 nm (ϵ 7670), 259 (5550); (pH 1.55) 223.5 (9000), 306 (9950); (pH 12.3) 279 (7550). Anal. Calcd for $C_8H_{11}N_2O_3Cl$: C, 43.95; H, 5.07; N, 12.81. Found: C, 43.72; H, 5.21; N, 12.91.

2-(*N,N*-Diethylamino)-4-nitrophenol Hydrochloride (5b). To a solution of 2-amino-4-nitrophenol (**4**, 92.5 g, 0.6 mol) and potassium carbonate (93.4 g, 0.69 mol) in acetone (500 ml) was added, dropwise, ethyl iodide (281.1 g, 1.8 mol) with stirring under reflux for 2 hr. The stirring was continued for 4 hr, and then the reaction mixture was evaporated to dryness under reduced pressure. The resulting syrup was dissolved in 2% aqueous sodium hydroxide (500 ml) and the solution was extracted with benzene (200 ml). The aqueous layer was mixed with acetic acid (50 ml) and extracted with three 100-ml portions of ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4, the solvent was removed by evaporation, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was passed through a column of silica gel (2.2 × 60 cm), and the product was eluted with $CHCl_3$–EtOH (10:1, v/v) and the eluates were evaporated to dryness. The residue was dissolved in ethanol (60 ml) and the solution was acidified with 35% ethanolic hydrogen chloride (80 ml). Addition of ether (300 ml) gave precipitates. The precipitates were collected by filtration and recrystallization from ethanol–ethyl ether to give **5b** (27.7 g, 19%) as pale yellow prisms: mp 220–222° dec; ν_{max} (Nujol) 2780–2300 ($-^+NH$), 1609, 1500 (Ph), 1535, 1347 cm^{-1} (NO_2); NMR (D_2O) 1.18 (t, 6, 2 CH_3), 3.80 (q, 4, 2 CH_2), 7.45 (d, 1, C_6H), 8.40 (q, 1, C_5H), 8.74 ppm (d, 1, C_3H); λ_{max} (H_2O) (pH 6.6) 387 nm (ϵ 16,800); (pH 2.0) 225.5 (8000), 305 (9300); (pH 12.5) 230 (8400), 281.5 (5500), 434 (14,800). Anal. Calcd for $C_{10}H_{15}N_2O_3Cl$: C, 48.69; H, 6.13; N, 11.36; Cl, 14.37. Found: C, 48.53; H, 6.25; N, 11.42, Cl, 14.45.

2-(*N,N*-Dimethylamino)-4-nitrophenyl Phosphate (6a). A mixture of 2-(*N,N*-dimethylamino)-4-nitrophenol hydrochloride (**5a**, 33.0 g, 0.15 mol) and phosphoryl chloride (230.4 g, 1.5 mol) was refluxed for 24 hr in the presence of a catalytic amount of potassium chloride (1.5 g) until the evolution of hydrogen chloride ceased. After removal of excess phosphoryl chloride by evaporation, anhydrous toluene (50 ml) was added, and the solution was evaporated repeatedly by adding anhydrous toluene (three 50-ml portions). The viscous residue was poured into ice–water (500 g). Pyridine (16 g) was added to the aqueous solution, which was stirred for 30 min. The solution was then passed through a column of Amberlite IR-45 resin (OH^- form, 2.2 × 50 cm) and the column was washed with water (500 ml). Concentrated ammonium hydroxide (28%) (4 ml) was added to the eluate. The solution was passed through a column of Dowex-50 (NH_4^+ form, 1.4 × 45 cm) and the column was washed with water (200 ml). The eluate was evaporated to dryness below 40°. The residue was crystallized with ethanol (200 ml) and yellow crystals were collected by filtration. Recrystallization from methanol–ethyl ether gave **6a** monoammonium salt (34.0 g, 81%) as pale yellow prisms: mp 171–172.5°; ν_{max} (Nujol) 3250–3050 ($-^+NH_4$), 1580, 1500 (Ph), 1510, 1352 (NO_2), 1278 (P=O), 1135, 1110 cm^{-1} (POC); NMR (D_2O) 2.97 (s, 6, 2 CH_3), 7.60 (d, 1, C_6H), 8.07 (q, 1, C_5H), 8.16 ppm (d, 1, C_3H); λ_{max} (H_2O) (pH 6.85 and 12.3) 228.5 nm (ϵ 12,400), 257 (14,400), 330 (9400); (pH 1.84) 217.5 (13,400), 283 (13,400). Anal. Calcd for $C_8H_{14}N_3O_6P{\cdot}O{\cdot}5H_2O$: C, 33.34; H, 5.25; N, 14.58. Found: C, 33.62; H, 5.33; N, 14.60.

2-(*N,N*-Diethylamino)-4-nitrophenyl Phosphate (6b). In a similar manner as described for **6a**, **6b** was obtained from 2-(*N,N*-diethylamino)-4-nitrophenol hydrochloride (**5b**) and phosphoryl chloride in 50% yield as a pale yellow powder: mp 161–164° (aqueous ethanol); ν_{max} (Nujol) 3250–3100 ($-^+NH_4$), 1585, 1495 (Ph), 1522, 1350 (NO_2), 1270 (P=O), 1171, 1120 cm^{-1} (POC); NMR (D_2O) 1.05 (t, 6, 2 CH_3), 3.24 (q, 4, 2 CH_3), 7.70 ppm (s, 3, Ph); λ_{max} (H_2O) (pH 6.6) 223 nm (ϵ 8600), 302.5 (9000); (pH 2.0) 219 (10,000), 285 (9700); (pH 12.5) 232 (7750), 261.5 (8600), 316 (7700).

Table I
Alkyl Dihydrogen Phosphates and 2-Aminoethyl Dihydrogen Phosphates 8

Compd[a]	Yield, %	Mp, °C	R_f
8a[b]	80	164–165	0.21[c]
8b[b]	86	154–156	0.53[d]
8c[b]	83	166–168	0.38[c]
8d[b]	65	170–171	0.42[c]
8e	79	234–235	0.12[c]
8f	73	78–80	0.18[c]

[a] The compounds were identified with authentic samples.[2,8-10] [b] Alkyl dihydrogen phosphates were isolated as their monoanilinium salts. [c] Solvent A. [d] Solvent B.

Anal. Calcd for $C_{10}H_{18}N_3O_6P{\cdot}0.33H_2O$: C, 38.40; H, 5.76; N, 13.40. Found: C, 38.56; H, 5.98; N, 13.62.

Alkyl Dihydrogen Phosphate 8a–d. General Procedure. To a solution of **6a** monotriethylammonium salt (3.63 g, 0.01 mol) in pyridine (30 ml) was added the alcohol (0.01 mol), acetic acid (1.80 g, 0.03 mol), and triethylamine (1.01 g, 0.01 mol). The reaction mixture was refluxed for 3 hr and concentrated to dryness. The residue was dissolved in water (50 ml). The solution was passed through a column of Dowex 50 (H^+ form, 1.0 × 50 cm) and the column was washed with water. The eluate was neutralized by the addition of aniline and evaporated to dryness under reduced pressure. The residue was crystallized from ethanol. Recrystallization from 95% ethanol gave the corresponding alkyl dihydrogen phosphates monoanilinium salts **8a–d** listed in Table I.

2-Aminoethyl Dihydrogen Phosphate 8e,f. General Procedure. To a solution of **6a** monotriethylammonium salt (3.63 g, 0.01 mol) in pyridine (30 ml) was added the 2-aminoethyl alcohol (0.01 mol), concentrated sulfuric acid (1.96 g, 0.02 mol), and triethylamine (1.01 g, 0.01 mol). The reaction mixture was refluxed for 3 hr and evaporated to dryness. The residue was dissolved in water (60 ml). Barium hydroxide (10.0 g, 0.032 mol) was added to the solution, which was saturated with carbon dioxide. After removal of the precipitates by filtration, the filtrate was adjusted to pH 4 with 10% H_2SO_4 and the precipitates were again removed by filtration. The filtrate was concentrated to dryness and the residue was crystallized from ethanol. Recrystallization from aqueous ethanol gave the corresponding 2-aminoethyl dihydrogen phosphates **8e,f** listed in Table I.

Phosphorylation of 2-Mercaptoethyl Alcohol using 6a. To a solution of **6a** monotriethylammonium salt (3.63 g, 0.01 mol) in pyridine (30 ml) was added 2-mercaptoethyl alcohol (0.78 g, 0.01 mol), acetic acid (1.80 g, 0.03 mol), and triethylamine (1.01 g, 0.01 mol). The reaction mixture was heated under reflux for 3 hr and evaporated to dryness. The residue was dissolved in water (40 ml). The solution was passed through a column of Dowex 50 (H^+ form, 2.8 × 40 cm) and the column was washed with water. The eluate and the washings were combined and neutralized with barium hydroxide. The precipitates were removed by filtration, the filtrate was evaporated to dryness, and the residue was crystallized with ethanol to give the crude barium salt (0.55 g). Paper chromatography (solvent B) exhibited two spots at R_f 0.23 and 0.30 as detected by Hanes–Isherwood's spray. The higher R_f spot was positive toward nitroprusside reagent, showing that the product is a mixture of 2-hydroxyethyl dihydrogen phosphorothioate (**9**) and 2-mercaptoethyl dihydrogen phosphate (**10**).

As an attempt to separate the mixture by DEAE cellulose column chromatography failed, the ratio of the products was determined to be 9:1 (**9**:**10**) by means of iodine titration according to Åkerfeld's method.[11]

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Registry No.—**4**, 99-57-0; **5a**, 55428-48-3; **5b**, 55428-49-4; **6a** monoammonium salt, 55428-50-7; **6a** monotriethylammonium salt, 55428-52-9; **6b** monoammonium salt, 55428-53-0; **8a**, 55428-54-1; **8b**, 55428-55-2; **8c**, 55428-56-3; **8d**, 55428-57-4; **8e**, 1071-23-4; **8f**, 6909-62-2; **9**, 55428-58-5; **10**, 55428-59-6; methyl iodide, 74-88-4;

ethyl iodide, 75-03-6; phosphoryl chloride, 10025-87-3; ethanol, 64-17-5; isobutyl alcohol, 78-83-1; benzyl alcohol, 100-51-6; cyclohexanol, 108-93-0; 2-aminoethanol, 141-43-5; 2-(dimethylamino)-ethanol, 108-01-0; 2-mercaptoethyl alcohol, 60-24-2.

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Micellar Effects upon the Reactions of 2,4-Dinitrophenyl Phosphate and Ethyl *p*-Nitrophenyl Phosphate with Amines

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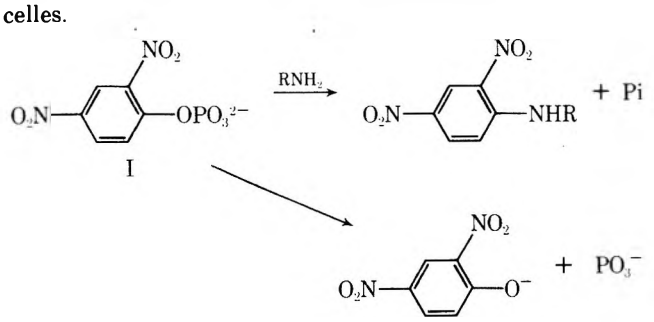
The spontaneous hydrolysis of 2,4-dinitrophenyl phosphate dianion (I) is catalyzed by cationic micelles of the choline-derived surfactant (II, n-$C_{16}H_{33}N^+Me_2CH_2CH_2OHBr^-$), but this surfactant is no more effective than cetyltrimethylammonium bromide, CTABr. Zwitterionic micelles (III, n-$C_{12}H_{25}N^+Me_2CH_2CO_2^-$) are relatively ineffective catalysts. Added primary amines increase reaction rate in the presence of micelles of CTABr or II, but much of the rate enhancement is due to attack by amine upon the aryl group. The effect of the amine increases with its chain length, but secondary amines have less effect, and no attack on the aryl group was found with tertiary amines. The reaction of ethyl *p*-nitrophenyl phosphate monoanion in the presence of CTABr or II is slightly inhibited by added primary amine. In the absence of micelles, amines increase overall reaction rate by attacking the aryl group without markedly catalyzing hydrolysis.

Micelles of cationic surfactants catalyze spontaneous hydrolyses of 2,4- and 2,6-dinitrophenyl phosphate[2,7a,b] and bimolecular nucleophilic attack upon di- and trisubstituted phosphate esters,[7b,8] and cationic surfactants containing nucleophilic[9a,b] or basic[10] groups are effective reagents for attack upon phosphoryl groups of di- and trisubstituted phosphates. Bimolecular attack upon phosphate ester dianions makes little contribution to the overall reaction in the presence or absence of micelles, except at very high pH,[7a,11-13] and in the absence of micelles amines can attack *p*-nitrophenyl phosphate upon the aryl group, as well as speed formation of *p*-nitrophenoxide ion.[14]

There are similarities between the spontaneous hydrolyses of dinitrophenyl phosphate dianions and 2,4-dinitrophenyl sulfate monoanion, in that both involve phenoxide ion elimination,[15] and are catalyzed by cationic micelles,[16] which also markedly change the relative importance of spontaneous hydrolysis of 2,4-dinitrophenyl sulfate monoanion and bimolecular attack by amines upon the aryl group.

The main aim of the present work was to investigate micellar effects upon the reactions of 2,4-dinitrophenyl phosphate dianion (I) in the presence of aliphatic amines which could in principle affect rate and products either by attacking the substrate or by changing the structure of the micelles.



The surfactants used in this work were cetyltrimethylammonium bromide (CTABr, n-$C_{16}H_{33}N^+Me_3Br^-$), *N,N*-dimethyl-*N*-2-hydroxyethylhexadecylammonium bromide (II), n-$C_{16}H_{33}N^+Me_2CH_2CH_2OHBr^-$, and *N,N,N*-dodecyldimethylglycine (III, n-$C_{12}H_{25}N^+Me_2CH_2CO_2^-$). We examined micelles of II because they are effective catalysts for attack upon di- and trisubstituted phosphate esters,[9b] and of III because they are effective catalysts for spontaneous decarboxylations.[17,18] A few experiments were made using ethyl *p*-nitrophenyl phosphate monoanion, because its reactions at high pH are catalyzed by micelles of II and CTABr.[9b]

Experimental Section

Materials. The preparation and purification of the surfactants and the phosphate esters have been described.[7,8,12] Samples of cyclohexylammonium-2,4-dinitrophenyl phosphate were 98–99% pure based on complete hydrolysis both chemically and enzymically using bacterial (*E. coli*) alkaline phosphatase.

Kinetics. The reactions were followed spectrophotometrically using a Gilford spectrophotometer with a water-jacketed cell compartment at 25.0°. The reactions of 2,4-dinitrophenyl phosphate dianion were followed at 358 nm and those of ethyl *p*-nitrophenyl phosphate monoanion were followed at 410 nm.[7-9,12] The first-order rate constants, k_ψ, are in reciprocal seconds. The rate constants for reactions in the absence of surfactants and in the presence of amines are the mean of at least duplicate measurements which agreed within 5%. All the reactions were at a sufficiently high pH that the amines were unprotonated. The substrate concentrations were ca. 2×10^{-5} *M*. The symbol C_D denotes the concentration of surfactant (detergent).

Products. The relative amounts of amine and phenoxide ion were determined after complete reaction of 2,4-dinitrophenyl phosphate by measuring the absorbance at 358 nm of the mixture of *N*-alkyl-2,4-dinitroaniline and 2,4-dinitrophenoxide ion and then reducing the pH of the solution so that the phenoxide ion was converted into phenol and the nitroaniline was unaffected. Under our conditions the difference, $\Delta\epsilon$, of the extinction coefficients of 2,4-dinitrophenoxide ion (ϵ 13,000) and 2,4-dinitrophenol (ϵ 2100) was 10,900 and was unaffected by added 0.01 *M* CTABr. We veri-

Table I
Effect of Added Amines on the Micellar Catalyzed Reactions of Ethyl *p*-Nitrophenyl Phosphate[a,c]

Amine	Registry no.	C_{amine}, M	$10^2 k_\psi$, sec^{-1}
			1.26
			2.30[b]
n-$C_6H_{13}NH_2$	111-26-2	0.01	1.14
n-$C_6H_{13}NH_2$		0.02	0.99
n-$C_8H_{17}NH_2$	111-86-4	0.01	0.96
n-$C_8H_{17}NH_2$		0.02	0.89
n-$C_{10}H_{21}NH_2$	2016-57-1	0.007	1.19
n-$C_{10}H_{21}NH_2$		0.01	1.21
n-$C_{10}H_{21}NH_2$		0.02	1.15
n-$C_{12}H_{25}NH_2$	124-22-1	0.02	1.21
n-$C_{12}H_{25}NH_2$		0.02	2.16[b]

[a] At 25.0° with 0.02 M surfactant, n-$C_{12}H_{25}N^+Me_2CH_2CH_2OHBr^-$ unless specified, and 0.1 M NaOH. In the absence of added surfactant[9b] $10^2 k_\psi$ = 0.075 sec^{-1}. [b] n-$C_{16}H_{33}N^+Me_2CH_2CH_2OHBr^-$. [c] Registry no., 17659-67-5.

fied that the absorbances of several of the *N*-alkyl-2,4-dinitroanilines were unaffected by this pH change. These experiments were done with 1.91×10^{-5} M 2,4-dinitrophenyl phosphate so that $[ArO^-] = 100\Delta A/(1.09 \times 0.191)$, where ΔA is the absorbance change on decreasing the pH and the concentration of ArO^- is in mole percent. Correction was made for the small amount of 2,4-dinitrophenoxide ion which was formed while the solutions were being made up.

Complete hydrolysis of 2,4-dinitrophenyl phosphate dianion in the presence of micellized II gives wholly phenoxide ion, as shown by the visible spectra at high and low pH, but in order to eliminate the possibility that the alkoxide moiety of II attacks the aryl group of 2,4-nitrophenyl phosphate with buildup of a 2,4-dinitrophenyl ether we made repetitive scans using 0.01 M surfactant and 0.01 M NaOH. There was a well-defined isosbestic point at 326 nm, plots of log $(A_\infty - A_t)$ against time were linear and parallel to each other when calculated from absorbances at 300, 347, 353, 358, 365, 370, 380, and 395 nm, and the spectrum of the product was that of 2,4-dinitrophenoxide ion. These repetitive scans were carried out using a Cary 15 spectrophotometer, using 0.1 M NaOH, 5×10^{-3} M II, and 4.3×10^{-5} M substrate and the average value of $k_\psi = 2.6 \times 10^{-4}$ sec^{-1} is in reasonable agreement with $k_\psi = 2.8 \times 10^{-4}$ sec^{-1} determined using 2×10^{-5} M substrate (Figure 1), so that it is safe to conclude that no other product is formed in appreciable concentration during reaction.

Results and Discussion

Reactions of Ethyl *p*-Nitrophenyl Phosphate. This hydrolysis is catalyzed by micelles of CTABr, and especially by functional micelles of the choline derivative (II).[9b] The rate constants for reaction in the absence of added amine agree with earlier results and added amines slightly reduce the reaction rate in the presence of micelles (Table I). Apparently nucleophilic attack by the amine upon this ester is too slow to compete with that of hydroxide ion or the alkoxide ion (IV) derived from II, and the rate reduction is caused by a change in micellar structure.

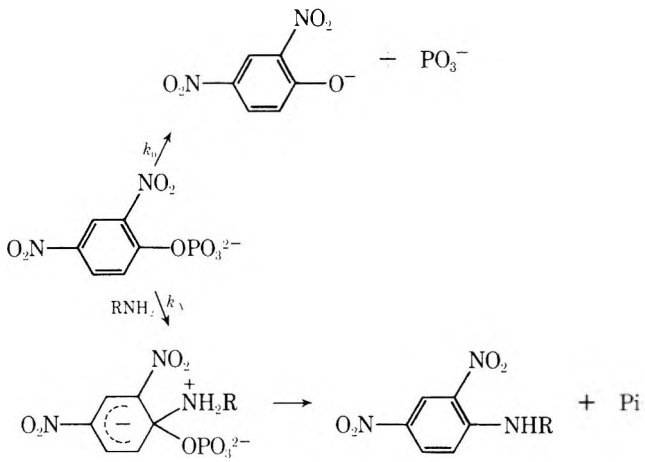
$$\underset{\text{II}}{RNMe_2CH_2CH_2OH} + OH^- \rightleftharpoons \underset{\text{IV}}{RNMe_2CH_2CH_2O^-}$$

$$R = n\text{-}C_{12}H_{25};\ n\text{-}C_{16}H_{33}$$

Nonmicellar Reactions of 2,4-Dinitrophenyl Phosphate Dianion in the Presence of Alkylamines. In the absence of surfactant, *n*-alkylamines increase the rate of the overall reaction, and both 2,4-dinitrophenoxide ion and *N*-alkyl-2,4-dinitroaniline are formed (Table II).

The rate of hydrolysis of the dianion of 2,4-dinitrophenyl phosphate is independent of pH until the hydroxide ion concentration is relatively large (>0.1 M),[11,12] and if the only effect of the added amine is to introduce a new reaction (attack upon the 2,4-dinitrophenyl group, Scheme I), k_0, the first-order rate constant for the spontaneous hydrolysis, calculated from the overall rate constants and the product composition (eq 1) should agree with the values of

Scheme I



$$k_0 = k_\psi/\{1 + ([ArNHR]/[AOH])\} \quad (1)$$

$k_0 = 0.83 \times 10^{-5}$ sec^{-1} (Table II and ref 12). The product compositions calculated from the values of k_0 and k_ψ and the results in Table II are in reasonable agreement with those observed. The amines might comicellize with the substrate; for example, comicelles have been observed in reactions of *n*-alkylamines with hydrophobic carboxylic esters,[19] and hydrophobic interactions between carboxylic esters and monomeric alkylamines also appear to be important.[20] However, the rate of spontaneous hydrolysis of 2,4-dinitrophenyl phosphate dianion is independent of added nonionic micelles[7a] and Table II shows that ethyl-, benzyl-, and *n*-hexylamine behave similarly, so that micellization with the amine is apparently unimportant. Hexamethylenediamine is a more effective reagent than the other primary amines, probably because the concentration of amino groups is twice that of a solution of equimolar primary amine.

Within experimental error the rate enhancements by added amine can be accounted for largely, but not completely, in terms of introduction of a new reaction, and there is some amine catalysis of the hydrolysis of 2,4-dinitrophenyl phosphate dianion (cf. ref 14).

General base catalysis of amine attack upon the *p*-nitrophenyl group was observed,[14a] and is explained in terms of loss of a proton from the tetrahedral intermediate which assists conversion of this intermediate to products.[21] However, our experiments were done in alkaline solution (0.01 M NaOH), so that proton loss should be rapid and not part of the rate-limiting step.

Micellar Catalyzed Hydrolysis of 2,4-Dinitrophenyl Phosphate Dianion. The pattern of the micellar catalysis is very simple in that the choline surfactant (II) is only a slightly better catalyst than CTABr (Figure 1), even at high pH where it is converted partially into the zwitterion IV, even though there is marked catalysis of reactions of di- and trisubstituted phosphate esters by II.[9b] (Our rate constants for the reaction in CTABr agree with those determined earlier.[7a]) The reaction of 2.4-dinitrophenyl phosphate dianion in the presence of II gives wholly 2,4-dinitrophenoxide ion (Experimental Section). Added hydroxide ion slightly increases the reaction rate at high concentration of II, possibly because of the nucleophilicity of the alkoxide ion moiety in IV (cf. ref 12, 13), but the small effect

Table II
Effect of Amines on the Reaction of 2,4-Dinitrophenyl Phosphate[f] in the Absence of Micelles[a]

Amine	Registry no.	$10^5 k_\psi$, sec^{-1}	[Phenol][b] Obsd	[Phenol][b] Calcd[c]	$10^5 k_0$,[c] sec^{-1}
		0.83[d]			
$C_2H_5NH_2$	75-04-7	1.04	74	80	0.77
$C_2H_5NH_2$[e]		1.70	55	49	0.93
$C_6H_{13}NH_2$		1.19	70	70	0.83
$C_6H_{13}NH_2$[e]		2.30	47	36	1.10
c-$C_6H_{11}NH_2$	108-91-8	1.00	79	83	0.79
$PhCH_2NH_2$	100-46-9	1.05	74	79	0.78
$PhCH_2NH_2$[e]		1.86	55	45	1.09
$PhCH_2CH_2NH_2$	64-04-0	1.30	73	64	0.94
$H_2N(CH_2)_5NH_2$	124-09-4	1.41	64	59	0.90

[a] At 25.0° in 0.01 *M* NaOH and 0.01 *M* amine unless specified. [b] Mole percent. [c] Calculated using eq 1. [d] Reference 12. [e] 0.05 *M* amine. [f] Registry no., 2566-26-9.

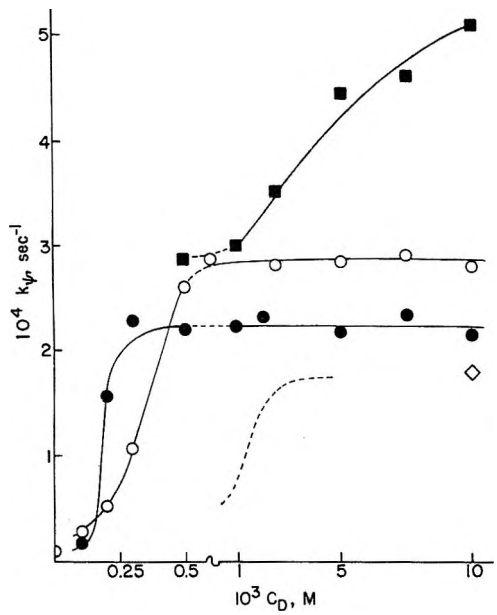


Figure 1. Reaction of 2,4-dinitrophenyl phosphate dianion at 25.0° in the presence of II (R = $C_{16}H_{33}$): ●, 0.01 *M* NaOH; ■, 0.01 *M* NaOH + equimolar *n*-hexylamine and II; ○, 0.1 *M* NaOH. The broken line is for reaction in CTABr at pH 9 (ref 7a), and ◊ is for 0.01 *M* NaOH in CTABr.

of hydroxide ion on k_ψ (Figure 1) shows that nucleophilic attack by IV is not a major reaction path.

The relation between k_ψ and concentration of II is typical of those observed for unimolecular reactions, with k_ψ increasing smoothly to a plateau value as the substrate is taken up by the micelles.[6,7]

The catalysis of the spontaneous hydrolysis of 2,4-dinitrophenyl phosphate by cationic micelles of CTABr is similar to, but smaller than, those upon spontaneous decarboxylations and in both reactions the negative charge of the substrate is delocalized in the transition state,[17,18,22] and both reactions are favored by addition of organic solvents to the aqueous solution.[11,12,23] Micelles of zwitterionic surfactants are very effective catalysts of decarboxylation,[17,18] but not of the spontaneous hydrolysis of 2,4-dinitrophenyl phosphate dianion (Table III). The high catalytic efficiency of zwitterionic micelles in decarboxylation was rationalized on the assumption that initial state Coulombic repulsions between the carboxylate moieties of the substrate and surfactant were lost in forming the carbanion-like transition state, which should interact much more strongly with the

Table III
Hydrolysis of 2,4-Dinitrophenyl Phosphate Dianion in the Presence of Zwitterionic Micelles of III[a]

$10^2 C_D$, *M*	pH 7[b]	0.01 *M* NaOH	0.1 *M* NaOH
0.33	10.6	9.23	11.4
2.00	15.7	14.3	10.5

[a] Values of $10^6 k_\psi$, sec^{-1}, at 25.0°. In the absence of surfactant $10^6 k_\psi = 8.3\ sec^{-1}$ at pH 6-12. [b] 0.02 *M* Tris buffer.

quaternary ammonium centers of a zwitterionic micelle than with water. The difference between the two systems may be that the transition state for hydrolysis of a phosphate dianion has considerable phenoxide ion like character.[11,12] A phenoxide ion, having considerable negative charge on oxygen, should be a harder base than a carbanion and would therefore gain less than the latter from interactions with such a soft reagent as a quaternary ammonium ion, relative to the interactions with water,[24] so that the greater cationic micellar catalysis of decarboxylation as compared with spontaneous phosphate ester hydrolysis can be rationalized in terms of this hard–soft reagent classification.

Effect of Amines upon the Micellar Catalyzed Reactions. The reactions of I in the presence of surfactants and added amines were examined at surfactant concentrations high enough that all the substrate is incorporated into the micelles. The addition of amines to cationic micelles of CTABr or II increases the rate constant for the overall reaction (Tables IV and V). However, as in the absence of surfactants, at least part of the rate increase is due to the incursion of a new reaction involving attack by the amine on the aryl group (Scheme I), although additions of amine will change the micellar structure and hence may affect the rate of heterolysis in the micelle. The reaction rate increases with increasing reagent and surfactant concentration with an equimolar mixture of the surfactant (II) and *n*-hexylamine (Figure 1), but here we do not observe the rate plateau which is found for the catalyzed unimolecular hydrolysis of the phosphate ester dianion in the absence of amine.

The overall rate constants and the products are shown in Tables IV and V. Fluoride ion was also examined as a nucleophile which shows high reactivity toward the phosphoryl group of di- and trisubstituted phosphates,[8] but it is unreactive in this system.

Added amines could change the overall reaction rate in the presence of cationic micelles, (1) by attacking the aryl

Table IV
Effect of Added Nucleophiles on the Reaction of 2,4-Dinitrophenyl Phosphate in Micelles of CTABr[a]

Reagent	$10^4 k_\psi$, sec^{-1}	[Phenol][b] Obsd	[Phenol][b] Calcd	$10^4 k_0^{mc}$, sec^{-1}
	1.81	100		
NaF	1.91	100		1.91
c-$C_6H_{11}NH_2$	1.82	93	99	1.69
$PhCH_2NH_2$	2.23	92	81	2.04
$H_2N(CH_2)_6NH_2$	2.21	89	82	1.97
$PhCH_2CH_2NH_2$	3.06	67	59	2.03
n-$C_6H_{13}NH_2$	5.05	46	36	2.32
n-$C_8H_{17}NH_2$	7.96	22	23	1.74
n-$C_9H_{19}NH_2$[d]	8.72	23	21	1.99
n-$C_{10}H_{21}NH_2$	9.63	34	19	3.34
n-$C_{12}H_{25}$-NHMe[e]	2.59	86	70	2.24
n-$C_{12}H_{25}$-NMe_2[f]	1.40	100		1.40

[a] At 25.0° in 0.01 *M* CTABr, 0.01 *M* NaOH, and 0.01 *M* reagent. [b] Mole percent. [c] Calculated using eq 1. [d] Registry no., 112-20-9. [e] Registry no., 7311-30-0. [f] Registry no., 112-18-5.

group to give an *N*-alkyl-2,4-dinitroaniline, (2) by assisting P–O scission with formation of phenoxide ion, cf. ref 14, or (3) by changing the micellar structure.

If 1 is of importance, as it is for the nonmicellar reaction (Table II), the values of k_0^m, the first-order rate constant for spontaneous hydrolysis in the micellar system, calculated using eq 1 should agree with those determined directly. Alternatively we could predict the product composition from the rate constants in the presence and absence of amines.

This condition is only qualitatively fulfilled for most of the amines (Tables IV and V). For example, *n*-decylamine increases the reaction rates in the presence of micelles of both CTABr and the choline surfactant II more than predicted by the product composition, whereas *N,N,N*-dimethyldodecylamine reduces the overall rate.

The relative amount of attack by the amine upon the 2,4-dinitrophenyl group increases with increasing length of the *n*-alkyl group of the primary amine and secondary amines are relatively ineffective. Hexamethylenediamine is much less effective than *n*-hexylamine both in increasing overall reaction rate and acting as a nucleophile, probably because having two relatively hydrophilic amino groups it does not fit readily into the micelle, whereas the *n*-alkylamines can insert readily into a micelle with the amino group at its surface and close to the substrate.

For a series of *n*-alkylamines the overall rate enhancements approximately follow the increasing amounts of amine attack (Tables IV and V). However, the correlation is not exact; for example, in reactions in micelles of CTABr *n*-decylamine gives the maximum overall rate, but the maximum yield of amine is given by *n*-octylamine, and with micelles of II the maximum rate is found with *n*-nonylamine and the maximum yield of amine with *n*-octylamine, suggesting that part of the effect of the amine is indeed to modify the micellar structure and therefore its catalytic effectiveness. (We assume that the amine will not act as a general base catalyst of breakdown of a tetrahedral intermediate at the pH of our experiments.) Bimolecular attack upon the phosphoryl residue seems to be relatively unimportant, and as in the absence of surfactant there is little amine catalysis of hydrolysis in the presence of micelles (Tables IV and V).

Table V
Effect of Amines on the Reaction of 2,4-Dinitrophenyl Phosphate in Micelles of II[a]

Amine	$10^4 k_\psi$, sec^{-1} 0.01 *M* OH^-	$10^4 k_\psi$, sec^{-1} 0.1 *M* OH^-	[Phenol][b] Obsd	[Phenol][b] Calcd	$10^4 k_0^{mc}$
	2.32	3.27	100		
$PhCH_2CH_2NH_2$	3.70		59	62	2.19
n-$C_6H_{13}NH_2$	5.10		44	45	2.23
n-$C_8H_{17}NH_2$	8.41	8.43	21	27	1.80
n-$C_9H_{19}NH_2$	10.8	11.3	25	20	2.70
n-$C_{10}H_{21}NH_2$	9.18	9.92	36	25	3.30
n-$C_{12}H_{25}NHMe$	2.63		83	88	2.18

[a] At 25.0° in 0.01 *M* II (R = $C_{16}H_{33}$) and 0.01 *M* amine. [b] Mole percent. [c] In 0.01 *M* NaOH. and calculated using eq 1.

It is not surprising that the optimum *n*-alkyl groups are different for maximum rate and maximum yield of amine. Amine attack upon the 2,4-dinitrophenyl group requires the amino and aryl groups to be favorably juxtaposed in the micelle, and this is not necessarily the condition for maximum catalytic efficiency of the micelle which depends upon its overall interactions with initial and transition states, and in addition micellar catalysis is often sensitive to the addition of small amounts of added solutes (cf. ref 4–7).

Micellar Effects upon Hydrolysis and Amine Attack. It is difficult to make meaningful comparisons of micellar effects upon hydrolysis and amine attack, because hydrolysis is a unimolecular reaction whose micellar catalysis depends only upon substrate incorporation and rate constant in the micellar pseudophase, whereas incorporation of both the substrate and the amine is important in the bimolecular reaction with an amine.

For the reactions shown in Scheme I the product ratio is given by eq 2.

$$[ArNHR]/[ArOH] = k_A[RNH_2]/k_0 \quad (2)$$

In the absence of surfactant the rate constants $k_A[RNH_2]$ and k_0 for Scheme I should be approximately independent of the length of the alkyl group of a primary alkylamine provided that the amine has no medium effect on the reactions. The values of $k_A[RNH_2]/k_0$ calculated for 0.01 *M* amine are similar for the monoamines which we examined (Table VI). The lower value for cyclohexylamine is understandable in terms of steric hindrance by the cyclohexyl group, and the larger value for hexamethylenediamine is understandable in terms of the higher concentration of amino groups. However, even in the absence of surfactant there are anomalies, for example k_A/k_0 decreases somewhat with increasing amine concentration, which is consistent with a weak amine catalysis of the hydrolysis (cf. ref 14). In addition both benzylamine and *n*-hexylamine give slightly larger values of k_A/k_0 than expected in terms of their basicities, and because these amines are more hydrophobic than ethylamine it seems that eq 1 and 2 are inadequate even for reaction in the absence of micelles. Amines weakly catalyze the hydrolysis of *p*-nitrophenyl and 2,4-dinitrophenyl phosphate dianion, probably by a medium effect, because of the insensitivity of the catalysis to amino basicity,[14] and our data are consistent with that hypothesis.

The situation is more complex for reaction in the presence of surfactant because the distribution of an amine between water and the micelles depends upon its concentration and structure and especially upon its hydrophobicity.

Table VI
Relative Rates of Amine Attack and Spontaneous Hydrolysis in the Presence and Absence of Surfactants[a]

Amine	Medium H_2O	0.01 *M* CTABr	0.01 *M* II[b]
$EtNH_2$	0.35 (0.82)		
n-$C_6H_{13}NH_2$	0.43 (1.13)	1.17	1.27
n-$C_8H_{17}NH_2$		3.55	3.76
n-$C_9H_{19}NH_2$		3.35	3.00
n-$C_{10}H_{21}NH_2$		1.94	1.78
c-$C_6H_{11}NH_2$	0.27	0.09	
$PhCH_2NH_2$	0.35 (0.82)	0.09	
$H_2N(CH_2)_6NH_2$	0.56[c]	0.12[c]	
$PhCH_2CH_2NH_2$	0.37	0.49	0.69
n-$C_{12}H_{25}NHMe$		0.16	0.21

[a] Values of $k_A[RNH_2]/k_0$ for 0.01 *M* amine, except for values in parentheses which are for 0.05 *M* amine. [b] R = $C_{16}H_{33}$. [c] Calculated using the molarity of the diamine.

In addition the rate constants for amine attack in the micelles will depend upon the hydrophobicity of the alkyl group, which will determine the extent to which the amino group is brought into the Stern layer of the micelle close to the aryl group of the substrate. The effects of reagent hydrophobicity in governing both the distribution of reagents between water and reactivity in the micellar pseudophase are well recognized.[3-6,26-28] Changes in micelle structure caused by incorporation of the amine may also affect the rate constants for both amine attack and hydrolysis in the micellar pseudophase. Despite the problems in separating the various factors which could affect values of k_0 and k_A both in the presence and absence of micelles it is evident that the structure of the organic residue of the amine is of key importance in the micellar reaction (Table VI), although our evidence does not distinguish between effects due to partitioning of the amine between water and the micelle and to reactivity differences in the micelle, although the partitioning cannot be the sole cause of the variations of k_A/k_0 which decreases with increasing length of the *n*-alkyl group above C_8 (Table VI).

Our results are therefore somewhat different from those of Fendler, Fendler, and coworkers for reactions of 2,4-dinitrophenyl sulfate.[16] The spontaneous hydrolysis of this ester, unlike that of 2,4-dinitrophenyl phosphate, is only weakly catalyzed by cationic micelles, which have a much larger effect upon the bimolecular attack of amines upon the aryl group so that here it is possible to change the product composition markedly by carrying out the reaction in the presence of cationic surfactant. In our reactions of 2,4-dinitrophenyl phosphate the cationic micelles assist amine attack, relative to hydrolysis, but only for the relatively hydrophobic *n*-alkylamines. (*n*-Hexylamine was the most hydrophobic *n*-alkylamine that we could use in the absence of surfactant.) Both cyclohexyl- and benzylamine are less effective reagents in CTABr than in water (relative to hydrolysis), probably because they fit into the micelles in such a way that the amino group is not favorably placed for reaction; for example the cyclohexyl group should fit less readily into the micelle than an *n*-alkyl group, and the decrease of reactivity shown by *n*-nonyl- and decylamine relative to *n*-octylamine could arise because the hydrophobic *n*-alkyl group takes this amine too deeply into the micelle.

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Trichlorosilane Reduction of Some Diazaphospholene Oxides

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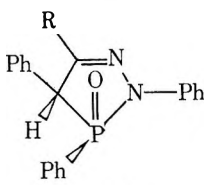
Trichlorosilane reduction of pure diazaphospholene oxides gives mixtures of cis and trans isomers of the corresponding phosphines; their configuration has been deduced from their NMR spectra. The lack of stereospecificity is explained in terms of formation of pentacoordinate phosphorus intermediates. Stereomutation of the starting phosphine oxides is observed on treatment with hexachlorodisiloxane as well as with silicon tetrachloride.

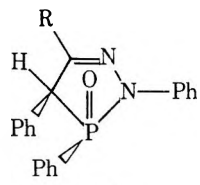
In the initiation of a general program designed to explore the synthesis,[1] chemical reactions, and physical properties of some derivatives of 1,2-diaza-5-phospholene 3-oxide which represent the first cases of a new heterocyclic system, we were prompted to investigate the trichlorosilane reduction of these compounds.

Several years ago, trichlorosilane was introduced as a reagent with high stereospecificity for reducing phosphine oxides to phosphines[2] and the method has since found wide use.[3]

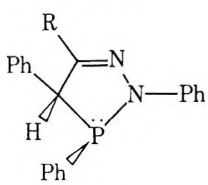
We have found that also the diazaphospholene oxides **1** react with $HSiCl_3$ in the presence of triethylamine in benzene solution to afford the corresponding phosphines **2** but with lack of stereospecificity. Reduction of the pure cis[4] or trans isomers of **1** with trichlorosilane under *identical* conditions gives mixtures of *different* proportions of cyclic phosphines, *cis*-**2** and *trans*-**2**.



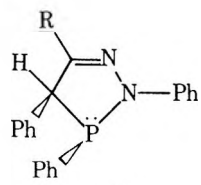
trans-**1**



cis-**1**



trans-**2**



cis-**2**

a, R = Ph
b, R = Ph·CH_2

Our results are summarized in Scheme I.

That the ring stayed intact in the reduction was borne out by NMR spectra and the fact that oxidation of **2** with hydrogen peroxide in acetone give back the corresponding oxides **1** with complete retention of configuration.

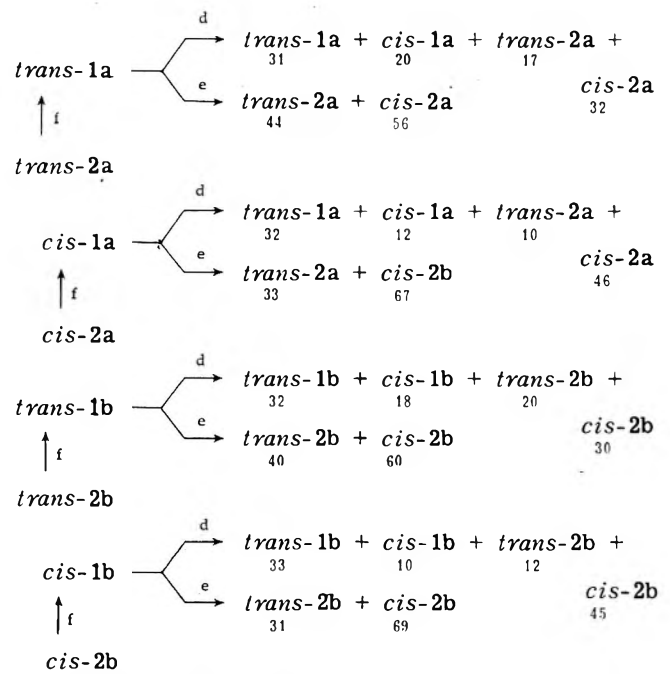
The two isomeric phosphines **2** can be isolated in pure form by fractional crystallization or by silica gel column chromatography. The isomer assignment in **1** have previously[1] been made on the basis of NMR spectra; the assignments in **2** are made on the same basis. The trans configuration is assigned to the isomer showing an upfield methine signal; this isomer has a much smaller value for J_{PCH} than the cis isomer. *trans*-**2a** showed the following values: δ 4.70 (d 1 H, J_{PCH} = 1.9 Hz); *cis*-**2a**, δ 5.49 (d, 1 H, J_{PCH} = 21.3 Hz); *trans*-**2b**, δ 3.94 (d, 1 H, J_{PCH} = 2 Hz); *cis*-**2b**, δ 4.66 (d, 1 H, J_{PCH} = 21.5 Hz).

The NMR data were also useful in determining the ratio of geometric isomers **1** and **2** in the reaction mixtures.

Although the known complexity of the trichlorosilane reduction[3] does not permit a definition of all possible pathways, we think that the lack of stereospecificity could be the result of stereomutation of the starting phosphine oxide **1** by reductant by-products, e.g., Si_2OCl_6, $SiCl_4$, or perchloropolysiloxanes $(OSiCl_2)_n$ which have been postulated as products in the trichlorosilane reduction of phosphine oxide.[5] This possibility is supported by the fact that a GLC analysis of the reduction mixtures shows the presence of $SiCl_4$ and Si_2OCl_6 and that the pure isomers of **1** are readily interconverted at room temperature by Si_2OCl_6 as well as by $SiCl_4$ to give essentially different equilibrium mixtures (see Table I). Control runs were performed under identical conditions using **2** (cis and trans) and no isomer interconversion was obtained (within the error limits of NMR integration, ~±5%).

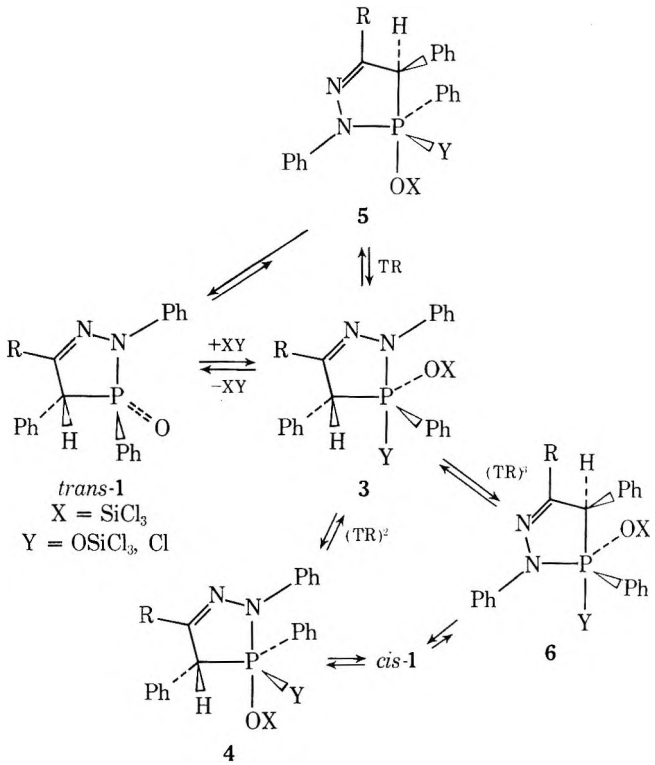
The most likely explanation of these stereomutations appears to be the formation of a pentacoordinate intermediate such as **3** (Scheme II). The importance of such intermediates in other organophosphorus reactions is clearly being recognized.[6] We favor the following mechanistic interpretation of our results: apical attack at the tetrahedral phosphorus atom of *trans*-**1** gives intermediate **3** which leads to **4**, **5**, and **6** after a sequence of turnstile rotation (TR) processes.[7]

Scheme I[a]



[a] Reagents: d, $SiHCl_3$–Et_3N, benzene for 0.5 hr at refluxing temperature; e, $SiHCl_3$–Et_3N, benzene for about 2 hr at refluxing temperature; longer reaction times caused no significant change in the proportion of the isomeric phosphines; f, H_2O_2–acetone. The numbers found below compounds **1a,b** and **2a,b** represent the diastereomeric ratios (±5%) determined as stated in the text. The ratios are the average of three separate runs.

Scheme II[9]



Another set of phosphoranes enantiomeric with structure **3** is generated by attack at a different enantiotopic face of the phosphorus tetrahedron. However, as a rule,[8] five-membered rings are unable, for reasons of strain, to occupy the diequatorial position of a trigonal bipyramid and, therefore, only conformers with apical–equatorial rings are considered to be participating in the pseudo-rotational process.

On the other hand, since more electronegative atoms tend to prefer the apical positions, the structures with apical nitrogen (**3, 4**) may be favored over those with apical ring carbon (**5, 6**); because of this we propose that the favored attack of the nucleophile Y is at the face opposite the P–N bond.

Apical departure (requirement of microscopic reversibility)[6a,7b] of Y from **6** yields the cis isomer. When Y = OX (XY = Si_2OCl_6) apical departure of OX from **4** also would yield the cis isomer; however, **3** may be favored over **4** (as well as **5** over **6**) because it avoids the steric interaction of *P*-phenyl with C_4-phenyl. This explanation is consistent with the observed equilibrium compositions.

In the case of the reduction reactions the different ratios of isomeric phosphines may also be due to differences in the relative rates of reduction of the phosphine oxide isomers as well as in stabilities of their intermediate phosphoranes.

The phosphines evidently do not arise from an equilibrium mixture of phosphine oxides by stereospecificity reactions since the equilibrium mixtures of oxides (Table I) differs from the isomer composition of the phosphines (route e in Scheme I). It is possible that phosphines are formed via phosphoranes by inversion *and* retention mechanisms and that these processes compete with stereomutation of phosphine oxides.[10] Also it is possible that the phosphine oxides are being intercepted in a stereospecific reduction process before equilibrium of phosphine oxides is established.

Finally, it should be pointed out that the isomers of **1** and **2** are not interconvertible in benzene solution at room temperature (also in the presence of $HSiCl_3$–Et_3N) or under the reaction conditions (refluxing benzene with Et_3N for about 2 hr) of the reduction stage.

Table I
Isomerization of 1a (0.002 mol) with XY (0.002 mol) in 70 ml Benzene Solution at Room Temperature

Phosphine oxide used	XY	Time, min	Trans:cis ratio in the reaction mixture
trans-**1a**	Si_2OCl_6	10	89:11
		40	78:22
		90	61:39
		120	61:39
cis-**1a**		10	39:61
		40	53:47
		90	61:39
trans-**1a**	$SiCl_4$	10	94:6
		40	86:14
		90	78:22
		120	71:29
		150	71:29
cis-**1a**		10	30:70
		40	49:51
		90	64:36
		120	71:29

Experimental Section

Trichlorosilane was treated with quinoline to remove hydrogen chloride and was isolated by fractional distillation under nitrogen. Triethylamine was refluxed (2 days) over barium oxide, distilled under nitrogen, and stored over potassium hydroxide. Benzene was dried in vacuo over a sodium mirror.

To obtain optimum yields of the phosphines, all operations were carried out with rigorous exclusion of oxygen under a nitrogen atmosphere. **1a** and **1b** were prepared by methods described previously.[1] Hexachlorodisiloxane and silicon tetrachloride are commercially available materials. All melting points are uncorrected.

The NMR spectra were determined on a Jeol J.M.M.C. 60 HL spectrometer. Proton NMR chemical shifts are expressed in parts per million from internal Me_4Si.

The microanalyses were performed on mixtures of the isomers as well as on pure isomers. The results obtained were practically identical.

Trichlorosilane Reduction of 1a. To 4 g (0.01 mol) of *trans*-**1a** in 350 ml of dry benzene, 1 g (0.01 mol) of dry triethylamine was added, and after cooling the solution in an ice bath, 1.35 g (0.01 mol) of trichlorosilane was dropped in slowly. The mixture was then brought to reflux, which was maintained for about 2 hr. The mixture was cooled, some ice added, and then 30 ml of 20% sodium hydroxide was slowly added. Additional benzene was added to give two distinct layers; the organic layer was separated, washed four times with saturated sodium chloride solution, and dried over sodium sulfate. The solvent was evaporated to give a crude solid which after crystallization from CH_2Cl_2–hexane gave 2.88 g of **2a** (73% yield). The NMR spectrum ($CDCl_3$) of the crude product showed two isomers in a 44:56 ratio (trans:cis) (estimated by relative integration of methine peaks). Separation of small amounts of pure isomers was accomplished by chromatography on a silica gel column and elution was performed by cyclohexane–benzene (9:1). The isomer *trans*-**2a** had mp 144–146°; its NMR spectrum ($CDCl_3$) showed absorption at δ 4.70 (d, 1 H, J_{PCH} = 1.9 Hz) and 6.4–7.8 (m, 20 H, aromatic).

cis-**2a** had mp 183–185°; its NMR spectrum ($CDCl_3$) showed peaks at δ 5.49 (d, 1 H, J_{PCH} = 21.3 Hz) and 6.4–7.9 (m, 20 H, aromatic). Larger quantities of isomers were obtained by fractional crystallization. The first fractions were richer in cis isomers, the final fractions in trans.

In a similar manner *cis*-**1a** was reduced and **2a** was obtained in 75% yield. The NMR of the product indicated two isomers in a 33:67 ratio (trans:cis).

Anal. Calcd for $C_{26}H_{21}N_2P$: C, 79.60; H, 5.39; N, 7.14; P, 7.89. Found: C, 79.76; H, 5.25; N, 7.03; P, 7.80.

Trichlorosilane Reduction of 1b. The same procedure as above was followed, using 4.22 g (0.01 mol) of *trans*-**1b** in 250 ml of

dry benzene, 1 g (0.01 mol) of dry triethylamine, and 1.35 g (0.01 mol) of trichlorosilane. **2b** was obtained in 72% yield.

The NMR spectrum ($CDCl_3$) of the crude product showed an isomer ratio of 40:60 (trans:cis). The isomer mixture was separated by silica gel column chromatography as well as by fractional crystallization. The trans isomer **2b** had mp 112–114°; its NMR spectrum ($CDCl_3$) showed absorption at δ 3.19–4.18 (AB multiplet, 2 H, CH_2Ph), 3.94 (d, 1 H, J_{PCH} = 2 Hz), and 6.30–7.40 (m, 20 H, aromatic). The cis isomer **2b** had mp 132–134°; its NMR spectrum ($CDCl_3$) showed peaks at δ 3.27–4.18 (AB multiplet, 2 H, CH_2Ph), 4.66 (d, 1 H, J_{PCH} = 21.5 Hz), and 6.20–7.40 (m, 20 H, aromatic).

In the same manner *cis*-**1b** was reduced and **2b** was obtained in 70% yield. The NMR of the product showed an isomer ratio of 31:69 (trans:cis). It is noteworthy that the isomers of **1** are not interconvertible in benzene solution at room temperature also in the presence of $HSiCl_3$-Et_3N.

Anal. Calcd for $C_{27}H_{23}N_3P$: C, 79.79; H, 5.70; N, 6.89; P, 7.62. Found: C, 79.85; H, 5.67; N, 6.78; P, 7.68.

GLC analyses were carried out directly on the reduction mixtures, using a 4-ft 10% silicone rubber UCCW-982 on 80–100 mesh Chromosorb W column at 70°, helium flow rate 35 ml/min. Results indicated that $SiCl_4$ and Si_2OCl_6 were present. Identification of the product was based on comparison on their GLC retention time (relative to air) with those for authentic $SiCl_4$ and Si_2OCl_6, 0.45 and 2.85 min, respectively.

Oxidation of 2a and 2b with Hydrogen Peroxide. To 3.92 g (0.01 mol) of *cis*-**2a** in 50 ml of acetone, 1.3 g (0.01 mol) of 30% hydrogen peroxide in 5 ml of acetone was added dropwise; the temperature was kept below 20° by ice-bath cooling. The reaction mixture was evaporated to yield 2.80 g (70%) of product, mp 174–177°. The NMR was identical with that of *cis*-**1a** and contained <10% of *trans*-**1a**; the infrared spectrum was also identical.

In a similar manner *trans*-**2a**, *trans*-**2b**, and *cis*-**2b** were individually oxidized at 0° to give *trans*-**1a**, *trans*-**1b**, and *cis*-**1b**, respectively.

Isomerization of 1a with Si_2OCl_6 and $SiCl_4$. To a stirred solution of 0.816 g (0.002 mol) of pure *trans*-**1a** in dry benzene (70 ml), 0.442 g (0.002 mol) of Si_2OCl_6 was added and the reaction was allowed to proceed at room temperature.

Aliquots (15 ml) were removed at various time intervals and were quenched by addition to 20% aqueous sodium hydroxide; additional benzene was added and the extracts were dried over sodium sulfate. The solvent was stripped off and the residues were extracted into $CDCl_3$. NMR analysis of these samples revealed a steady decrease in the amount of the trans isomer and that after ca. 90 min an equilibrium mixture of **1a** was obtained in which the trans:cis ratio was 61:39. Repetition of this reaction starting with *trans*-**1a** led to isolation of the same equilibrium mixture of **1a** (trans:cis 61:39) after 90 min.

Similar procedures were followed in the isomerization with $SiCl_4$ using a solution of 0.816 g (0.002 mol) of *trans*-**1a** and *cis*-**1a** in dry benzene (70 ml) and adding 0.338 g (0.002 mol) of $SiCl_4$.

The ratios of isomeric phosphine oxides are reported in Table I.

Acknowledgment. We wish to thank Miss Ascia Ismail, who carried out some of the experiments, and the Italian CNR for financial support.

Registry No.—*trans*-**1a**, 51849-78-6; *cis*-**1a**, 51849-79-7; *trans*-**1b**, 51849-80-0; *cis*-**1b**, 51849-81-1; *trans*-**2a**, 55520-53-1; *cis*-**2a**, 55520-54-2; *trans*-**2b**, 55520-55-3; *cis*-**2b**, 55520-56-4; $HSiCl_3$, 10025-78-2; Si_2OCl_6, 14986-21-1.

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(7) (a) In a turnstile rotation, the five ligands around pentacoordinated phosphorus, by undergoing slight but significant angular distortions, divide themselves into two sets, a trio and a pair. Stereomutation is postulated to occur by mutual counterrotation of these two sets with subsequent collapse to a new trigonal bipyramid. In four- and five-membered cyclic phosphoranes, the ring must always play the role of the pair in the single and multiple TR processes, and the remaining three ligands the role of the trio. (b) For a discussion of the permutational isomerization of phosphoranes by the turnstile rotation process, see P. Gillespie, F. Ramirez, I. Ugi, and D. Marquarding, *Angew. Chem., Int. Ed. Engl.*, **12**, 91 (1973), and references cited therein. (c) Isomer **5** can also be generated from **3** by one Berry pseudo-rotation mechanism: R. S. Berry, *J. Chem. Phys.*, **32**, 933 (1960).
(8) (a) F. Ramirez, *Acc. Chem. Res.*, **1**, 168 (1968); (b) D. Gorenstein and F. H. Westheimer, *J. Am. Chem. Soc.*, **92**, 634 (1970); (c) I. Ugi and F. Ramirez, *Chem. Br.*, **8**, 198 (1972).
(9) Although the trans isomer is used as an illustration in Scheme II, the cis isomer can be used with parallel conclusions.
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Synthesis of the Pyrimido[5,4-*e*]-*as*-triazine Antibiotics Fervenulin and 2-Methylfervenulone[1,2]

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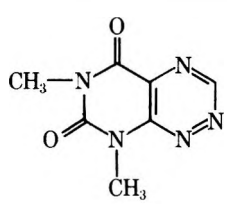
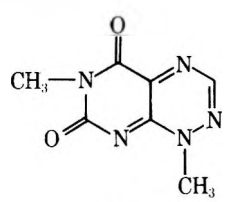
The antibiotic fervenulin (6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione, **1**) has been synthesized by two different methods starting with 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-hydrazinouracil (**3**). In the first, **3** was cyclized with sodium ethoxide to fervenulone (6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2*H*,6*H*,8*H*)-trione, **5**), which was then converted to **1** by a sequence of reactions involving chlorination to 3-chloro-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (**6**), reaction with hydrazine to give the 3-hydrazino derivative (**7**), and oxidation with mercuric oxide. In the second, **3** was converted to **1** *in a single step* by heating with a mixture of dimethylformamide and phosphorus oxychloride. The mechanism of this remarkable transformation is discussed. Treatment of **3** with diethyl azodicarboxylate or with lead tetraacetate gave 4-carbethoxyamino-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(4*H*,6*H*,8*H*)-trione ethanolate (**15**). The structure of **15** was unequivocally established by hydrogenolysis to 1,2-dihydro-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(4*H*,6*H*,8*H*)-trione ethanolate (**16**), which was then synthesized independently from 1,3-dimethyl-6-(2-carbethoxyhydrazino)uracil by nitrosation, reduction of the resulting 5-nitroso derivative, and finally base-catalyzed intramolecular cyclization. Treatment of **16** with DDQ or, less efficiently, by exposure of solutions of **16** to air, provided a second synthesis of fervenulone (**5**). The antibiotic MSD-92 (2-methylfervenulone, 2,6,8-trimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2*H*,6*H*,8*H*)-trione, **17**) has been synthesized by methylation of fervenulone (**5**) with methyl iodide or diazomethane, as well as by an unequivocal total synthesis. Thus, reaction of 1,3-dimethyl-5-carbethoxyaminobarbituric acid with phosphorus oxychloride gave 1,3-dimethyl-5-isocyanato-6-chlorouracil (**29**). Addition of methylhydrazine to **29** then gave **32**, which was cyclized to **17** with aqueous sodium acetate in the presence of a stream of air. A number of chemical transformations of these compounds and the preparation of the remaining monomethyl derivatives of fervenulone (**18** and **20**) are described.

Fervenulin. Fervenulin (**1**), also known as planomycin, is a crystalline, broad-spectrum antibiotic, isolated from cultures of *Streptomyces fervens* n. Sp.[3] and from *Streptomyces rubrireticuli*,[4] which possesses an interesting spectrum of biological activities.[5] It has been identified[6] as 6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (**1**),[7] and is a representative of a unique family of naturally occurring pyrimido[5,4-*e*]-*as*-triazine (7-azapteridine) antibiotics which includes toxoflavin (**2**)[3b,8] and 2-methylfervenulone (MSD-92, **17**) (vide infra).[2b,9] There has been considerable recent interest in the development of synthetic approaches to fervenulin;[10-15] in this paper we present a full account of our own investigations.[2a]



1

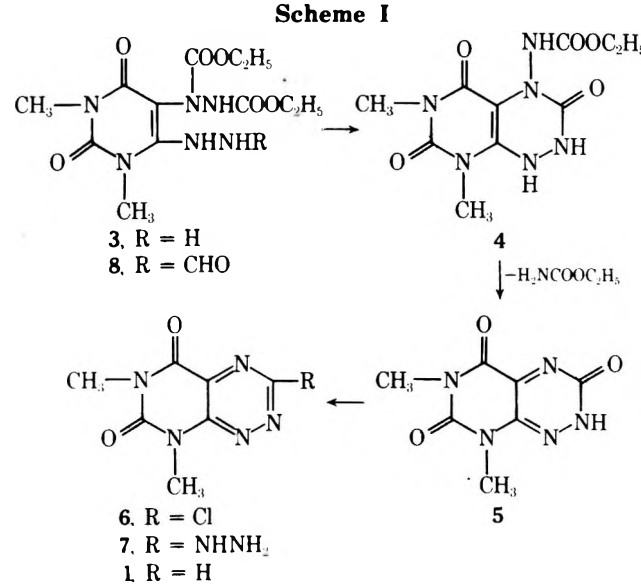


2

We have recently reported[16] that 5-(1,2-dicarbethoxyhydrazino)pyrimidines are readily formed by the reaction of 6-amino- or 6-hydrazinopyrimidines with diethyl azodicarboxylate. Thus, 1,3-dimethyl-6-hydrazinouracil reacts with diethyl azodicarboxylate to give 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-hydrazinouracil (**3**) in 71% yield. We now report the conversion of this readily available intermediate by two different routes to the antibiotic fervenulin.

In the first of these routes, treatment of the Michael adduct **3** with sodium ethoxide in absolute ethanol (under scrupulously anhydrous conditions) led directly to the formation of 6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7-(2*H*,6*H*,8*H*)-trione (**5**), for which, in view of its role as a crucial intermediate for the synthesis of both fervenulin and 2-methylfervenulone and its structural relationship to both of these antibiotics, we propose the name *fervenulone*. It seems reasonable to assume an initial cyclization of **3** to 1,4-dihydro-4-carbethoxyamino-6,8- dimethylpyrimido[5,4-*e*]- *as*-triazine-3,5,7(2*H*,6*H*,8*H*)- trione (**4**), which then aromatizes by base-catalyzed 1,4 elimination of ethyl carbamate (see Scheme I). Fervenulone (**5**) could alternately be prepared in somewhat better overall yield by initial formylation of **3** to give 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-(2-formylhydrazino)uracil (**8**), followed by cyclization with sodium ethoxide in absolute ethanol. Fervenulone (**5**) forms stable solvates which, in contrast to the anhydrous, unsolvated compound, are elegantly crystalline. Thus, recrystallization of **5** from ethanol gave a crystalline ethanolate, which upon recrystallization from water then gave a hydrate; the cycle can also be reversed.

Scheme I



3, R = H
8, R = CHO

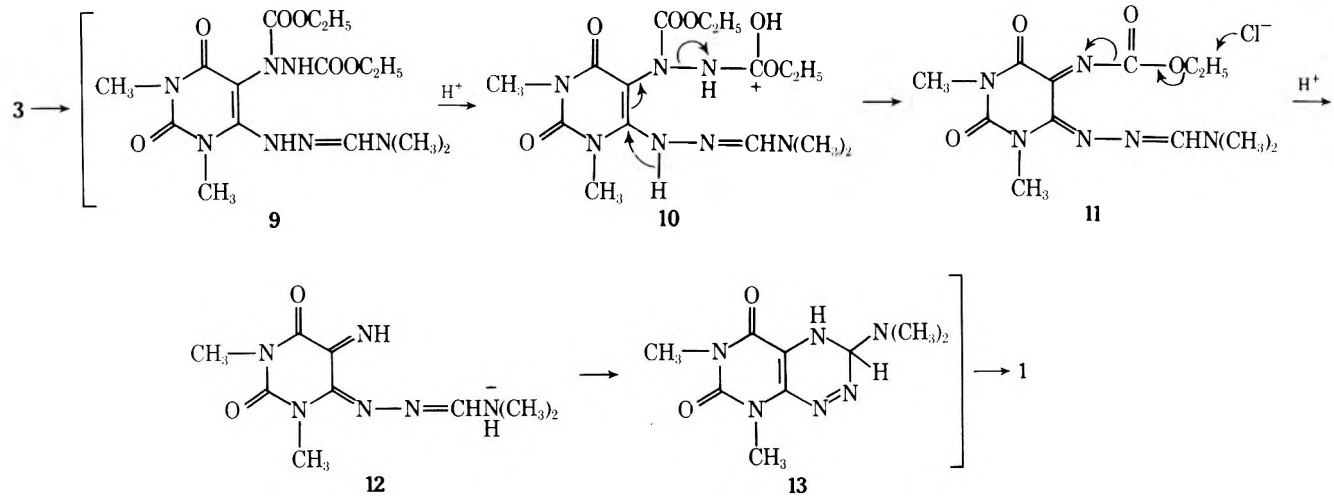
4

6, R = Cl
7, R = $NHNH_2$
1, R = H

5

Conversion of fervenulone (**5**) to fervenulin (**1**) was accomplished as follows. Treatment of **5** with phosphorus oxychloride (or, less satisfactorily, with phosphorus pentachloride) gave 3-chloro-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (**6**). Reductive removal of the 3-chloro substituent was then carried out in two steps (direct

Scheme II



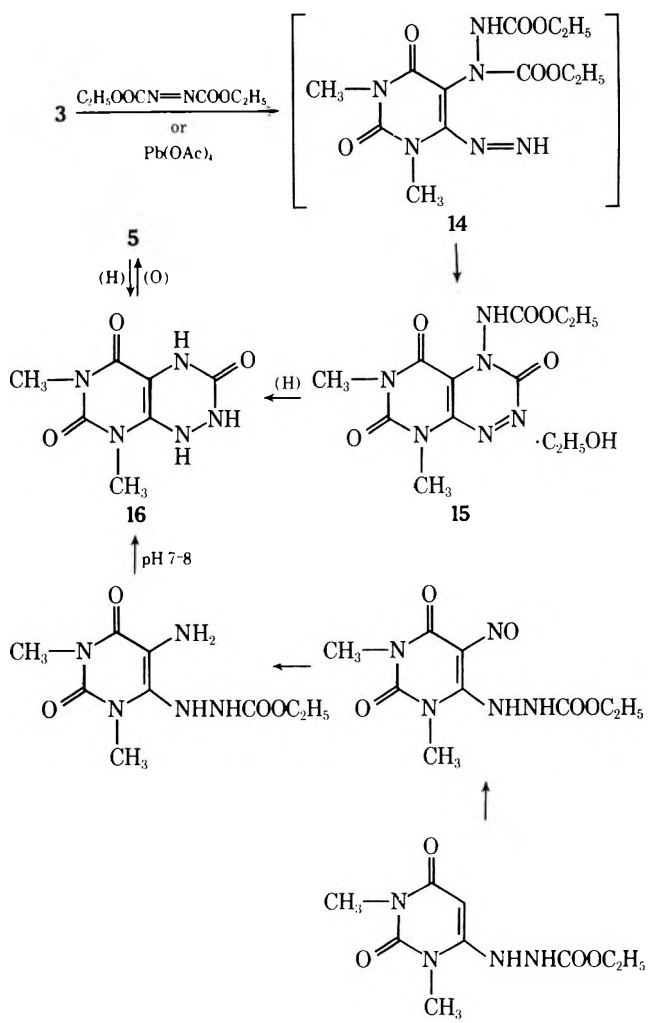
reduction was avoided because of the presence of the sensitive azo linkage in 1) by (a) reaction with hydrazine to give the 3-hydrazino derivative **7**, and (b) oxidation of **7** with mercuric oxide.[17] The product was identical in every respect with authentic fervenulin.[18]

The second method for the conversion of **3** to fervenulin (**1**) is, because of its extraordinary simplicity, without question the method of choice for the preparation of this antibiotic. Thus, fervenulin was formed in a single step by treatment of **3** with phosphorus oxychloride–dimethylformamide. When the reaction was carried out at 60° rather than at 125°, 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-dimethylaminomethylenehydrazinouracil (**9**)[19] separated directly from the reaction mixture, suggesting that a possible reaction course for this remarkable ring annelation might be as depicted in Scheme II. Key steps in the overall conversion are the loss of ethyl carbamate from **10** (for which the aromatization of **4** to **5** under basic conditions provides a precedent), loss of the carbethoxy grouping from **11** (for which there is ample precedent in carbamate chemistry),[20] and the cyclization step (**12** → **13** → **1**) involving the loss of dimethylamine (for which the Fischer indole synthesis provides a parallel,[21] although a concerted, electrocyclic reaction followed by aromatization with loss of dimethylamine cannot be excluded).

In the preparation of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-hydrazinouracil (**3**) from 1,3-dimethyl-6-hydrazinouracil and diethyl azodicarboxylate, a very small amount of a by-product could be isolated from the mother liquors which has been identified as 4-carbethoxyamino-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(4*H*,6*H*,8*H*)-trione ethanolate (**15**). This compound proved to be the major product of the reaction of 1,3-dimethyl-6-hydrazinouracil with 2 mol of diethyl azodicarboxylate, and we suggest that it is probably formed by the sequence of reactions outlined in Scheme III. Since **3** does not cyclize in the absence of base, the initial reaction of the Michael adduct **3** with excess diethyl azodicarboxylate may well be oxidation of the hydrazino substituent to a diimide (**14**),[22] which then ring closes with loss of ethanol to **15**.[23,24] Some support for this suggestion comes from the observation that the conversion of **3** to **15** could also be effected with lead tetraacetate, a reagent known to oxidize arylhydrazines to aryldiimides.[25]

The structure of **15** was confirmed by reduction to 1,4-dihydro-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2*H*,6*H*,8*H*)-trione (dihydrofervenulone, **16**), identical

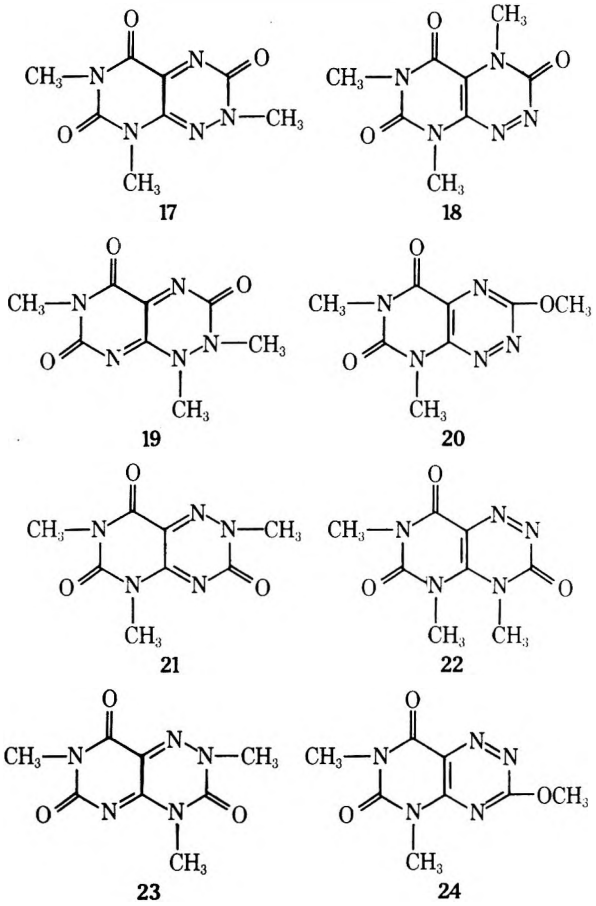
Scheme III



with an authentic sample prepared by the sequence of reactions depicted in Scheme III, as well as by reduction of fervenulone (**5**) itself. Conversion of **16** to fervenulone (**5**) could be readily accomplished by dehydrogenation with DDQ in chloroform solution, or even by repeated recrystallization from ethanol.

2-Methylfervenulone (MSD-92). The antibiotic MSD-92 was isolated from the fermentation broth of an unidentified actinomycete as a fluorescent, bright yellow,

crystalline compound possessing broad in vitro antibiotic activity.[9] On the basis of spectral and microanalytical data, this antibiotic was correctly identified by the Merck workers as a trimethylpyrimidotriazinetrione in either the [5,4-*e*] or [4,5-*e*] series. Of the eight possible structures for MSD-92 (structures **17–24**), only structure **20** (3-methoxyfervenulin) could be positively rejected; the Merck workers suggested structures **18, 19, 22,** and **23** as the most plausible. We present below several independent syntheses of this antibiotic which unequivocally support the assignment of structure **17** to MSD-92.



We were immediately able to eliminate structures **19–24** by the observation that methylation of fervenulone (**5**) with methyl iodide gave a trimethylpyrimido[5,4-*e*]-*as*-triazinetrione which was identical in every respect with the naturally occurring antibiotic. Thus MSD-92 must possess either structure **17** or **18**, and a decision in favor of **17** was readily made on the basis of the following unambiguous synthesis.

Hydrolysis[26] of the readily available 1,3-dimethyl-5-nitroso-6-aminouracil (**25**) provided a convenient route to 1,3-dimethylvioluric acid (**26**),[27] which on catalytic reduction gave 1,3-dimethyluramil (**27**).[28] Treatment of **27** in alkaline solution with ethyl chloroformate gave the 5-carbethoxyamino derivative **28**,[29] which was then converted in a single operation by reaction with phosphorus oxychloride to 1,3-dimethyl-5-isocyanato-6-chlorouracil (**29**).[30] Rapid work-up and drying of **29** proved to be essential, since relaxation of such precautions led to a mixture of **30** and the sym urea **31**. Addition of 1 equiv of methylhydrazine to an acetonitrile or chloroform solution of **29** then gave the semicarbazide **32**, whose structure was readily established by microanalysis and by conversion with benzaldehyde to the semicarbazone **33**. No evidence could be found for the formation of the isomeric semicarbazide which would have resulted from the alternate mode of addition of methylhydrazine to the isocyanate **29**.

An attempt to bring about cyclization of **32** with sodium ethoxide was unsuccessful, and led only to displacement of the 6-chloro substituent by an ethoxy group to give **34**. However, treatment of **32** with aqueous sodium acetate at 65–75° while passing a vigorous stream of air through the reaction solution resulted in the formation of 2,6,8-trimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2*H*,6*H*,8*H*)-trione (2-methylfervenulone, **17**), identical in every respect (melting point, mixture melting point, TLC, uv, ir, NMR, and microbiological assay)[31] with the naturally occurring antibiotic. These reactions are summarized in Scheme IV.

Presumably the initial product of cyclization of **32** is the dihydro derivative **35**, which then undergoes oxidation to **17** under the reaction conditions. The ready interconvertibility of **17** and **35** could be demonstrated independently by catalytic reduction of **17** to give the dihydro derivative **35**, which then could be reconverted to **17** by air oxidation (as above), or by repeated recrystallization from ethanol, or (in the highest yield) by dehydrogenation with DDQ.

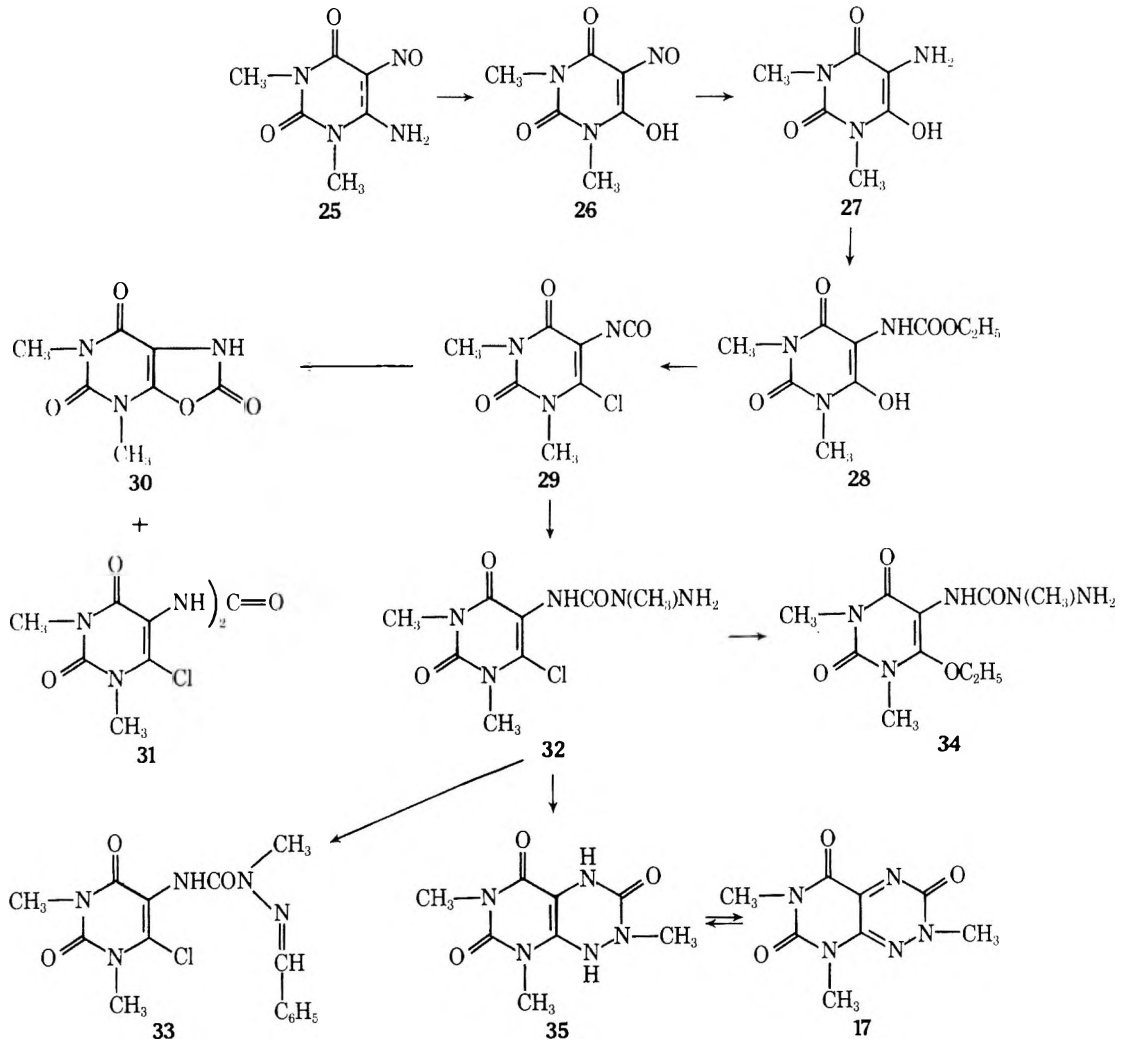
The identification and isolation of 2-methylfervenulone (MSD-92, **17**) was complicated by a number of polymorphic modifications whose formation depended upon the solvent employed in its purification. The form obtained upon recrystallization from ethyl acetate consisted of shining, thick yellow needles, mp 174–175°. Recrystallization of carefully dried **17** from ethanol gave thick, glistening plates melting at 181–182° dec; this was the form encountered by the Merck group, who reported that MSD-92 possessed mp 183–183.5° dec.[9] This same modification could be obtained by recrystallization from water, which initially gave **17** as small yellow plates, mp 92–93° dec, but which after prolonged drying at 100° then melted at 180–181° dec. This latter polymorphic form could be shown by mass spectroscopy to contain traces of water. Perhaps as a consequence of the presence of water, this latter form upon recrystallization from ethyl acetate gave small yellow plates, mp 157–158°, but which upon resolidification then remelted at 180–181° dec. Recrystallization of **17** from wet ethanol yielded a hemiethanolate, mp 155–156° dec, which tenaciously retained the solvent of recrystallization, even under prolonged drying in vacuo.

An attempt to convert **32** to **35** by pyrolysis led to a surprising result. The colorless needles which were formed were neither **35** nor **17**, but proved to be isomeric with **35**. However, although **35** (prepared independently as described above by catalytic reduction of **17**) could readily be dehydrogenated to **17** with DDQ, the fusion product, isomeric with **35**, could not be dehydrogenated under any conditions, and instead underwent extensive decomposition. We were thus led to suspect that this unexpected pyrolysis product was 1,4-dihydro-1,6,8-trimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2*H*,6*H*,8*H*)-trione (**36**), a structural assignment which was then verified by an independent but unequivocal synthesis of **36** (see Scheme V).

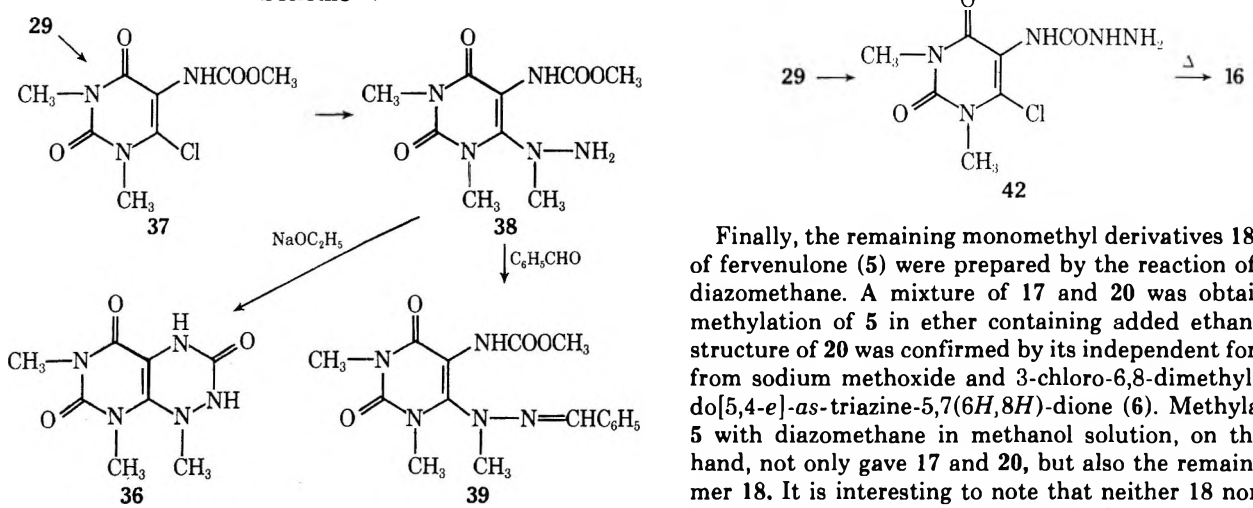
Thus, heating **29** in methanol solution gave 1,3-dimethyl-5-carbomethoxyamino-6-chlorouracil (**37**), which upon treatment in acetonitrile solution with methylhydrazine gave 1,3-dimethyl-5-carbomethoxyamino-6-(1-methylhydrazino)uracil (**38**). The structure of **38** was confirmed by its conversion with benzaldehyde to the benzylidene derivative **39**. Finally, treatment of **38** with sodium ethoxide resulted in cyclization to give **36**, identical in all respects with the product derived from pyrolysis of **32**.

The rearrangement which had occurred in the conversion of **32** to **36** has been observed previously with substituted hydrazines,[32] and presumably involves a diaziridine inter-

Scheme IV



Scheme V



mediate (e.g., **40**). The unidirectional ring opening to give the isomeric semicarbazide **41** results from the greater basicity of the nitrogen bearing the methyl group (Scheme VI).

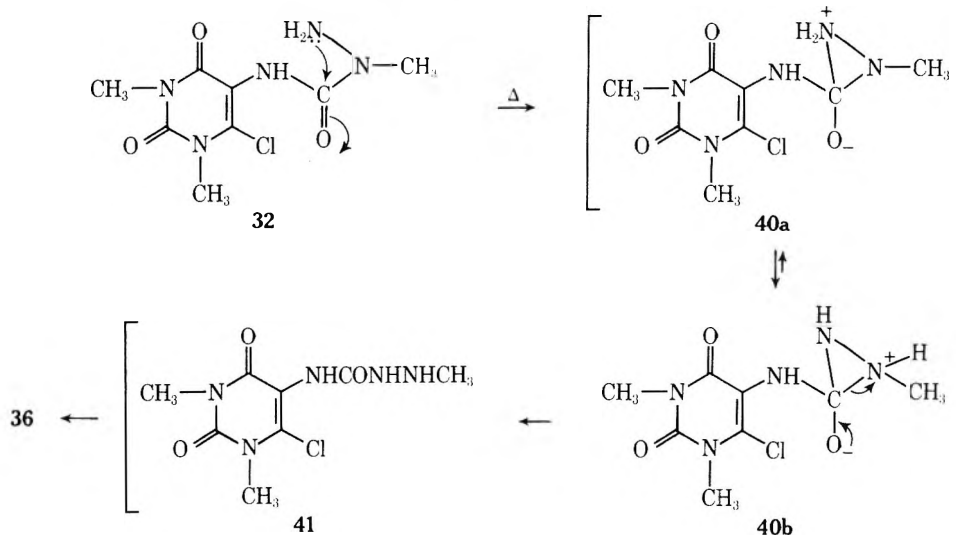
As would be expected, pyrolysis of the unsubstituted semicarbazide **42** (prepared from the isocyanate **29** and hydrazine) proceeded normally to give dihydrofervenulone (**16**). Since dehydrogenation of **16** was shown above to give fervenulone (**5**), this series of transformations constitutes a further useful preparation of this important synthetic precursor both to fervenulin and to MSD-92.

Finally, the remaining monomethyl derivatives **18** and **20** of fervenulone (**5**) were prepared by the reaction of **5** with diazomethane. A mixture of **17** and **20** was obtained by methylation of **5** in ether containing added ethanol. The structure of **20** was confirmed by its independent formation from sodium methoxide and 3-chloro-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (**6**). Methylation of **5** with diazomethane in methanol solution, on the other hand, not only gave **17** and **20**, but also the remaining isomer **18**. It is interesting to note that neither **18** nor **20** exhibited any in vitro antibiotic activity.[31]

Experimental Section

6,8-Dimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2*H*,6*H*,8*H*)-trione (Fervenulone, 5). Method A. To a stirred, ice-cooled solution of 0.115 g (0.005 mol) of sodium in 50 ml of dried, distilled absolute ethanol was added 1.72 g (0.005 mol) of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-hydrazinouracil (**3**),[16] and the mixture was stirred with continued cooling for 1.5 hr. The precipitate of the sodium salt of fervenulone which gradually separated (mp 317–319° dec) was collected by filtration, washed with absolute ethanol, and then dissolved in warm glacial acetic acid. Filtration removed a small amount of insoluble material; evaporation of the

Scheme VI



filtrate to a small volume and dilution with absolute ethanol resulted in the separation of 0.81 g (63%) of the ethanolate of fervenulone (**5**), mp 259–261° dec.

Anal. Calcd for $C_7H_7N_5O_3 \cdot C_2H_5OH$: C, 42.35; H, 5.14; N, 27.44. Found: C, 42.56; H, 5.15; N, 27.21.

The hydrate of fervenulone (**5**) was obtained by warming 0.75 g of the ethanolate in water for 30 min, concentrating to a small volume, and cooling. Filtration gave 0.62 g of yellow crystals,. mp 259–261° dec.

Anal. Calcd for $C_7H_7N_5O_3 \cdot H_2O$: C, 37.01; H, 4.00; N, 30.82. Found: C, 37.23; H, 4.24; N, 30.82.

Anhydrous fervenulone (**5**), mp 260–261° dec, was obtained by drying the hydrate in vacuo at 125° for 5 hr.

Anal. Calcd for $C_7H_7N_5O_3$: C, 40.19; H, 3.38; N, 33.48. Found: C, 39.98; H, 3.47; N, 33.30.

Method B. A stirred suspension of 1.86 g (0.005 mol) of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-(2-formylhydrazino)uracil (**8**) (see below) in a solution of 0.35 g (0.015 mol) of sodium in 25 ml of absolute ethanol was heated under reflux for 1 hr. The reaction mixture was then worked up as described above to give, after recrystallization from water, 0.92 g (81%) of deep yellow crystals, mp 260–261° dec, identical (ir spectrum) with fervenulone hydrate prepared as described above under method A. (See below for methods C and D.)

1,3-Dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-(2-formylhydrazino)uracil (8). A suspension of 3.44 g (0.01 mol) of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-hydrazinouracil in a formylation mixture prepared from 1.02 g (0.01 mol) of acetic anhydride and 10 ml of formic acid was heated at 50–60° for 15 min and then concentrated to dryness under reduced pressure. The residue was suspended in 10 ml of water and reconcentrated to a small volume. Cooling gave 2.91 g (78%) of **8**, mp 203–204° dec.

Anal. Calcd for $C_{13}H_{20}N_6O_7$: C, 41.94; H, 5.41; N, 22.57. Found: C, 41.93; H, 5.53; N, 22.37.

3-Chloro-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (6). Method A. To a stirred solution of 3.47 g (0.024 mol) of diethylaniline and 100 ml of phosphorus oxychloride was added with cooling (in an ice bath) 5.0 g (0.024 mol) of 6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2*H*,6*H*,8*H*)-trione (fervenulone, **5**). The suspension was then heated gently under reflux in an oil bath maintained at 110–115° for 30 min, excess phosphorus oxychloride was removed by distillation under reduced pressure, and the residual syrup was poured over 25 g of crushed ice. Cooling of the resulting solution and filtering then gave 1.73 g of yellow crystals which were recrystallized from 20 ml of absolute ethanol to give 1.24 g (23%) of **6**, mp 146–147°.

Anal. Calcd for $C_7H_6N_5O_2Cl$: C, 36.94; H, 2.65; N, 30.77; Cl, 15.58. Found: C, 37.06; H, 2.76; N, 30.58; Cl, 15.29.

Method B. An intimate mixture of 5.10 g (0.002 mol) of fervenulone (**5**) ethanolate and 8.32 g (0.04 mol) of phosphorus pentachloride was gradually heated in an oil bath from an initial temperature of 110° to a final temperature of 140° over a period of 1 hr. The reaction mixture was then freed of volatile material by concentration under reduced pressure, the residue was stirred with ice, and the resulting solution was extracted with two 100-ml portions of chloroform. The combined, dried extracts were evaporated to a gummy red residue which was extracted with three 250-ml portions of ether. Concentration of the combined extracts and crystallization of the residue from absolute ethanol gave 2.06 g (45%) of **6**, identical with the material prepared by method A.

3-Hydrazino-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (7). A solution of 1.08 g (0.00475 mol) of 3-chloro-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione in 50 ml of absolute ethanol cooled to 0° was added during 5 min to a solution of 4.69 g (0.0143 mol) of 97% hydrazine in 25 ml of absolute ethanol. The reaction mixture was then maintained at room temperature for 18 hr, cooled to 0°, and filtered to give bronze-colored platelets which were suspended in 30 ml of saturated sodium bicarbonate solution and stirred for 30 min. The suspended solid was collected by filtration, the filtrate was extracted with 50 ml of chloroform, the dried extract was evaporated to dryness, and the residue was combined with the above solid to give 1.05 g (99%) of crude **7**, mp 223–227° dec. Recrystallization from water afforded 0.51 g of pure **7**, mp 225–227° dec.

Anal. Calcd for $C_7H_9N_7O_2$: C, 37.67; H, 4.07; N, 43.93. Found: C, 37.82; H, 4.10; N, 44.04.

6,8-Dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (Fervenulin, 1). Method A. To a solution of 0.53 g (0.0024 mol) of 3-hydrazino-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (**7**) in 75 ml of water was added, in one portion, 1.04 g (0.0048 mol) of yellow mercuric oxide, and the mixture was stirred vigorously for 3 hr. The dark green reaction mixture was filtered through a mat of Celite and the filtrate was concentrated to dryness under reduced pressure. The residual yellow crystals were dissolved in 25 ml of hot water containing 0.35 g of concentrated hydrochloric acid, the solution was filtered and reconcentrated to dryness, and the pale yellow crystalline residue (0.29 g) was washed well with ice water. Recrystallization from 15 ml of water then gave 0.19 g (41%) of pure fervenulin, mp 177–178°, identical (melting point, mixture melting point, spectral comparisons) with authentic natural fervenulin: NMR (CF_3COOH) δ 3.18 (s, 3 H, NCH_3), 3.48 (s, 3 H, NCH_3), 9.48 (s, 1 H, C-3 proton).

Anal. Calcd for $C_7H_7N_5O_2$: C, 43.52; H, 3.65; N, 36.26. Found: C, 43.48; H, 3.71; N, 36.49.

Recrystallization of fervenulin from ethanol gave a polymorphic form, mp 171–172°, mmp 171–172° with authentic fervenulin of mp 177–178°.

Anal. Found: C, 43.36; H, 3.59; N, 36.16.

Method B. To a stirred, ice-cooled suspension of 5.16 g (0.015 mol) of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-hydrazinouracil in 10 ml of dimethylformamide was added, over a period of 5 min, 2.53 g (0.0165 mol) of phosphorus oxychloride. After 10 min the ice bath was replaced by an oil bath maintained at 125–130°, and the reaction mixture was heated for 2 hr. It was then concentrated to dryness under reduced pressure, and the residue was triturated in ice water and filtered to give 2.30 g of bright yellow crystals of crude fervenulin (**1**), mp 169–171° slight dec. The crude product was dissolved in 100 ml of hot benzene and filtered from a small amount of insoluble material, and the filtrate was cooled and then chromatographed on a 25 × 450 mm column of Florisil, using

a 9:1 mixture of benzene and ethyl acetate as the eluent. Evaporation of the eluate to dryness and recrystallization of the residue from benzene then gave chunky yellow needles of pure fervenulin, mp 177–178°, identical with authentic fervenulin. Yields in three representative preparations were 1.37 (47%), 1.55 (53%), and 1.65 g (57%).

1,3-Dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-dimethylaminomethylenehydrazinouracil (9). To a suspension of 3.44 g (0.01 mol) of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-hydrazinouracil in 10 ml of dimethylformamide, cooled in an ice bath, was added over a period of 15 min 1.53 g (0.01 mol) of phosphorus oxychloride. The reaction mixture was then heated at 60° (oil bath) for 20 min. A copious precipitate of a colorless solid gradually separated during this period. The mixture was cooled, diluted with an equal volume of ethanol, and filtered to give 3.42 g (85%) of **9**, mp 183–184° dec. For analysis it was recrystallized from absolute ethanol and dried at 30° for 24 hr in vacuo.

Anal. Calcd for $C_{15}H_{25}N_7O_6 \cdot HCl \cdot \frac{1}{2}H_2O$: C, 40 49; H, 6.12; N, 22.04. Found: C, 40.33; H, 6.08; N, 22.07.

4-Carbethoxyamino-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7-(4*H*,6*H*,8*H*)-trione Ethanolate (15). Method A. A stirred suspension of 6.88 g (0.02 mol) of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-hydrazinouracil in 250 ml of anhydrous ether was treated during 15 min with 19.6 g (0.04 mol) of 90% lead tetraacetate, added in small portions. The mixture was then heated under reflux for 30 min and filtered (to remove lead acetate, 12.10 g, 95% of theory), and the ethereal filtrate was shaken with a solution of sodium bicarbonate and then dried over anhydrous magnesium sulfate. Evaporation of the ether gave a reddish oil which was dissolved in ethanol. Cooling resulted in the separation of 1.29 g (19%) of deep yellow crystals of **15**: mp 148–149°; NMR (DMSO-d_6) δ 1.04 (2 t, 6 H), 3.08 (s, 3 H, NCH_3), 3.18 (s, 3 H, NCH_3), 3.93 (m, 4 H).

Anal. Calcd for $C_{10}H_{12}N_6O_5 \cdot C_2H_5OH$: C, 42.10; H, 5.31; N, 24.56; mol wt, 342. Found: C, 42.34; H, 5.50; N, 24.68; mol wt, 346.

Method B. To a solution of 5.1 g (0.030 mol) of 1,3-dimethyl-6-hydrazinouracil in 25 ml of dimethylformamide was added dropwise, over a period of 30 min, 11.0 g (0.063 mol) of diethyl azodicarboxylate. The reaction mixture was stirred for an additional 30 min, heated at 90–100° for 1 hr, and then evaporated to dryness. The residue was triturated with ethanol, and the crystals which separated were collected by filtration and recrystallized from cyclohexane–benzene (4:1) to give 3.43 g (33%) of **15**, mp 131–133°.

A mixture melting point with a sample of **15** (mp 148–149°), prepared by method A, melted at 148–149°. When a cyclohexane–benzene solution of the lower melting polymorph was seeded with the higher melting material, the product which crystallized melted at 148–149°. These polymorphs were interconvertible; slow crystallization from a dilute solution favored formation of the higher melting material, whereas rapid recrystallization from concentrated solutions, particularly from nonpolar solvents, gave the lower melting material.

1,3-Dimethyl-6-(2-carbethoxyhydrazino)uracil. To a stirred slurry of 53.4 g (0.315 mol) of 1,3-dimethyl-6-hydrazinouracil in 300 ml of 50% aqueous dioxane at 50° was added dropwise, and simultaneously, a solution of 16.0 g (0.4 mol) of sodium hydroxide in 100 ml of water and 43.5 g (0.4 mol) of ethyl chloroformate. The reaction mixture was concentrated to one-half its volume under reduced pressure, and the crystals which separated were collected by filtration, air dried, and recrystallized from acetonitrile to give 22.9 g (30%) of large, shiny plates: mp 219–220° dec; NMR (DMSO-d_6) δ 1.11 (t, 3 H), 3.02 (s, 3 H, NCH_3), 3.20 (s, 5 H, NCH_3 and NHNH), 4.66 (s, 1 H, C_5H).

Anal. Calcd for $C_9H_{14}N_4O_4$: C, 44.62; H, 5.83; N, 23.13. Found: C, 44.78; H, 5.71; N, 23.34.

1,3-Dimethyl-5-nitroso-6-(2-carbethoxyhydrazino)uracil. A suspension of 18.13 g (0.076 mol) of 1,3-dimethyl-6-(2-carbethoxyhydrazino)uracil in 50 ml of absolute ethanol was treated with 15.4 g (0.15 mol) of isoamyl nitrite, 1 drop of concentrated hydrochloric acid was added, and the vigorously reacting mixture was maintained at 10–15° by immersion in an ice bath. After 15 min, the golden yellow plates which had separated were collected by filtration, washed with several small portions of absolute ethanol followed by ether, and dried to give 17.45 g (87%) of the pure 5-nitroso derivative, mp 134–135°. The compound was recrystallized from ethanol for analysis without change in the melting point: NMR (DMSO-d_6) δ 1.15 (t, 3 H, CH_3), 3.04 (s, 3 H, NCH_3), 3.19 (s, 3 H, NCH_3), 3.32 (s, 2 H, NHNH), 4.11 (q, 2 H, CH_2).

Anal. Calcd for $C_9H_{13}N_5O_5$: C, 39.85; H, 4.84; N, 25.83. Found: C, 39.74; H, 4.75; N, 25.54.

1,3-Dimethyl-5-amino-6-(2-carbethoxyhydrazino)uracil. A solution of 16.51 g (0.061 mol) of 1,3-dimethyl-5-nitroso-6-(2-carbethoxyhydrazino)uracil in 200 ml of absolute ethanol was hydrogenated at room temperature under 50 psi of hydrogen in the presence of 2.0 g of 10% Pd/C. The reaction mixture was heated to boiling to dissolve the partially separated product and filtered, and the filtrate was concentrated under reduced pressure to about ¼ its volume. Cooling and filtering then gave 9.76 g (62%) of small platelets, mp 159–160°.

Anal. Calcd for $C_9H_{15}N_5O_4$: C, 42.03; H, 5.88; N, 27.23. Found: C, 42.30; H, 5.79; N, 27.33.

1,3-Dimethyl-5-carbethoxyaminobarbituric Acid (28). 1,3-Dimethyluramil (1,3-dimethyl-5-aminobarbituric acid, **27**)[28] was prepared most conveniently from 1,3-dimethyl-5-nitroso-6-aminouracil by acid hydrolysis[26] to 1,3-dimethylvioluric acid (**26**),[27] followed by catalytic reduction in methanol solution over 5% Pd/C catalyst. To a stirred solution of 34.2 g of **27** in 100 ml of 2 *N* sodium hydroxide at 40° was added dropwise, and simultaneously, 26.1 g of ethyl chloroformate and 100 ml of 2 *N* sodium hydroxide over a period of 30 min. The reaction mixture was then stirred for an additional 30 min, cooled, and filtered, and the filtrate was acidified to give 38.7 g (80%) of colorless crystals of **28**, mp 135–136° (lit.[29] mp 134°).

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.23; H, 5.37; N, 17.10.

1,3-Dimethyl-5-isocyanato-6-chlorouracil (29). To 150 ml of phosphorus oxychloride was added with stirring 24.3 g of 1,3-dimethyl-5-carbethoxyaminobarbituric acid, followed immediately by 6 ml of water (in small portions). As soon as the initial exothermic reaction had subsided, the reaction mixture was heated under reflux for 45 min, cooled, and filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure until all of the residual phosphorus oxychloride had been removed, and the residue was triturated with 100 g of crushed ice and then filtered. The very light green solid which was collected was washed thoroughly with water and then dried to give 13.9 g (65%) of **29**, mp 144–145°. The analytical sample, mp 146–147°, was prepared by recrystallization from acetonitrile followed by vacuum sublimation, ir (Nujol) 2225 cm^{-1} (NCO).

Anal. Calcd for $C_7H_6N_3O_3Cl$: C, 38.99; H, 2.80; N, 19.50. Found: C, 39.22; H, 2.88; N, 19.51.

1,4-Dihydro-4,6-dimethyloxazolo[5,4-*d*]pyrimidine-2,5,7(6*H*)-trione (30). A sample of 8.7 g of **29** was stored in a desiccator (atmospheric pressure) for 1 week. During this period the intensity of the isocyanate band (2225 cm^{-1}) decreased markedly, with a corresponding increase in the intensity of bands at 3060 and 3270 cm^{-1}. The material was then extracted with 250 ml of hot dioxane, and the extract was evaporated under reduced pressure, cooled, and filtered. Recrystallization of the residue from acetonitrile then gave 2.5 g (32%) of **30**, mp 201–202° dec, ir 1840 cm^{-1} (lactone).

Anal. Calcd for $C_7H_7N_3O_4$: C, 42.64; H, 3.58; N, 21.32. Found: C, 42.97; H, 3.48; N, 20.97.

Concentration of the dioxane filtrate above resulted in the separation of 1.0 g of unchanged **29**, mp 146–147°.

***sym*-(6-Chloro-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)urea (31).** The residue from the hot dioxane extraction above weighed 1.72 g (21%), mp 272–273° dec. The same compound could be prepared alternately from **29** by heating in DMF followed by cooling.

Anal. Calcd for $C_{13}H_{14}N_6O_5Cl_2$: C, 38.53; H, 3.48; N, 20.74; Cl, 17.51. Found: C, 38.72; H, 3.43; N, 20.64; Cl, 17.32.

4-(1,3-Dimethyl-6-chloro-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-methylsemicarbazide (32). To a solution of 15.1 g (0.07 mol) of 1,3-dimethyl-5-isocyanato-6-chlorouracil in 100 ml of acetonitrile was added with stirring a solution of 3.55 g (0.077 mol) of methylhydrazine in 100 ml of acetonitrile. A spontaneous, exothermic reaction resulted, and a voluminous mass of colorless crystals separated. The reaction mixture was stirred at room temperature for 24 hr, concentrated to 250 ml, and filtered, and the crude product (13.5 g, mp 183–185° dec) was recrystallized from 750 ml of methanol to give 8.4 g (46%) of **32** as colorless needles, mp 197–199° dec.

Anal. Calcd for $C_8H_{12}N_5O_3Cl$: C, 36.71; H, 4.62; N, 26.76; Cl, 13.55. Found: C, 36.75; H, 4.49; N, 26.69; Cl, 13.71.

This compound was converted into its benzylidene derivative (**33**) by heating with a slight excess of benzaldehyde in ethanol. Recrystallization of the crude product from ethanol gave colorless crystals (80%), mp 182–183°.

Anal. Calcd for $C_{15}H_{16}N_5O_3Cl$: C, 51.50; H, 4.61; N, 20.02; Cl,

10.14. Found: C, 51.34; H, 4.73; N, 20.00; Cl, 9.31.

4-(1,3-Dimethyl-6-ethoxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-methylsemicarbazide (34). To a nitrogen-blanketed solution of sodium ethoxide in ethanol (prepared from 50 ml of absolute ethanol and 0.27 g of sodium) was added with stirring 3.1 g (0.012 mol) of carefully dried 4-(1,3-dimethyl-6-chloro-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-methylsemicarbazide (**32**). The clear solution was heated under reflux for 1.5 hr, filtered from the suspended sodium chloride, and cooled to give a flocculent precipitate which was collected by filtration, yield 2.8 g (89%), mp 199–200° dec. The analytical sample was prepared by recrystallization from ethanol.

Anal. Calcd for $C_{10}H_{17}N_5O_4$: C, 44.27; H, 6.32; N, 25.82. Found: C, 44.41; H, 6.23; N, 25.96.

2,6,8-Trimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2*H*,6*H*,8*H*)-trione (2-Methylfervenulone, 17). Method A. To a well stirred, ice-cooled solution of 2.9 g (0.014 mol) of 6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2*H*,6*H*,8*H*)-trione (fervenulone, **5**) (dried in vacuo for 2 hr at 120° immediately prior to use) in 25 ml of dry DMF was added in small portions over a period of 15 min 0.84 g (0.018 mol) of a 50% dispersion of sodium hydride in mineral oil. The mixture was stirred for an additional 15 min and 2.8 g (0.02 mol) of methyl iodide was added to the partial suspension of the sodium salt of **5**. The ice bath was replaced by an oil bath (70°) for 3 hr, and the mixture was then stirred at room temperature for 40 hr. An atmosphere of dry nitrogen was maintained at a slight positive pressure over the reaction mixture during the entire reaction period. The neutral mixture was then filtered and concentrated to dryness under reduced pressure, and the residue was partitioned between 50 ml of chloroform and 25 ml of water. The chloroform solution was washed with a fresh portion of water, dried (anhydrous $MgSO_4$), and concentrated under reduced pressure to give a thick, yellow syrup, which was thoroughly extracted with pentane. Trituration of this residual syrup with water then gave 0.68 g of yellow crystals, mp 162–163°, which were recrystallized from a small amount of water to give 0.35 g (11%), mp 179–180°. One further recrystallization from ethanol then gave shining, thick, yellow plates, mp 181–182°, identical with the material obtained by methods B and C below, and also with the naturally occurring antibiotic MSD-92.[31]

Anal. Calcd for $C_8H_9N_5O_3$: C, 43.05; H, 4.07; N, 31.38. Found: C, 43.18; H, 4.03; N, 31.22.

Method B. To a stirred, ice-cooled solution of 1.24 g (0.054 mol) of sodium in 150 ml of absolute ethanol, kept under a slight positive pressure of nitrogen, was added 15.9 g (0.046 mol) of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-hydrazinouracil (**3**), and the reaction mixture was stirred for 2 hr. The thick slurry of pale yellow solid was then collected by filtration, washed with cold ethanol, and resuspended in 100 ml of absolute ethanol, and 14.2 g (0.10 mol) of methyl iodide was added. The mixture was then heated in an oil bath maintained at 50° for 2 hr. The resulting solution was concentrated to dryness under reduced pressure, and the residue was dissolved in 50 ml of water. Cooling then gave 3.9 g of yellow crystals; extraction of the aqueous filtrate with chloroform and evaporation of the chloroform extract gave an additional 6.8 g of product. Recrystallization from ethyl acetate then gave 6.2 g (60%) of the polymorphic form of **17** melting at 174–175°.

Anal. Calcd for $C_8H_9N_5O_3$: C, 43.05; H, 4.07; N, 31.38. Found: C, 43.07; H, 4.01; N, 31.27.

Recrystallization of a sample of these glistening yellow needles, mp 174–175°, from absolute ethanol gave yellow plates, mp 181–182°, identical with the material prepared by method A above, which upon subsequent recrystallization from ethyl acetate reverted to the yellow needles melting at 174–175°.

Recrystallization of a sample of either polymorphic form from water gave small, yellow plates, mp 92–93° dec. Drying this material for 48 hr under reduced pressure at 40° gave a pale yellow solid, mp 180–181°, identical with the material prepared above by method A.

Recrystallization from ethyl acetate of a sample of the material (mp 92–93°) obtained from water did not give the typical chunky, yellow needles usually obtained upon recrystallization of **17** from this solvent, but thick plates, mp 157–158° dec; the melting point did not change upon prolonged drying in vacuo.

Anal. Calcd for $C_8H_9N_5O_3$: C, 43.05; H, 4.07; N, 31.38. Found: C, 42.89; H, 3.88; N, 31.28.

Method C. A mixture of 1.05 g of 4-(1,3-dimethyl-6-chloro-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-methylsemicarbazide (**32**), 0.33 g of sodium acetate, and 50 ml of water was heated at 65–75° for 7 hr while a vigorous stream of air was passed through the solution. The reaction mixture (which exhibited a strong greenish-blue fluorescence) was then cooled and extracted with three 50-ml portions of chloroform. The combined extracts were dried ($MgSO_4$) and evaporated to give a gummy yellow residue (0.89 g). Trituration of this residue with ethyl acetate gave yellow crystals, which were collected by filtration; the filtrate was evaporated to dryness and the residue was triturated with water. The collected yellow solid was combined with the yellow solid above, dried thoroughly in vacuo, and recrystallized from ethyl acetate to give 0.37 g (41%) of yellow needles, mp 175–176°, identical in all respects with the material prepared above from ethyl acetate under method B.

Reduction of 2-Methylfervenulone (17) to 1,4-Dihydro-2,6,8-trimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2*H*,6*H*,8*H*)-trione (35). A solution of 1.12 g of 2-methylfervenulone (**17**) in 200 ml of warm water (50°) was reduced with 50 psi of hydrogen in the presence of 100 mg of Pd/C catalyst. After 30 min hydrogen uptake had ceased, and the reaction mixture was heated to boiling, filtered, concentrated, and cooled to give 0.67 g of a colorless solid, mp 245–246° dec. Attempted recrystallization of this material from ethyl acetate resulted in its gradual reconversion to bright yellow **17**, mp 174–175°.

Oxidation of 35 to 17. To a stirred solution of 0.28 g (0.00125 mol) of 2,3-dichloro-5,6-dicyanoquinone (DDQ) in 100 ml of chloroform was added 0.225 g (0.001 mol) of 1,4-dihydro-2,6,8-trimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2*H*,6*H*,8*H*)-trione (**35**), prepared as described above, and the mixture was heated under reflux for 30 min. It was then filtered to remove the precipitated hydroquinone, and the filtrate was concentrated to dryness under reduced pressure. Recrystallization of the residue from ethyl acetate gave 0.14 g (63%) of 2-methylfervenulone (**17**), mp 157–158°.

1,3-Dimethyl-5-carbomethoxyamino-6-chlorouracil (37). A solution of 6.3 g of 1,3-dimethyl-5-isocyanato-6-chlorouracil (**29**) in 100 ml of absolute methanol was heated under reflux for 1 hr, concentrated to a small volume under reduced pressure, and cooled. The yellow crystals which had separated were collected by filtration and recrystallized from methanol to give 5.8 g (80%) of **37**, mp 169–170° dec.

Anal. Calcd for $C_8H_{10}N_3O_4Cl$: C, 38.80; H, 4.07; N, 16.97. Found: C, 38.65; H, 3.99; N, 16.85.

1,3-Dimethyl-5-carbomethoxyamino-6-(1-methylhydrazino)uracil (38). A mixture of 2.5 g (0.01 mol) of 1,3-dimethyl-5-carbomethoxyamino-6-chlorouracil (**37**) and 0.9 g (0.02 mol) of methylhydrazine in 100 ml of acetonitrile was heated under reflux for 2 hr and filtered to remove a small amount of suspended solid, and the filtrate was concentrated to dryness under reduced pressure. The residual solid, consisting of methylhydrazine hydrochloride and **38**, was washed with acetonitrile and then extracted with 20 ml of warm absolute ethanol. Recrystallization of the residual solid from acetonitrile then gave 1.2 g (46%) of **38**, mp 179–180° dec.

Anal. Calcd for $C_9H_{15}N_5O_4$: C, 42.02; H, 5.88; N, 27.23. Found: C, 42.14; H, 5.80; N, 27.29.

This compound was converted to its benzylidene derivative (**39**) in 75% yield by heating with a slight excess of benzaldehyde in methanol solution for 1 hr, evaporation to a small volume, and addition of ether, mp 159–160°.

Anal. Calcd for $C_{16}H_{19}N_5O_4$: C, 55.64; H, 5.55; N, 20.28. Found: C, 55.71; H, 5.53; N, 20.24.

1,4-Dihydro-1,6,8-trimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2*H*,6*H*,8*H*)-trione (36). Method A. Pyrolysis of 3.0 g of 4-(1,3-dimethyl-6-chloro-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-methylsemicarbazide (**32**) at 135° (0.01 mm) for 3 hr gave a dark lavender mass which was dissolved in a small amount of hot acetonitrile. Cooling resulted in the separation of colorless crystals, which were then recrystallized from acetonitrile to give 1.7 g (66%) of **36**, mp 241–242°.

Anal. Calcd for $C_8H_{11}N_5O_3$: C, 42.66; H, 4.93; N, 31.10. Found: C, 42.64; H, 4.89; N, 31.24.

Method B. To a solution of sodium ethoxide in ethanol (prepared from 0.05 g of sodium and 50 ml of absolute ethanol) was added 0.51 g of 1,3-dimethyl-5-carbomethoxyamino-6-(1-methylhydrazino)uracil (**38**), and the golden solution was heated under reflux for 1 hr. It was then cooled, acidified by the addition of 1.2 ml of 2 *N* ethereal hydrogen chloride, and filtered, and the filtrate was evaporated to dryness. The dry residue was extracted with hot acetonitrile; evaporation of the extracts then gave crude **36**, which was recrystallized from acetonitrile, yield 0.17 g (38%), mp 241–242°. The product was identical in all respects with the material prepared by method A above.

4-(1,3-Dimethyl-6-chloro-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)semicarbazide (42). To a stirred solution of 7.1 g (0.033 mol) of 1,3-dimethyl-5-isocyanato-6-chlorouracil (**29**) in 250 ml of chloroform was added a solution of 1.3 g (0.04 mol) of anhydrous hydrazine (97%) in 250 ml of chloroform. After 72 hr of stirring, the mixture was filtered to give 6.5 g of crude **42**, mp 178–179° dec. Two recrystallizations from water then gave 2.6 g (33%) of pure **42**, mp 194–195° dec.

Anal. Calcd for $C_7H_{10}N_5O_3Cl$: C, 33.95; H, 4.06; N, 28.28. Found: C, 34.13; H, 4.16; N, 28.53.

1,4-Dihydro-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2*H*,6*H*,8*H*)-trione (16). Method A. To a stirred solution of 2.57 g of 1,3-dimethyl-5-amino-6-(2-carbethoxyhydrazino)uracil in 50 ml of water was added dropwise over a period of 20 min a total of 10 ml of 1 *N* NaOH. The pH was adjusted to 5, the deep orange solution was concentrated to dryness under reduced pressure, and the residue was extracted with 100 ml of chloroform. The extract was dried and evaporated to dryness, and the residue was triturated with water, dried, and recrystallized from absolute ethanol to give 0.51 g (20%) of the ethanolate of **16**, mp 167–168° dec.

Anal. Calcd for $C_7H_9N_5O_3 \cdot C_2H_5OH$: C, 42.03; H, 5.88; N, 27.23. Found: C, 41.92; H, 5.45; N, 27.12.

Recrystallization of the ethanolate of **16** from water gave **16**, mp 251–252° dec.

Anal. Calcd for $C_7H_9N_5O_3$: C, 39.80; H, 4.30; N, 33.16. Found: C, 39.81; H, 4.11; N, 33.07.

Method B. A solution of 0.21 g of 4-carbethoxyamino-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(4*H*,6*H*,8*H*)-trione ethanolate (**15**) in 25 ml of absolute ethanol containing 0.20 g of 10% Pd/C was hydrogenated under 50 psi of hydrogen at room temperature for a period of 2 hr. The mixture was then filtered, the filtrate was concentrated to 2–3 ml, and the crystals were collected by filtration, yield 0.06 g, mp 167–168° dec, identical in every respect (melting point, mixture melting point, ir and NMR spectra) with a sample of **16** ethanolate prepared by method A.

Method C. Pyrolysis of 1.0 g of 4-(1,3-dimethyl-6-chloro-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)semicarbazide (**42**) at 175–180° for 2.5 hr gave a violet-colored glass which was cooled, crushed to a powder, and extracted with 25 ml of boiling water. Cooling of the extract resulted in the separation of colorless crystals which were collected by filtration, washed with water, and dried to give 0.23 g (27%) of **16**, mp 251–252° dec, identical with the material prepared as described above.

Method D. A solution of 2.35 g of 2-methylfervenulone (**5**) ethanolate in 200 ml of absolute ethanol was shaken with 50 psi of hydrogen over 0.12 g of 10% Pd/C catalyst. Hydrogen uptake ceased after 1 hr. The mixture was filtered and the collected solids were extracted with 250 ml of boiling water. Concentration of the plum-colored filtrate and cooling then gave 1.1 g (56%) of colorless crystals of **16**, mp 251–252° dec, identical with the material prepared by methods A, B, and C above.

6,8-Dimethylpyrimido[5,4-*e*]-*as*-triazine-3,5,7(2*H*,6*H*,8*H*)-trione (Fervenulone, 5). Method C. Repeated crystallization of a sample of **16** from ethanol gave fervenulone ethanolate, mp 259–260° dec, identical in every respect with authentic material.

Method D. Dehydrogenation of **16** to fervenulone could also be accomplished somewhat more efficiently by heating under reflux for 30 min a solution of 0.53 g of **16** and 0.68 g of DDQ in 50 ml of chloroform. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure, and the residue was recrystallized from ethanol to give fervenulone ethanolate (0.56 g, 88%), mp 260–261° dec, identical with authentic material.

Reaction of Fervenulone (5) with Diazomethane. Formation of 2-Methylfervenulone (17). A stirred suspension of 1.28 g of fervenulone (**5**), solvated with ethanol, in 50 ml of a mixture of anhydrous ether and absolute ethanol (10:1) and 50 ml of 0.1 *M* ethereal diazomethane was stirred for 18 hr and then filtered. The filtrate was evaporated to dryness and the residue was dissolved in 10 ml of water and extracted with three 20-ml portions of chloroform. The combined, dried ($MgSO_4$) extracts were evaporated to dryness and the residue was crystallized from ethyl acetate to give 0.12 g (11%) of 2-methylfervenulone (**5**), mp 174–175°, identical with an authentic sample.

Formation of 3-Methoxy-6,8-dimethylpyrimido[5,4-e]-*as*-triazine-5,7(6*H*,8*H*)-dione (20). Method A. The collected solid material from the reaction of **5** with diazomethane (above) was extracted with hot absolute ethanol, and the extracts were evaporated to a small volume, cooled, and filtered to give 0.12 g of yellow crystals. Evaporation of the filtrate and trituration of the residual gum with ethanol gave a further 0.22 g of the same material, combined yield 0.34 g (30%), mp 143–144°.

Anal. Calcd for $C_8H_9N_5O_3$: C, 43.05; H, 4.06; N, 31.38. Found: C, 42.83; H, 4.01; N, 31.16.

Method B. To a stirred solution of 1.14 g (0.005 mol) of 3-chloro-6,8-dimethylpyrimido[5,4-e]-*as*-triazine-5,7(6*H*,8*H*)-dione (**6**) in 50 ml of absolute methanol, under a slight positive pressure of nitrogen, was added dropwise a solution of sodium methoxide in methanol (from 0.115 g, 0.005 mol, of sodium and 18 ml of methanol). The reaction mixture was then heated under reflux for 15 min and filtered, and the filtrate was concentrated under reduced pressure to ca. 5 ml. Cooling resulted in the separation of 0.95 g (85%) of yellow needles, mp 144–145°, identical in all respects with the material prepared by method A above.

Formation of 4,6,8-Trimethylpyrimido[5,4-e]-*as*-triazine-3,5,7(4*H*,6*H*,8*H*)-trione (18). To a stirred solution of 2.65 g (0.01 mol) of fervenulone (**5**), solvated with ethanol, in 200 ml of absolute methanol was added 100 ml of ethereal diazomethane (0.01 mol). Stirring was continued for 6 hr, and the yellow solution was then evaporated to dryness. Dissolution of the residual gum in hot ethanol followed by cooling gave 0.74 g of a pale yellow solid, mp 208–210°, which was then recrystallized three times from ethanol to give 0.12 g (5%) of **18**, mp 218–220°.

Anal. Calcd for $C_8H_9N_5O_3$: C, 43.05; H, 4.06; N, 31.38. Found: C, 42.92; H, 4.42; N, 31.05.

Registry No.—**1**, 483-57-8; **3**, 18969-82-9; **5**, 22712-37-4; **6**, 18969-84-1; **7**, 18969-85-2; **8**, 54632-29-0; **9**, 54632-30-3; **15**, 54667-56-0; **16**, 22712-36-3; **17**, 22712-32-9; **18**, 22712-42-1; **20**, 22712-41-0; **27**, 54632-31-4; **28**, 54632-32-5; **29**, 22712-33-0; **30**, 54632-33-6; **31**, 54632-34-7; **32**, 22712-34-1; **33**, 54632-35-8; **34**, 54632-36-9; **35**, 54632-37-0; **36**, 22712-38-5; **37**, 22712-39-6; **38**, 22712-40-9; **39**, 54632-38-1; **42**, 22712-35-2; 1,3-dimethyl-6-(2-carbethoxyhydrazino)uracil, 54632-39-2; 1,3-dimethyl-5-nitroso-6-(2-carbethoxyhydrazino)uracil, 54667-57-1; 1,3-dimethyl-5-amino-6-(2-carbethoxyhydrazino)uracil, 54632-40-5.

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Synthesis of Isofervenulin and 2-Methylisofervenulone[1]

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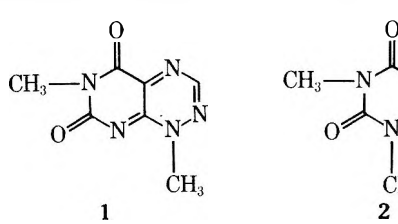
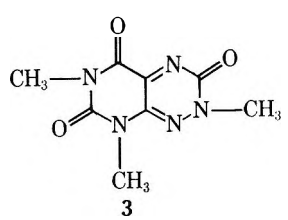
Syntheses of 5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-6,8(5*H*,7*H*)-dione (isofervenulin, **13**) and 2,5,7-trimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (2-methylisofervenulone, **10**) are described from a common intermediate, 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil (**4**). Although these compounds are ring isomers of the naturally occurring antibiotics fervenulin (**2**) and 2-methylfervenulone (MSD-92, **3**), neither exhibited antibiotic activity.

Derivatives of the pyrimido[4,5-*e*]-*as*-triazine (6-azapteridine) ring system have received considerable recent attention,[2] primarily because of their demonstrated antiviral activity,[3] and as a consequence of their close structural relationship to the pteridines and their isomeric relationship with the pyrimido[5,4-*e*]-*as*-triazine ring system present in the naturally occurring antibiotics toxoflavin (**1**), fervenulin (**2**), and 2-methylfervenulone (MSD-92, **3**).[4] We report in the present paper the synthesis of 5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-6,8(5*H*,7*H*)-dione (isofervenulin, **13**) and 2,5,7-trimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (2-methylisofervenulone, **10**). Both of these compounds are of considerable potential interest as ring isomers of the antibiotics **2** and **3**, respectively.



1

2

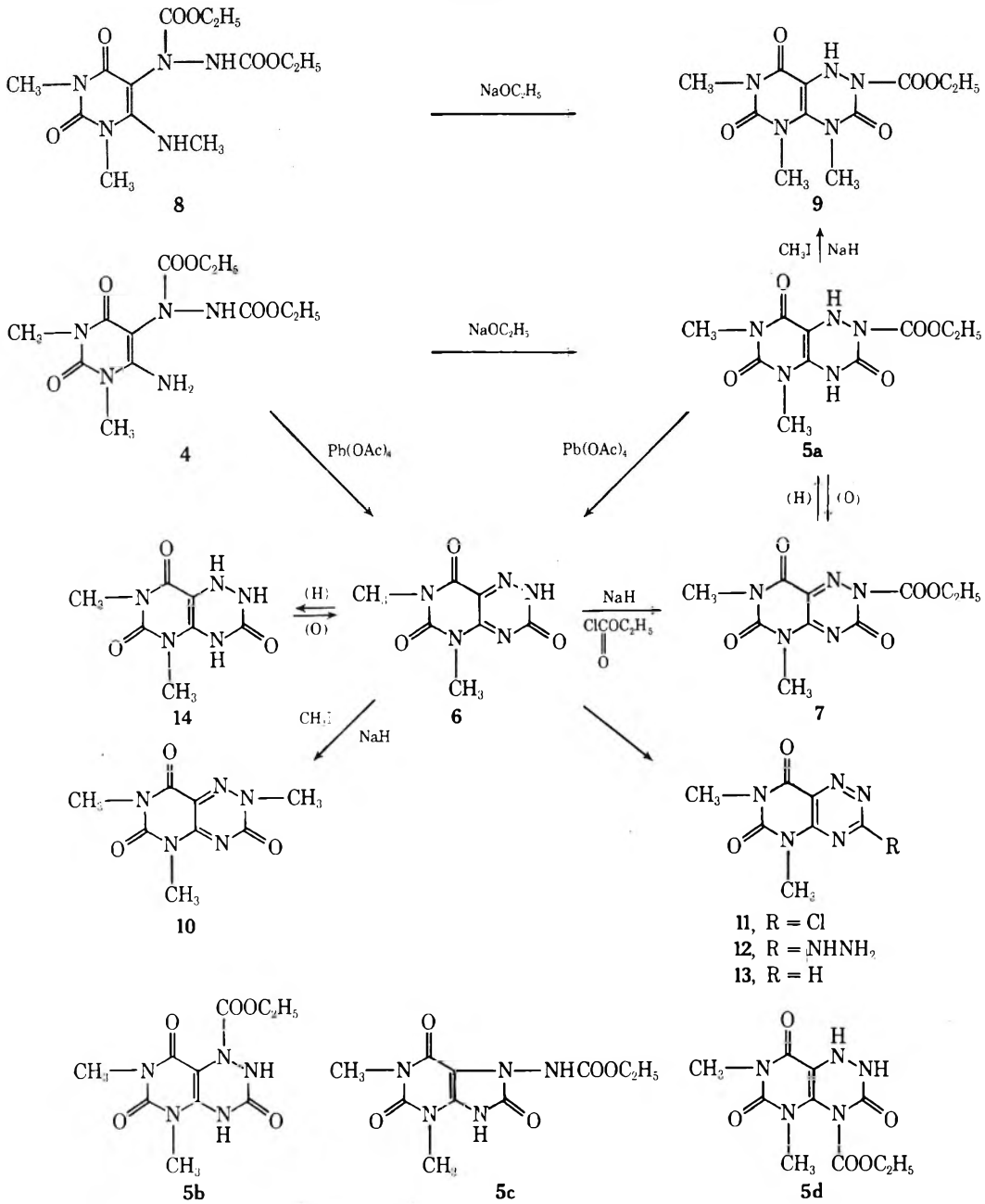


3

We have recently reported[5] a new method for C-5 functionalization of a variety of 6-amino- and 6-hydrazinopyrimidines which involves Michael addition to diethyl azodicarboxylate. This gives rise to a 5-(1,2-dicarbethoxyhydrazino) derivative which can then be converted (a) to a 5-carbethoxyamino derivative by Raney nickel reduction, or (b) to derivatives of the pyrimido[5,4-*e*]-*as*-triazine ring system (in the case of 6-hydrazino-substituted pyrimidines) by a variety of cyclization procedures.[4] We have now found that 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil (**4**), readily available in high yield from 1,3-dimethyl-6-aminouracil and diethyl azodicarboxylate,[5] can be smoothly cyclized with sodium ethoxide in ethanol to **5a**, a derivative of the isomeric pyrimido[4,5-*e*]-*as*-triazine ring system. Although it might have been expected that base-catalyzed intramolecular cyclization of **4** would have led to compound **5b** or **5c**, we present below convincing evidence that the structure of this intramolecular cyclization product of **4** possesses structure **5a**, in which the carbethoxy group is attached to N-2 of the pyrimidotriazine ring.

Thus, compound **5a** could be dehydrogenated with either phosphorus oxychloride or thionyl chloride to 2-carbethoxy-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**7**), which could then be reconverted to **5a** by catalytic reduction. This simple sequence of interconversions thus serves to eliminate both structures **5b** and **5c** from consideration. It seems reasonable to suggest that the 1-carbethoxy derivative **5b** is probably the initial product of intramolecular cyclization of **4**, but that a subsequent intramolecular acyl transfer of the carbethoxy group from N-1 to N-2 then ensues. Steric hindrance at N-1 in compound **5b** may well be responsible for this unidirectional rearrangement. The structure of **5a** was further confirmed as follows. Treatment with sodium hydride followed by addition of methyl iodide gave 2-carbethoxy-1,4-dihydro-4,5,7-trimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**9**), whose structure was then firmly established by its independent synthesis by base-catalyzed cycli-

Scheme I



zation of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-methylaminouracil (8). This sequence of reactions eliminates the final alternative structure **5d**, which is implausible in any event on both mechanistic and steric grounds.

Compound **5a** was then converted in a single step with lead tetraacetate to 5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione[6] (isofervenulone, **6**), which could alternately be prepared directly from **4** by treatment with lead tetraacetate, although somewhat more vigorous conditions were required. To complete this series of interrelationships, **7** was obtained independently from **6** by reaction with ethyl chloroformate in the presence of sodium hydride. 2-Methylisofervenulone (**10**) was then prepared, by a reaction analogous to the conversion of **6** to **7**, by methylation of **6** with methyl iodide in the presence of sodium hydride.

Isofervenulin (**13**) was readily prepared from isofervenulone (**6**) by chlorination with phosphorus oxychloride in the presence of diethylaniline to **11**, conversion to the substituted hydrazine **12** with alcoholic hydrazine hydrate, and then "oxidative reduction" of **12** with aqueous mercuric oxide. It is interesting to note that although isofervenulone (**6**) could be smoothly reduced to dihydroisofervenulone (**14**), we were able to confirm previous observations[2a] that **11** could not be reductively dehydrohalogenated without destruction of the ring system. All of the reactions discussed above are summarized in Scheme I.

Neither isofervenulin (**13**) nor 2-methylisofervenulone (**10**) exhibited any in vitro antibiotic activity, which thus appears to be restricted to the [5,4-*e*] series.

Experimental Section

2-Carbethoxy-1,4-dihydro-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (5a). To a solution of sodium ethoxide, prepared from 11.98 g (0.521 mol) of sodium and 300 ml of absolute ethanol, was added at room temperature 34.25 g (0.101 mol) of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil (**4**) hemihydrate.[5] Stirring and heating to reflux produced complete solution followed by separation of a colorless solid. After 1 hr, the mixture was cooled in an ice bath, and 89.3 ml of 5.83 *M* (0.52 mol) alcoholic hydrogen chloride was added in small portions with continued cooling and stirring. The mixture was

then heated to reflux and filtered, and the inorganic material was extracted with a second 500-ml portion of hot ethanol. The combined extracts were concentrated to dryness and the product was washed with ether and recrystallized by solution in 650 ml of boiling ethanol, repeated filtration, concentration to one-fourth of the original volume, and cooling, yield 21.75 g (76%) of colorless crystals, mp 228–229° dec. The analytical sample was recrystallized from acetonitrile.

Anal. Calcd for $C_{10}H_{13}N_5O_5$: C, 42.40; H, 4.63; N, 24.72. Found: C, 42.33; H, 4.62; N, 24.43.

5,7-Dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (6). Method A. To a stirred solution of 16.46 g (0.049 mol) of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil (**4**) hemihydrate in 35 ml of glacial acetic acid, kept under a slight positive pressure of nitrogen, was added during 1 hr 22.15 g (0.05 mol) of lead tetraacetate in small portions. The reaction mixture was kept in an oil bath maintained at 75–80° during the reaction period. After the addition of each portion of the oxidant, a strong initial lavender coloration appeared which gradually faded to a pale yellow. The product began to separate from solution toward the end of the addition period, and after stirring for 1 hr, the mixture was cooled and filtered. The mother liquors were treated with 17.0 ml of 5.83 *M* alcoholic hydrogen chloride, and the precipitated solid was collected by filtration and extracted with 50 ml of hot ethanol. The combined filtrate and extract were concentrated to dryness, and the combined solids were recrystallized from water to give 5.83 g (67%) of **6**, mp 287–289° dec (lit.[2a] mp 284–285° dec).

Anal. Calcd for $C_7H_7N_5O_3$: C, 40.18; H, 3.38; N, 33.48. Found: C, 40.15; H, 3.42; N, 33.55.

Method B. A stirred suspension of 2.89 g (0.01 mol) of 2-carbethoxy-1,4-dihydro-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**5a**) in 25 ml of glacial acetic acid was treated with 4.87 g (0.011 mol) of lead tetraacetate, added portionwise over a period of 10 min. During this period the reaction temperature rose from 26 to 33°, and the product began to separate. After stirring for 1 hr, the product was filtered and the mother liquors were partially concentrated and cooled to give an additional quantity of product. The combined solids were washed with cold water and recrystallized from water to give 1.39 g (66%) of **6**, mp 287–289° dec, identical in every respect with the product prepared by method A.

2-Carbethoxy-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (7). Method A. A mixture of 8.5 g of 2-carbethoxy-1,4-dihydro-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**5a**) and 300 ml of thionyl chloride was heated under reflux for 1 hr. The resulting clear solution was then concentrated under reduced pressure to remove excess thionyl chloride, and the residual solid was dissolved in 75 ml of chloroform, 25 ml of water was added, and sodium bicarbonate was added in small portions to pH 7. The aqueous phase was separated and extracted with chloroform, and the combined chloroform extracts were washed with water, dried, and concentrated to dryness. The residual oil was crystallized by treatment with benzene and then recrystallized from benzene to give 5.36 g (63%) of **7**, mp 124–125° dec.

Anal. Calcd for $C_{10}N_{11}N_5O_5$: C, 42.71; H, 3.94; N, 24.90. Found: C, 42.64; H, 3.86; N, 24.90.

Method B. A mixture of 1.0 g of **5a**, 25 ml of phosphorus oxychloride, and 1 g of diethylaniline was heated under reflux for 15 min and then worked up as described above to give 0.45 g (45%), mp (after recrystallization from methanol) 124–125° dec, identical with the material obtained by method A.

Method C. To an ice-cooled solution of 4.19 g (0.02 mol) of 5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**6**) in 25 ml of DMF was added 1.20 g (0.025 mol) of a 50% dispersion of sodium hydride in mineral oil, and the mixture was stirred for 15 min. The resulting gray-green, gelatinous suspension of the sodium salt of **6** was then treated with 3.26 g (0.03 mol) of ethyl chloroformate. A vigorous reaction ensued, accompanied by the immediate separation of sodium chloride. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was extracted with 50 ml of chloroform; the extract was washed with three 25-ml portions of water, dried ($MgSO_4$), and concentrated to dryness. The residual solid was separated from 1.19 g of unreacted starting material by extraction with two 25-ml portions of hot benzene. The combined extracts were concentrated and the crystalline residue was washed with a small amount of cold ethanol and dried, yield 2.55 g (45%) of **7**, mp 124–125° dec, identical with the material prepared by methods A and B above.

Catalytic reduction of **6** in absolute ethanol, using 10% Pd/C as catalyst, resulted in quantitative reconversion to **5a**, mp 228–229° dec.

2-Carbethoxy-1,4-dihydro-4,5,7-trimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (9). Method A. A solution of 1.60 g (0.005 mol) of 2-carbethoxy-1,4-dihydro-5,7-dimethylpyrimido[4,5-*e*0-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**5a**) in 10 ml of DMF was stirred for 15 min with 0.31 g of a 53% dispersion of sodium hydride in mineral oil, and then treated with 4.3 g (0.028 mol) of methyl iodide. The reaction mixture was heated under reflux for 1 hr and filtered, and the filtrate was concentrated under reduced pressure to dryness. The residue was dissolved in chloroform, washed with water, dried ($MgSO_4$), and concentrated, and the residual crystals (1.21 g) were recrystallized from ethanol to give 1.15 g (77%) of **9**, mp 191–192° dec.

Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.43; H, 5.09; N, 23.56. Found: C, 44.61; H, 5.17; N, 23.35.

Method B. A solution of 17.2 g (0.05 mol) of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-methylaminouracil (**8**) in 150 ml of absolute ethanol containing 2.4 g (0.104 mol) of sodium was heated under reflux for 1 hr, cooled, and acidified to Congo Red by the addition of alcoholic hydrogen chloride. The mixture was then filtered, the collected solid was extracted with two 50-ml portions of boiling ethanol, and the combined filtrate and extracts were evaporated under reduced pressure. Trituration of the residue with ether gave a solid, which was recrystallized first from ethanol–ether (1:1) and then from a small amount of ethanol to give 3.60 g (24%) of **9**, mp 191–192° dec. This material was identical with a sample of **9** prepared by method A.

2,5,7-Trimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,-7*H*)-trione (2-Methylisofervenulone, 10). To an ice-cooled solution of 4.19 g (0.02 mol) of 5,7-dimethylpyrimido[4,5-e]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**6**) in 35 ml of DMF was added with stirring 1.20 g (0.025 mol) of a 50% dispersion of sodium hydride in mineral oil, and the mixture was stirred for 30 min. The slurry of the sodium salt of **6** was then treated with 14.2 g (0.10 mol) of methyl iodide; the mixture was heated under reflux for 30 min and concentrated to dryness, and the residue was partitioned between 100 ml of chloroform and 25 ml of water. The chloroform extract was dried ($MgSO_4$) and concentrated, and the residue was recrystallized from ethanol to give 3.89 g (87%) of **10**, mp 184–185° dec.

Anal. Calcd for $C_8H_9N_5O_3$: C, 43.05; H, 4.06; N, 31.38. Found: C, 42.96; H, 4.27; N, 31.42.

3-Chloro-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-6,8(5*H*,7*H*)-dione (11). To a stirred solution of 3.74 g (0.025 mol) of diethylaniline in 50 ml of phosphorus oxychloride was added 5.22 g (0.025 mol) of 5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**6**), and the mixture was heated in an oil bath under reflux for 15 min. The product gradually separated from the solution during this period. Excess phosphorus oxychloride was then removed by distillation under reduced pressure, the residue was stirred with crushed ice and filtered, and the collected solid was washed well with ethanol and ether, yield, 5.55 g (96%). The analytical sample was prepared by sublimation (200°, 1.5 mm) followed by recrystallization from acetonitrile, and melted at 252–253° (lit.[2a] mp 251–253°).

Anal. Calcd for $C_7H_6ClN_5O_2$: C, 36.94; H, 2.65; N, 30.77; Cl, 15.58. Found: C, 36.65; H, 2.55; N, 30.71; Cl, 15.37.

3-Hydrazino-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-6,8(5*H*,7*H*)-dione (12). To a warm (50°) solution of 0.454 g (0.002 mol) of 3-chloro-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-6,8-(5*H*,7*H*)-dione (**11**) in 100 ml of ethanol was added 0.236 g (0.004 mol) of 85% hydrazine hydrate. The reaction mixture turned deep orange, and bronze-colored plates began to separate almost immediately. The mixture was cooled and filtered, and the collected solid was washed with ethanol followed by ether to give 0.425 g (95%) of **12**, mp 253–255° dec. The analytical sample was prepared by recrystallization from ethanol without change in the melting point.

Anal. Calcd for $C_7H_9N_7O_2$: C, 37.66; H, 4.06; N, 43.93. Found: C, 37.52; H, 4.16; N, 43.75.

5,7-Dimethylpyrimido[4,5-*e*]-*as*-triazine-6,8(5*H*,7*H*)-dione (Isofervenulin, 13). A solution of 1.11 g (0.005 mol) of 3-hydrazino-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-6,8(5*H*,7*H*)-dione (**12**) and 1.63 g (0.0075 mol) of yellow mercuric oxide in 250 ml of water was stirred vigorously for 48 hr and then centrifuged. The supernatant liquid was filtered through a mat of Hy-flo, while the collected solid above was extracted with 100 ml of hot ethanol, and the extract was filtered through Hy-flo. The combined filtrates were then concentrated to a small volume, cooled and filtered, and

the yellow solid thus collected recrystallized from ethanol to give 0.43 g (44%) of **13**, mp 211.5–212°.

Anal. Calcd for $C_7H_7N_5O_2$: C, 43.52; H, 3.65; N, 36.26. Found: C, 43.53; H, 3.61; N, 36.12.

1,4-Dihydro-5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (14). A solution of 1.04 g of 5,7-dimethylpyrimido[4,5-*e*]-*as*-triazine-3,6,8(2*H*,5*H*,7*H*)-trione (**6**) in 100 ml of glacial acetic acid was hydrogenated in the presence of 0.2 g of 10% Pd/C catalyst at 50 psi of hydrogen. The uptake of hydrogen was rapid, and reduction was complete in 3 min. The mixture was filtered, the filtrate was evaporated to dryness, and the residual solid was triturated with ether and then filtered. Recrystallization from acetic acid then gave 0.59 g of colorless crystals, mp 264–265° dec. This compound is probably a solvate with acetic acid, since prolonged drying under reduced pressure at 110° raised the melting point to 326–328° dec. The analytical sample was recrystallized from water without change in the melting point.

Anal. Calcd for $C_7H_9N_5O_3$: C, 39.80; H, 4.30; N, 33.16. Found: C, 39.86; H, 4.30; N, 32.98.

Repeated recrystallization of **14** from water led to air oxidation and the separation of starting material (**6**), mp 287–289° dec, in quantitative yield.

Registry No.—**4**, 18969-87-4; **5a**, 54632-24-5; **6**, 7271-90-1; **7**, 54632-25-6; **8**, 49810-14-2; **9**, 54632-26-7; **10**, 26154-55-2; **11**, 54632-27-8; **12**, 18969-88-5; **13**, 16044-79-4; **14**, 54632-28-9.

References and Notes

(1) This work was supported by grants to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service (CA-12876) and Eli Lilly and Co., Indianapolis, Ind.

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(5) E. C. Taylor and F. Sowinski, *J. Org. Chem.* **39**, 907 (1974).

(6) This compound had been prepared independently by the condensation of 1,3-dimethylalloxan with *S*-methylisothiosemicarbazide, followed by hydrolysis, as an intermediate in an unsuccessful attempt to synthesize isofervenulin (ref 2a).

Pteridines. XXXIV. Synthesis of 8-Hydroxy-7(8*H*)-pteridinones (Pteridine Hydroxamic Acids)[1,2]

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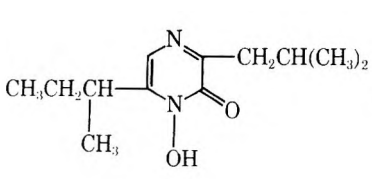
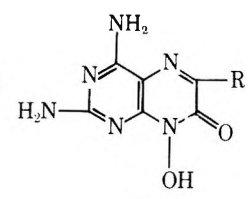
A series of 2,4-diamino-6-substituted 8-hydroxy-7(8*H*)-pteridinones (pteridine hydroxamic acids) (**2**) has been prepared from 2,4-diamino-6-substituted pteridine 8-oxides (**5**) by chlorination in glacial acetic acid, followed by cleavage of the resulting pteridine hydroxamic acid anhydrides (**13**) with ethanolic HCl. An alternative but less satisfactory route to 2,4-diamino-6-methyl-8-hydroxy-7(8*H*)-pteridinone (**2a**) involved condensation of pyruvohydroxamoyl chloride (**6**) with aminomalononitrile (**3**) tosylate to give 2-amino-3-cyano-5-methyl-6-chloropyrazine 1-oxide (**7**), hydrolysis to the pyrazine hydroxamic acid **9**, and cyclization with guanidine.

The striking antibacterial activity of the naturally occurring pyrazine antibiotic aspergillic acid (**1**)[3–5] has stimulated work on the preparation of numerous analogs, among them being hydroxamic acids of pyridine,[6] pyrimidine,[7] quinoline,[8] and quinazoline.[9] By far the greatest efforts, however, have been concentrated on the synthesis of variously substituted pyrazine hydroxamic acids,[10] and in some instances the in vitro antibacterial activity of these synthetic analogs has actually exceeded that of aspergillic acid itself. Despite the incorporation of a pyrazine ring within the pteridine nucleus, and the broad spectrum of biological activities associated with pteridine derivatives, there are no reports of the preparation of pteridine analogs of aspergillic acid.[11] We describe in the present paper the synthesis and properties of a number of 8-hydroxy-7(8*H*)-pteridinones (pteridine hydroxamic acids) of structure **2**.



1



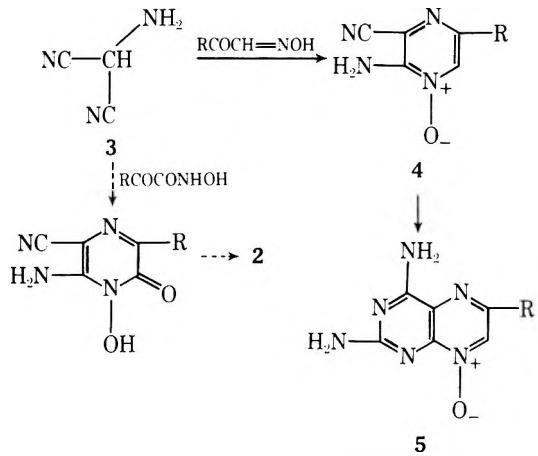
2

These compounds should be of considerable potential pharmacological interest, not only because of their obvious structural relationship to **1**, but also because of their similarity to the clinically important 2,4-diamino-6-substituted pteridines.[12]

We have recently described the condensation of aminomalononitrile (**3**) with α-keto aldoximes to give 2-amino-3-cyano-5-substituted pyrazine 1-oxides[13] (**4**), which were then cyclized with guanidine to give 2,4-diamino-6-substituted pteridine 8-oxides (**5**). For the purpose of preparing pyrazine, and subsequently pteridine, hydroxamic acids, this general reaction sequence requires as a modification the condensation of **3** with an α-keto hydroxamic acid (see Scheme I). Similar conversions were briefly explored by Ramsey and Spring,[10c] who reported that the action of pyruvohydroxamic acid bisulfite with aminoacetone led in moderate yield to 1-hydroxy-3,6-dimethyl-2(1*H*)-pyrazinone. In spite of this encouraging precedent, we were unable to bring about condensation of aminomalononitrile (**3**) either with pyruvohydroxamic acid or its bisulfite derivative; no reaction could be detected at room temperature, and a rapid conversion to ammonium tosylate and a number of unidentified noncrystalline materials occurred at temperatures exceeding 40°. This approach was therefore abandoned, and a second potential synthetic route to the desired pteridine hydroxamic acids was explored as follows.

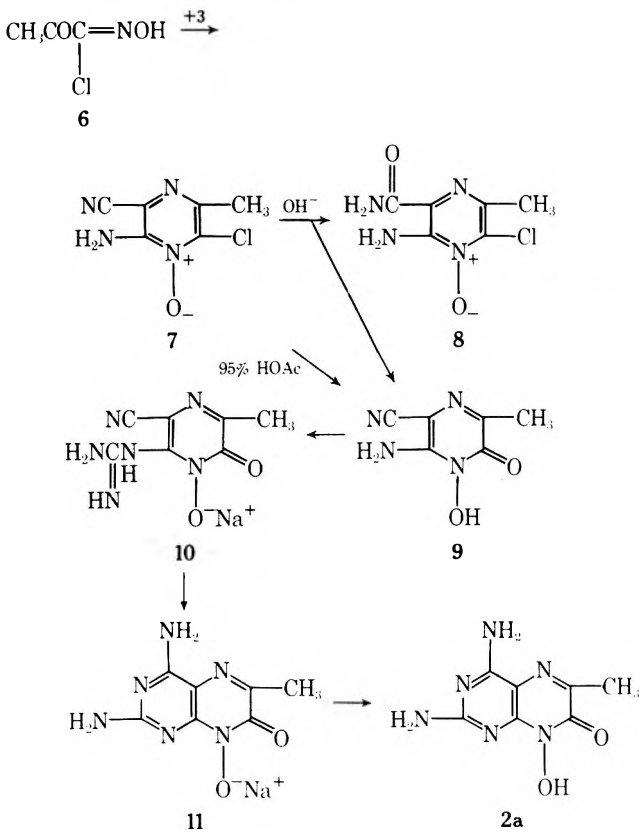
Chlorination of oximinoacetone in benzene solution,[14] or preferably nitrosation of chloroacetone,[15] gave pyruvohydroxamoyl chloride (**6**), which, in contrast to pyruvohy-

Scheme I



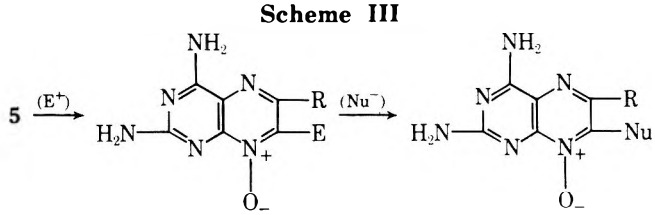
droxamic acid, reacted smoothly with **3** in 2-propanol to give 2-amino-3-cyano-5-methyl-6-chloropyrazine 1-oxide (**7**). As anticipated, the 6-chloro substituent of **7** proved to be extremely reactive to nucleophilic displacement, since it is both ortho to the *N*-oxide grouping and para to the nitrile substituent. Thus, treatment of **7** with 0.5 *N* sodium hydroxide led to a separable mixture of the carboxamide derived from **7** (i.e., **8**) and 1-hydroxy-2-amino-3-cyano-5-methyl-6(1*H*)-pyrazinone (**9**) (see Scheme II). More satisfactory was the hydrolysis of **7** in 95% acetic acid to give only **9** in 82% yield. This appeared to be an ideal intermediate for eventual conversion to the desired pteridine hydroxamic acid (**2a**). Contrary to all expectations, however, the annelation of a pyrimidine ring presented numerous difficulties. Treatment of **9** with guanidine in refluxing methanol–sodium methoxide did not lead to the expected 2,4-diaminopteridine, but rather to intermediate **10**. Heating **10** in refluxing dimethylformamide, however, did give **11**, which was finally converted to 2,4-diamino-6-methyl-8-hydroxy-7(8*H*)-pteridinone (**2a**) hemihydrate by suspension in water followed by careful acidification. The water of hydration in **2a** proved extremely difficult to remove. For example, the hemihydrate was recovered unchanged after many hours at 150° (0.1 Torr) over phosphorus pentoxide. Anhydrous material was finally obtained by conversion of the hemihydrate to its tosyl salt (again a hemihydrate), followed by rigorous drying and final treatment with dry methanolic pyridine. Alternatively, **2a** could be obtained more directly, although again in poor yield, by treatment of either **10** or **11** with methanolic *p*-toluenesulfonic acid, followed by conversion of the resulting tosyl salt to **2a** as described above. However, despite the fact that one representative of the desired pteridine hydroxamic acids (**2**) was now in hand, it was clear that the above synthetic route, which suffered from low overall yields, sensitive starting materials (α-ketohydroxamoyl chlorides), and numerous difficulties in isolation and product characterization, could not be considered generally useful.

Scheme II



As a possible alternative approach to the desired hydroxamic acids (**2**), the direct conversion of the readily available pteridine 8-oxides[13] was considered. Although several reagents have been employed in the past for the direct conversion of nitrones and aromatic *N*-oxides to hydroxamic acids (i.e., $FeCl_3$[16] and $Pb(OAc)_4$[17]), the reaction of pteridine 8-oxides with such reagents is severely complicated by the presence of five oxidatively labile nitrogen atoms, and by the insolubility of 2,4-diaminopteridine 8-oxides in common organic solvents. In the light of these inherent complications, we explored a potentially more subtle method for effecting this overall conversion, as illustrated in general terms in Scheme III. This sequence exploits the remarkable amphoteric ability of the *N*-oxide grouping to activate α and γ positions to both electrophilic addition and nucleophilic substitution reactions.[18] Similar sequential operations on aromatic *N*-oxides often represent the method of choice for the functionalization of heterocycles; the electrophile is most usually NO_2^+, SO_3, or Hg^{2+}, and the resulting substituted aromatic *N*-oxides are then subjected to nucleophilic displacement reactions to give the final product.

Scheme III

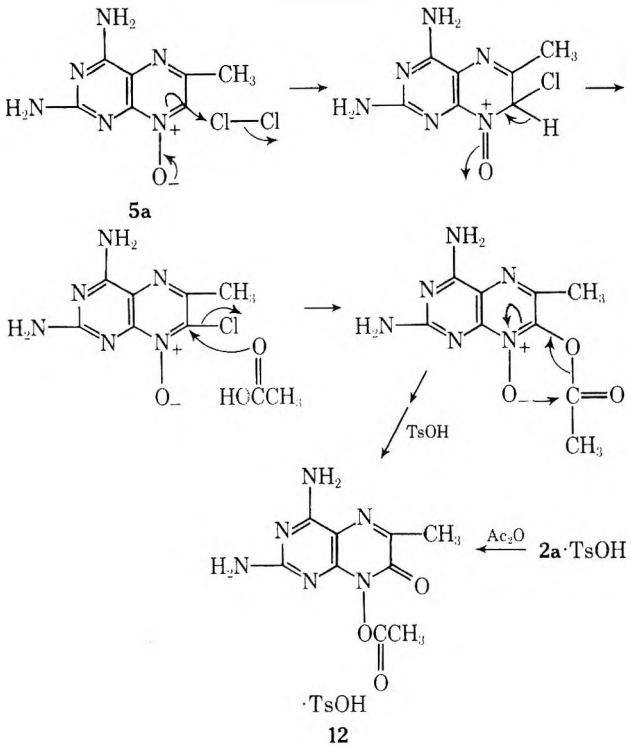


Initial efforts to nitrate 2,4-diamino-6-methylpteridine 8-oxide (**5a**) led only to extensive decomposition, and no homogeneous products could be isolated. Similar disappointing results were obtained upon attempted sulfonation, and **5a** failed to react with mercuric acetate under conditions which proved to be successful with other heterocyclic *N*-oxides. More encouraging results, however, were obtained upon attempted chlorination. When **5a** was suspended in glacial acetic acid containing a slight excess of chlorine, and the resulting mixture was stirred at 65° in a small glass pressure device, a single product was isolated as its tosyl salt (**12**). This product analyzed for $C_9H_{10}N_6O_3 \cdot TsOH$ and thus corresponded to the oxidative introduction of an acetoxy substituent. The NMR spectrum of **12** showed that the 6-methyl group was intact (δ 2.00 vs. δ 2.25 for the C_6 methyl group of **5a**), but that the C_7 proton present in the starting material had been eliminated. The ir spectrum of the oxidation product **12** revealed strong car-

bonyl absorption at 1825 cm^{-1}. Such high carbonyl stretching frequencies are characteristic of acetylated hydroxamic acids[19] and suggested that **12** was, in fact, the tosyl salt of 2,4-diamino-6-methyl-8-acetoxy-7(8*H*)-pteridinone. That this was indeed the case was readily established by the acetylation of authentic 2,4-diamino-6-methyl-8-hydroxy-7(8*H*)-pteridinone (**2a**) tosyl salt; the product of this reaction was identical in every respect with **12**.

It seems reasonable to suggest that the conversion of **5a** to **12** results from electrophilic substitution of chlorine at position 7 followed by nucleophilic displacement on the resulting 2,4-diamino-6-methyl-7-chloropteridine 8-oxide by acetate ion, and a subsequent intramolecular acyl transfer as depicted in Scheme IV. Each of the individual transformations depicted in Scheme IV has ample precedent in *N*-oxide chemistry.

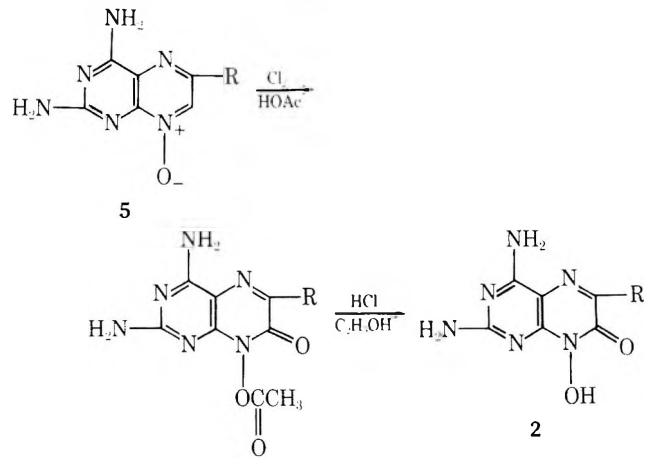
Scheme IV



With the identity of **12** firmly established, there remained only the problem of hydrolysis of the acetyl group in **12** to give the parent hydroxamic acid **2a**. Although this transformation is an apparently trivial one, it should be remembered that the previously observed, almost irreversible, hydration of **2a** precludes the use of aqueous solvents. After extensive experimentation, the most satisfactory method found for effecting this simple cleavage was ethanolysis in the presence of dry hydrogen chloride. In fact, it was found that isolation of **12** was unnecessary. The bright orange solution resulting from chlorination of **5a** in acetic acid was concentrated in vacuo to give the crude acetylated hydroxamic acid as a dark semicrystalline mass. Upon addition of dry ethanolic HCl, the color of the mixture changed almost immediately to a pale yellow, and, after stirring overnight, the hydroxamic acid **2a** separated as its hydrochloric acid salt in a high state of purity. The free base was then readily obtained by treatment with dry methanolic pyridine. This material was identical in all respects with authentic **2a** prepared by the alternative route described above.

This procedure for the conversion of 2,4-diamino-6-methylpteridine 8-oxide to the hydroxamic acid **2a** is remarkable in the facility with which it may be carried out, and it stands in marked contrast to the previous approaches, which were beset with difficulties. The generality of this latter approach to pteridine hydroxamic acids is demonstrated by its utilization for the preparation of the homologs listed in Scheme V. Overall yields in all cases were

Scheme V



a, R = CH_3
b, R = CH_2CH_3
c, R = $CH_2CH_2CH_3$
d, R = $CH(CH_3)_2$
***e**, R = $CH_2CH(CH_3)_2$
f, R = $(CH_2)_4CH_3$

80–90% starting from the corresponding pteridine 8-oxides. Compound **2e**, marked with an asterisk, is the pteridine counterpart of aspergillic acid.

All of these pteridine hydroxamic acids are undergoing wide-spectrum pharmacological testing. Preliminary results have indicated that these compounds, as a class, possess significant activity as inhibitors of ribonucleotide reductase.

These studies demonstrate the synthetic potential of the pteridine 8-oxide grouping and illustrate its utilization for the controlled introduction of substituents into the pyrazine ring. The following paper describes an extension of this principle to the total synthesis of asperopterin B.[20]

Experimental Section

2-Amino-3-cyano-5-methyl-6-chloropyrazine 1-Oxide (7). A suspension of 6.0 g of purified pyruvohydroxamoyl chloride (**6**)[15] and 12.0 g of aminomalononitrile (**3**) tosylate was stirred as a thick slurry in isopropyl alcohol (40 ml). After 48 hr the reaction mixture was concentrated and cooled to give 10.0 g of crude product which was washed thoroughly with water and ethanol to remove any starting materials. The crude material was then dissolved in the minimum amount of boiling DMF and treated with active charcoal. Following filtration, the hot solution was diluted with twice its volume of absolute ethanol and cooled to yield 8.5 g (93%) of pale yellow **7** as elongated needles: mp 257–258° dec; NMR (DMSO-d_6) δ 2.33 (3, s, C_5 CH_3), 7.67 (2, br, NH_2).

Anal. Calcd for $C_6H_5N_4OCl$: C, 39.00; H, 2.71; N, 30.36. Found: C, 38.94; H, 2.81; N, 30.53.

1-Hydroxy-2-amino-3-cyano-5-methyl-6(1*H*)-pyrazinone (9). Method A. Basic Hydrolysis of 2-Amino-3-cyano-5-methyl-6-chloropyrazine 1-Oxide (7). Forty milliliters of 1 *N* NaOH was added dropwise to a stirred suspension of 4.0 g of **7** in 40 ml of water. After completion of NaOH addition the reaction mixture had assumed a bright orange color. After 48 hr of stirring, the deep red solution was extracted with ethyl acetate, and 10% HCl was then added dropwise until the solution became nearly opaque (pH 4). At this point the solution was cooled to 0° and extracted four times with ethyl acetate. The combined extracts of the acid solution were filtered through a cone of anhydrous $MgSO_4$

and evaporated to dryness to give 3.0 g of bright yellow 1-hydroxy-2-amino-3-cyano-5-methyl-6(1*H*)-pyrazinone (**9**). The crude material was recrystallized from glacial acetic acid to give 2.1 g (56%) of **9**: mp 260–261° dec; NMR (DMSO-d_6) δ 2.07 (3, s, C_5CH_3), 7.51 (2, br, NH_2).

Anal. Calcd for $C_6H_6N_4O_2$: C, 43.37; H, 3.64; N, 33.73. Found: C, 43.14; H, 3.75; N, 33.82.

The ethyl acetate extract from the initially basic reaction mixture, as described above, was filtered through a cone of anhydrous $MgSO_4$ and evaporated to dryness to give 1.0 g (22%) of bright yellow 2-amino-3-carbamoyl-5-methyl-6-chloropyrazine 1-oxide (**8**). Recrystallized from methanol, the analytical sample had mp 244–245° dec, NMR (DMSO-d_6) δ 2.32 (3, s, C_5CH_3).

Anal. Calcd for $C_6H_7N_4O_2Cl$: C, 35.57; H, 3.49; N, 27.66. Found: C, 35.64; H, 3.54; N, 27.76.

Method B. Hydrolysis of 2-Amino-3-cyano-5-methyl-6-chloropyrazine 1-Oxide (7) with Glacial Acetic Acid. Five grams of **7** was dissolved in 75 ml of 95% acetic acid at 100°, and the solution was stirred at 100° for 3 hr before cooling overnight. Filtration, followed by thorough washing with ethanol, then gave 3.7 g (82%) of golden yellow **9** identical in all respects with the material prepared by method A above.

2,4-Diamino-6-methyl-8-hydroxy-7(8*H*)-pteridinone (2a) by Guanidine Cyclization of 1-Hydroxy-2-amino-3-cyano-5-methyl-6(1*H*)-pyrazinone (9). To a solution of guanidine in methanol (prepared by addition of 5.8 g of guanidine hydrochloride to a solution of 10.8 g of sodium methoxide in 300 ml of anhydrous methanol, and removing the precipitated sodium chloride by filtration) was added 6.5 g of **9**, and the resulting mixture was heated under reflux for 24 hr. After cooling and subsequent filtration, 7.4 g of light brown material was obtained. Spectroscopic evidence (ir ν_{max} 2200 cm^{-1}) indicated that this initially isolated material was the sodium salt of 1-hydroxy-2-guanidino-3-cyano-5-methyl-6(1*H*)-pyrazinone (**10**). Treatment of **10** overnight in refluxing DMF completed the desired cyclization, giving 2,4-diamino-6-methyl-8-hydroxy-7(8*H*)-pteridinone sodium salt (**11**, overall yield 32%), which upon suspension in water followed by acidification with 6 *N* HCl gave 2,4-diamino-6-methyl-8-hydroxy-7(8*H*)-pteridinone (**2a**) hemihydrate. Crystallization of the crude residue from glacial acetic acid afforded 2.0 g (23%) of pale yellow crystals: mp >300°; NMR (CF_3COOH) δ 2.08 (3, s, C_6CH_3).

Anal. Calcd for $C_7H_8N_6O_2 \cdot \frac{1}{2}H_2O$: C, 38.70; H, 4.18; N, 38.70. Found: C, 38.85; H, 4.16; N, 38.65.

It was subsequently found that the treatment of either **10** or **11** with 1 equiv of *p*-toluenesulfonic acid in methanol led in a more convenient manner to 2,4-diamino-6-methyl-8-hydroxy-7(8*H*)-pteridinone (**2a**) hemihydrate (overall yield 65%), identical with the material prepared above. This material could only be freed of water by the following procedure. One gram of the hemihydrate of **2a** was suspended in 30 ml of anhydrous methanol which had previously been saturated with *p*-toluenesulfonic acid. The resulting suspension was heated to boiling and maintained there until all materials had dissolved. Cooling then afforded 1.1 g (61%) of the hemihydrate of the tosyl salt of **2a**: mp 288° dec; NMR (DMSO-d_6) δ 2.15 (3, s C_6CH_3), 1.96 (3, s), 7.17 (4, q, tosyl acid).

Anal. Calcd for $C_{14}H_{16}N_6O_5S \cdot \frac{1}{2}H_2O$: C, 43.17; H, 4.41; N, 21.58. Found: C, 43.17; H, 4.73; N, 21.74.

In contrast to the hemihydrate of **2a**, this material could be successfully dehydrated by drying at 150° (0.5 Torr) over P_2O_5 for 24 hr to give the anhydrous tosyl salt of **2a**: mp 288° dec; NMR (DMSO-d_6) δ 2.15 (3, s, C_6CH_3), 1.96 (3, s), 7.17 (4, q, tosyl acid).

Anal. Calcd for $C_{14}H_{16}N_6O_5S$: C, 44.20; H, 4.25; N, 22.10. Found: C, 44.24; H, 4.12; N, 22.07.

This material in turn, upon treatment with hot, anhydrous pyridine, was converted in quantitative yield to very pale yellow 2,4-diamino-6-methyl-8-hydroxy-7(8*H*)-pteridinone (**2a**): mp >300°; NMR (CF_3COOH) δ 2.08 (3, s, C_6CH_3); uv λ_{max} (0.1 *N* NaOH) 357 nm (log ϵ 4.16), 345 (4.12), 257 (4.43), 245 (4.45).

Anal. Calcd for $C_7H_8N_6O_2$: C, 40.38; H, 3.87; N, 40.37. Found: C, 40.04; H, 3.93; N, 40.09.

2,4-Diamino-6-methyl-8-acetoxy-7(8*H*)-pteridinone Tosyl Salt (12). To a solution of 0.5 g of chlorine in 20 ml of glacial acetic acid was added 0.5 g of rigorously purified 2,4-diamino-6-methylpteridine 8-oxide (**5a**), and the resulting suspension was stirred at 60–65° in a small glass pressure device. Solution (bright orange) was generally complete within 15 min, and after stirring for 45 min the reaction mixture was concentrated in vacuo to a dark oil (temperature not exceeding 40°). The residue was taken up in a solution of 1.0 g of *p*-toluenesulfonic acid in 10 ml of absolute ethanol, and after decolorizing and cooling overnight, 0.52 g (47%) of pale yellow **12** was collected. The analytical sample, recrystallized from ethanol, had mp 218° dec; NMR (DMSO-d_6) δ 2.00 (3, s, C_6CH_3), 2.18 (3, s, –NOAc), 1.96 (3, s), 7.17 (4, q, tosyl acid); ir (KBr) ν_{max} 1820 cm^{-1} (–NOAc).

Anal. Calcd for $C_{16}H_{18}N_6O_6S$: C, 45.48; H, 4.30; N, 19.90. Found: C, 45.59; H, 4.55; N, 19.64.

The above material was shown to be identical in all respects with the product obtained upon acetylation of authentic (vide supra) 2,4-diamino-6-methyl-8-hydroxy-7(8*H*)-pteridinone (**2a**) tosyl salt.

2,4-Diamino-6-methyl-8-hydroxy-7(8*H*)-pteridinone (2a) by Chlorination of 2,4-Diamino-6-methylpteridine 8-Oxide (5a). To a solution of 1.0 g of chlorine in 40 ml of glacial acetic acid was added 1.1 g of rigorously purified and finely ground **5a**, and the resulting suspension was stirred at 60–65° in a small glass pressure device. Solution (bright orange) was generally complete within 15 min, and after stirring for 45 min the reaction mixture was concentrated in vacuo to a dark oil (temperature not exceeding 40°). Residual acetic acid was removed as its benzene azeotrope, and the solid mass remaining (**13a**) was dissolved in 20 ml of anhydrous ethanol with gentle heating and transferred to a small erlenmeyer flask. After cooling, 1.0 g of dry HCl was slowly bubbled into the solution, and the reaction mixture was covered and stirred at room temperature. After stirring for 24 hr, the mixture was filtered to yield 0.97 g of **2a** hydrochloride, which was washed with 5 ml each of 2-propanol and diethyl ether. The combined mother liquor and washings were concentrated to about 10 ml to yield an additional 0.26 g of product (total yield 1.23 g, 86%). The free base was easily obtained by covering with a small amount of 10% pyridine–methanol and boiling gently for 10–15 min. Upon cooling, very pale yellow 2,4-diamino-6-methyl-8-hydroxy-7(8*H*)-pteridinone was obtained in nearly quantitative yield. The material was identical in all respects with authentic **2a** prepared as previously described (vide supra).

The following compounds were prepared similarly.

2,4-Diamino-6-ethyl-8-hydroxy-7(8*H*)-pteridinone (2b): 84% yield; mp >300°; NMR (CF_3COOH) δ 0.92 (3, t), 2.55 (2, q, CH_2CH_3); uv λ_{max} (0.1 *N* NaOH) 353 nm (log ϵ 4.14), 346 (4.16), 257 (4.39), 244 (4.40).

Anal. Calcd for $C_8H_{10}N_6O_2$: C, 43.24; H, 4.54; N, 37.83. Found: C, 43.01; H, 4.77; N, 37.67.

2,4-Diamino-6-*n*-propyl-8-hydroxy-7(8*H*)-pteridinone (2c): 80% yield; mp 295° dec; NMR (CF_3COOH) δ 0.58 (3, t), 1.39 (2, hex), 2.49 (2, t, *n*-propyl); uv λ_{max} (0.1 *N* NaOH) 354 nm (log ϵ 4.16), 346 (4.20), 257 (4.40), 244 (4.43).

Anal. Calcd for $C_9H_{12}N_6O_2$: C, 45.76; H, 5.12; N, 35.58. Found: C, 45.76; H, 5.31; N, 35.70.

2,4-Diamino-6-isopropyl-8-hydroxy-7(8*H*)-pteridinone (2d): 89% yield; mp 291° dec; NMR (CF_3COOH) δ 1.00 (6, d), 2.90 (1, hep, isopropyl); uv λ_{max} (0.1 *N* NaOH) 355 nm (log ϵ 4.15), 346 (4.18), 257 (4.38), 244 (4.42)

Anal. Calcd for $C_9H_{12}N_6O_2$: C, 45.76; H, 5.12; N, 35.58. Found: C, 45.65; H, 5.22; N, 35.60.

2,4-Diamino-6-isobutyl-8-hydroxy-7(8*H*)-pteridinone (2e): 84% yield; mp >300°; NMR (CF_3COOH) δ 0.53 (6, d), 1.87 (1, m), 2.46 (2, d, isobutyl); uv λ_{max} (0.1 *N* NaOH) 356 nm (log ϵ 4.19), 347 (4.23), 258 (4.44), 244 (4.46).

Anal. Calcd for $C_{10}H_{14}N_6O_2$: C, 47.99; H, 5.64; N, 33.58. Found: C, 47.74; H, 5.66; N, 33.78.

2,4-Diamino-6-*n*-pentyl-8-hydroxy-7(8*H*)-pteridinone (2f): 79% yield; mp 275° dec; NMR (CF_3COOH) δ 0.46 (3, t), 0.7–1.7 (6, m), 2.53 (2, t, *n*-pentyl); uv λ_{max} (0.1 *N* NaOH) 357 nm (log ϵ 4.08), 347 (4.12), 258 (4.36), 245 (4.37).

Anal. Calcd for $C_{11}H_{16}N_6O_2$: C, 49.99; H, 6.10; N, 31.80. Found: C, 49.70; H, 6.28; N, 31.70.

Registry No.—**2a**, 54642-86-3; **2a** tosyl salt, 54642-87-4; **2b**, 54642-88-5; **2c**, 54642-89-6; **2d**, 54642-90-9; **2e**, 54642-91-0; **2f**, 54642-92-1; **3** tosylate, 5098-14-6; **5a**, 19994-63-9; **6**, 5471-68-1; **7**, 54642-93-2; **8**, 54642-94-3; **9**, 54642-95-4; **12**, 54642-97-6.

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Pteridines. XXXV. Total Synthesis of Asperopterin B[1,2]

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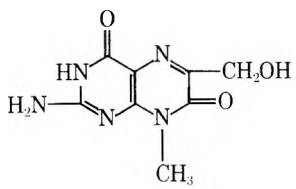
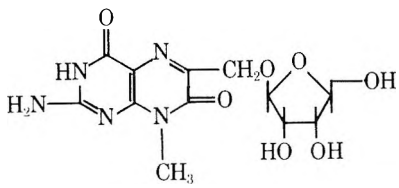
Asperopterin B (1) is found in the culture broth of *Aspergillus oryzae*. We describe in this study two independent routes to 2,4-diamino-6-hydroxymethyl-7(8*H*)-pteridinone (3), and the conversion of this latter compound to asperopterin B. Both syntheses of 3 use our recently described new synthetic approach to pteridines.

Asperopterin B (1) is the aglycone of asperopterin A (2), and both compounds are found in the culture broth of *Aspergillus oryzae*.[3] These multifunctional pteridines offered an interesting objective for the application of our recently described new approach to pteridines.[4]

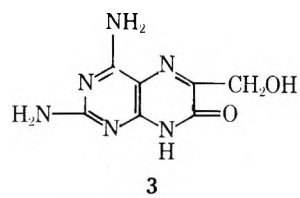


1



2

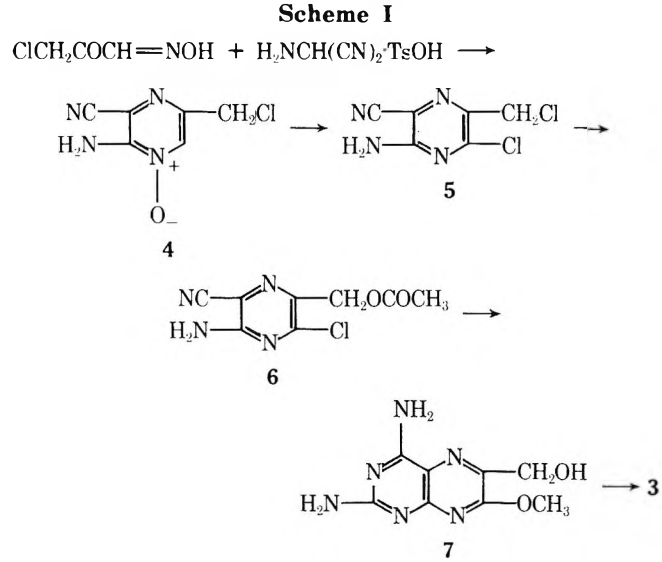
Our approach to asperopterin B (1) centered upon the preparation of 2,4-diamino-6-hydroxymethyl-7(8*H*)-pteridinone (3), since we anticipated that this multifunctional intermediate should be capable of conversion to 1 either by methylation at N-8 followed by hydrolysis of the 4-amino group or, alternatively, by initial hydrolysis followed by terminal methylation. We describe in this paper two independent synthetic routes to 2,4-diamino-6-hydroxymethyl-7(8*H*)-pteridinone (3), and the successful conversion of this key intermediate to asperopterin B.



3

Treatment of 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide (4)[4c] with phosphorus oxychloride in dimethylformamide resulted in deoxygenation, with concomitant introduction of chlorine at position 6, to give 2-amino-3-cyano-5-chloromethyl-6-chloropyrazine (5). Selective displacement of halogen in 5 with anhydrous sodium acetate in dimethylformamide gave the 5-acetoxymethyl derivative (6) in high yield. Cyclization of 6 with guanidine in the presence of an excess of sodium methoxide in anhydrous methanol afforded 2,4-diamino-6-hydroxymethyl-7-methoxypteridine (7), which was smoothly hydrolyzed to 3 with 5% sodium hydroxide solution (Scheme I).

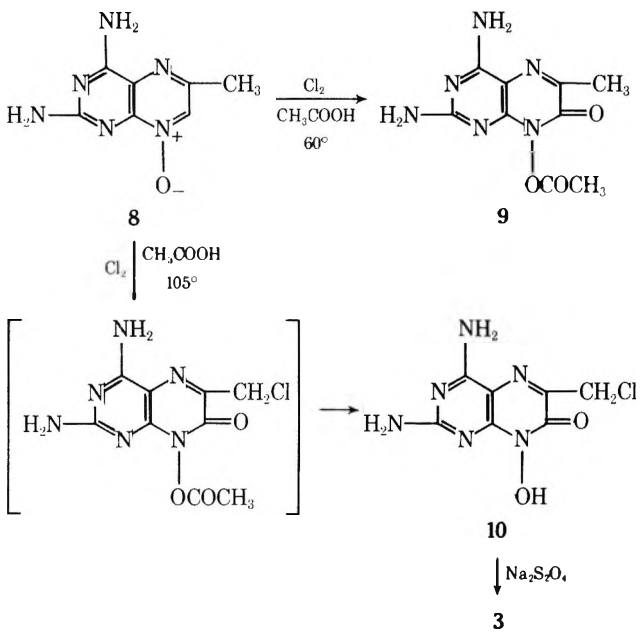
Scheme I



An alternative and more direct synthesis of 3 resulted from an extension of work described in the accompanying paper[1] which utilized the pteridine 8-oxide functionality for the specific introduction of substituents into the pyrazine ring. We had observed the formation of 2,4-diamino-6-methyl-8-acetoxy-7(8*H*)-pteridinone (9) on treatment of 2,4-diamino-6-methylpteridine 8-oxide (8) in glacial acetic acid with chlorine at 60°. We have now found that this chlorination, when carried out under more vigorous condi-

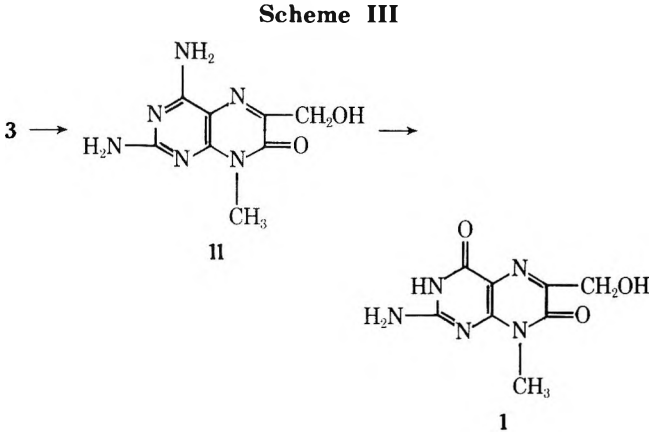
tions (105° and a large excess of chlorine), led exclusively to a new product (**10**), $C_7H_7N_6O_2Cl$·HCl, corresponding to the oxidative introduction of a hydroxyl and a chloro substituent. This new product (**10**) was readily shown to be a hydroxamic acid by the characteristic red color reaction which it gave upon treatment with ferric chloride in methanol, and by the ir spectrum of its acylated derivative ($\bar{\nu}_{CO}$ 1822 cm^{-1}). The NMR spectrum of **10** exhibited only one signal at 4.25 ppm; an integrated spectrum of its tosylate showed that this signal was due to the absorption of two protons. The chlorination product thus appeared to be 2,4-diamino-6-chloromethyl-8-hydroxy-7(8*H*)-pteridinone (**10**), and this structural assignment was corroborated by reductive hydrolysis to **3** with aqueous sodium dithionite. The reduction product (**3**) was identical in all respects with authentic **3** obtained as outlined in Scheme I. These interconversions are outlined in Scheme II.

Scheme II

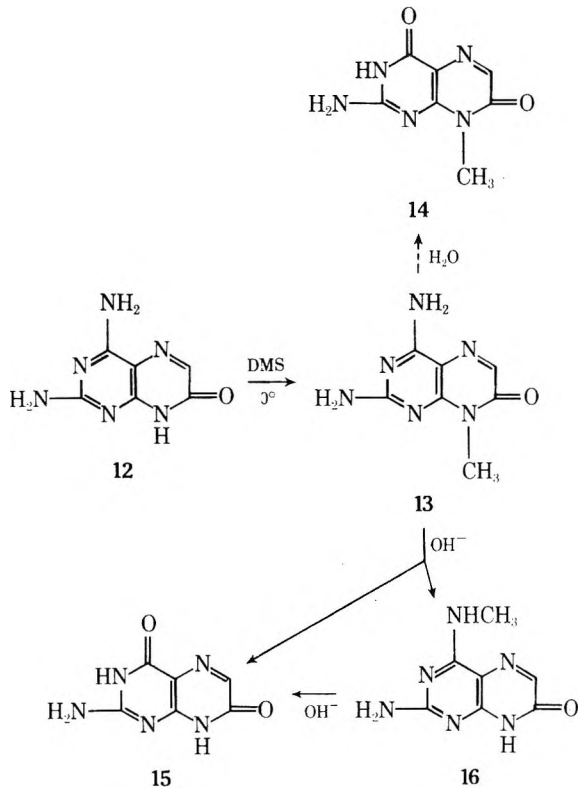


We then turned our attention to the conversion of **3** to asperopterin B (**1**). Our projected route, as outlined in Scheme III, consisted of the apparently trivial methylation of **3** to give 2,4-diamino-6-hydroxymethyl-8-methyl-7(8*H*)-pteridinone (**11**), followed by hydrolysis of the 4-amino group to give **1**. In order to determine the feasibility of this approach, a number of experiments were performed with more easily accessible model compounds. The results are of sufficient interest to warrant discussion.

Scheme III



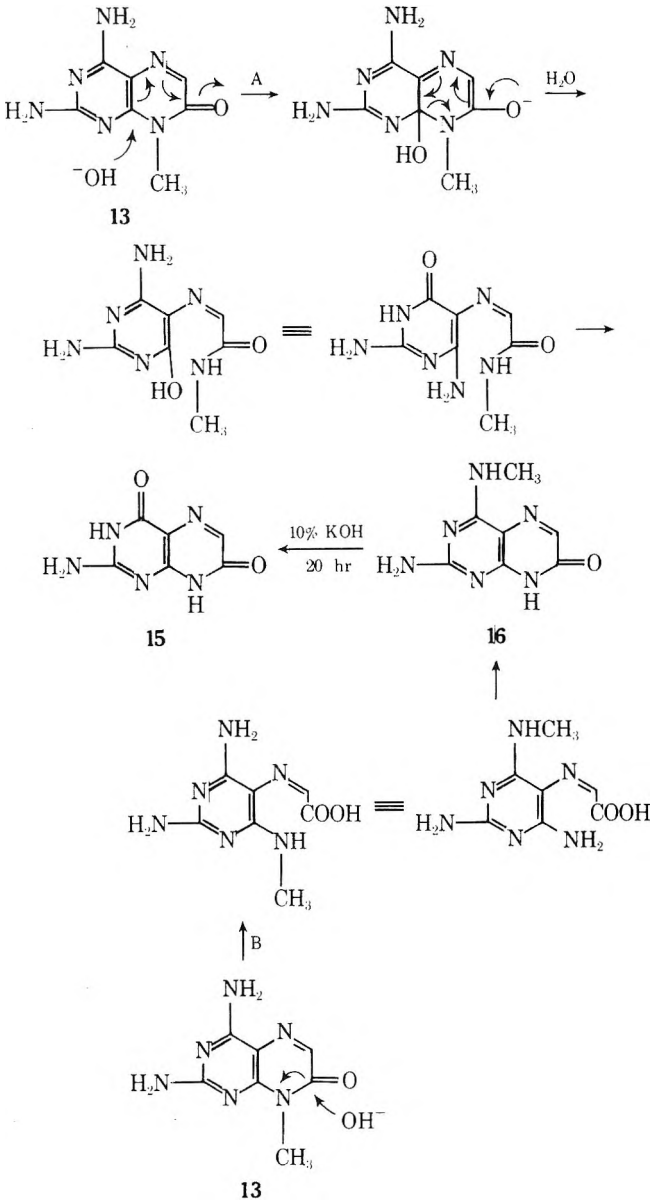
Scheme IV



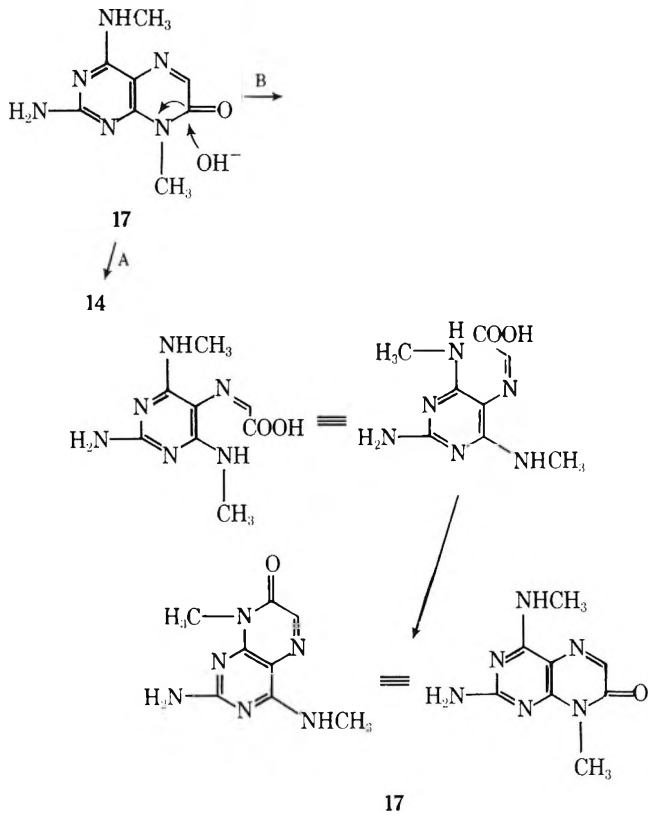
The primary model compound chosen for exploratory methylation and hydrolysis studies was 2,4-diamino-7(8*H*)-pteridinone (**12**)[5] (Scheme IV). Methylation at N-8 of compound **12** was readily achieved with dimethyl sulfate in dilute alkali (pH 9). The N-methylated compound (**13**) precipitated out of the reaction solution in a high state of purity and in excellent yield. The only remaining step was the hydrolysis of **13** to give the compound **14**, which could be identified readily by comparison with an authentic sample.[6] Acidic hydrolysis of **13** was disappointing; although it did afford **14** in trace amounts, the major product was an intractable tar. Therefore, we turned our attention to the basic hydrolysis of **13**, but again unexpected results were obtained. Treatment of **13** with hot 5% sodium hydroxide solution resulted in the almost immediate disappearance of starting material (by paper chromatography), and in the formation of two new products, neither of which was the expected **14**. The minor component (ca. 5%) of this mixture was shown to be isoxanthopterin (**15**), while the major component (95%) proved to be 2-amino-4-methylamino-7(8*H*)-pteridinone (**16**). The structure of this latter compound was established conclusively by spectral data and by alkaline hydrolysis of the 4-methylamino group to give isoxanthopterin (**15**). Indeed, the observed hydrolysis of the 4-methylamino group of **16** made it logical to assume that **16** was the precursor of isoxanthopterin, which accompanied it in the above reaction mixture. However, this assumption proved incorrect, because closer scrutiny indicated that the formation of isoxanthopterin from 2,4-diamino-8-methyl-7(8*H*)-pteridinone (**13**) could not have involved **16** as an intermediate, since the conversion of **16** to isoxanthopterin required 24 hr of refluxing in 10% aqueous sodium hydroxide. The inescapable conclusion was that **15** and **16** had formed by two distinct reaction pathways in the alkaline hydrolysis of **13**.

We suggest that the observed results are best rationalized by invoking two independent Dimroth rearrangements, as depicted in Scheme V.

Scheme V

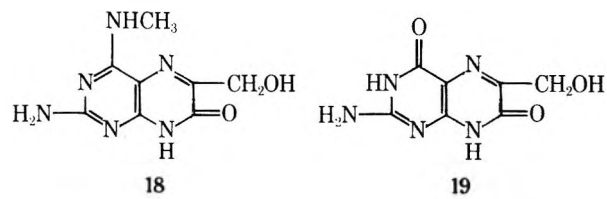


Scheme VI



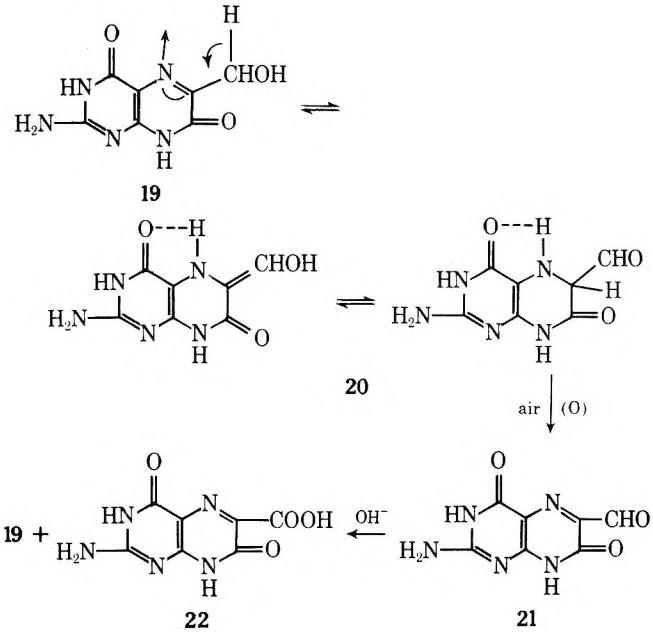
It is intriguing to note that it was possible to prepare the desired 2-amino-8-methyl-4,7(3*H*,8*H*)-pteridinedione (**14**) from **16** in the following manner. Methylation of **16** proceeded normally to give 2-amino-4-methylamino-8-methyl-7(8*H*)-pteridinone (**17**), which on base hydrolysis led directly to **14** by *apparent* hydrolysis of the 4-methylamino grouping. In view of the results described in Scheme V, however, we believe that this latter conversion probably involves a Dimroth rearrangement analogous to pathway A in Scheme V. Note that the alternative Dimroth rearrangement, initiated by attack of base at the 7-carbonyl group (pathway B in Scheme V) would regenerate starting material, and hence would not be detected by product analysis (see Scheme VI). The efficiency observed in the conversion of **17** to **14** is truly remarkable in view of the complexity of the reactions involved.

Armed with these interesting results obtained in the model series, we attempted their extrapolation to the preparation of asperopterin B from 2,4-diamino-6-hydroxymethyl-8-methyl-7(8*H*)-pteridinone (**11**), which was readily obtained by methylation of **3** with dimethyl sulfate in dilute alkali. Unfortunately, complexities introduced by the presence of the 6-hydroxymethyl substituent vitiated the desired extrapolations. Thus, treatment of **11** with 5% sodium hydroxide at 70° led to a rapid disappearance of the starting material (by paper chromatography) as observed with the model compound (**13**) (Scheme IV). In the present case, however, *six* new fluorescent products were obtained. Following qualitative separation by thin layer chromatography on cellulose, two of these products were identified tentatively as 2-amino-4-methylamino-6-hydroxymethyl-7(8*H*)-pteridinone (**18**) and 6-hydroxymethylisoxanthopterin (**19**) by comparison of their ultraviolet absorption spectra with the spectra of 2-amino-4-methylamino-7(8*H*)-pteridinone (**16**) and isoxanthopterin (**15**), respectively. The mechanism of their formation from **11** is presumably analogous to the formation of **16** and **15** from **13** as depicted in Scheme V.



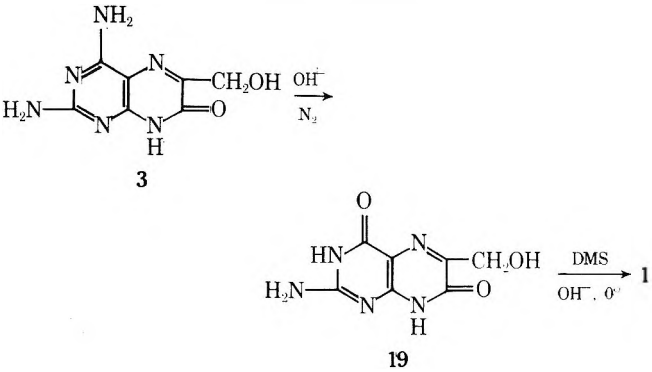
A third product of the above hydrolysis reaction mixture was shown to be isoxanthopterin-6-carboxylic acid (**22**) by comparison with an authentic sample.[7] We believe that compound **22** is formed by the series of reactions outlined in Scheme VII. The intramolecular oxidation–reduction equilibrium represented by **19** ⇄ **20** is characteristic of hydroxyalkyl-substituted pterins; air oxidation of **20** to isoxanthopterin-6-carboxaldehyde (**21**) makes this series of prototropic equilibria irreversible, and in the strongly basic medium **21** undergoes a Cannizzaro reaction to give isoxanthopterin-6-carboxylic acid (**22**) and regenerates **19**, which reenters the reaction cycle. The complexity of these results led us to abandon hydrolysis of 2,4-diamino-6-hydroxymethyl-8-methyl-7(8*H*)-pteridinone (**11**) as a viable synthetic route to asperopterin B.

Scheme VII



An alternative approach for the conversion of 2,4-diamino-6-hydroxymethyl-7(8*H*)-pteridinone (**3**) to asperopterin B involves the reverse of the above sequence of reactions, namely, initial hydrolysis of **3** to 6-hydroxymethylisoxanthopterin (**19**) followed by selective methylation at N-8. It was encouraging that isoxanthopterin does, indeed, undergo selective methylation at 0° in 0.1 *N* NaOH solution with dimethyl sulfate to give 8-methylisoxanthopterin. An initial problem, however, was the conversion of **3** to **19**. It was anticipated that this conversion would also result in the formation of some isoxanthopterin-6-carboxylic acid (**22**). This expectation was readily confirmed. Furthermore, an additional complication was the difficulty experienced in attempts to separate the isoxanthopterin-6-carboxylic acid (**22**) from the desired 6-hydroxymethylisoxanthopterin (**19**). This problem was overcome, however, by employing anaerobic conditions for the hydrolysis of **3**, which completely eliminated the formation of **22**. Pure 6-hydroxymethylisoxanthopterin (**19**) was thus available, and its methylation proceeded regiospecifically to give asperopterin B, whose ir and uv spectra, and chromatographic data, were identical with those of the naturally occurring material. The final synthetic route is summarized in Scheme VIII.

Scheme VIII



Experimental Section

2-Amino-3-cyano-5-chloromethyl-6-chloropyrazine (5). To a solution of 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide (**4**) in 30 ml of DMF, maintained at 5–10°, was added 6.0 ml of phosphorus oxychloride with stirring. After the initial exothermic reaction was over, the mixture was stirred at 25° for 17 hr and then poured onto crushed ice. The aqueous mixture was stirred at room temperature for an additional 16 hr and cooled to give a crystalline precipitate of crude **5** (2.6 g, 78%). The analytical sample, recrystallized from benzene–cyclohexane, had mp 190–191°; NMR (DMSO-d_6) δ 4.75 (2, s, $-CH_2Cl$), 7.96 (2, br s, $-NH_2$).

Anal. Calcd for $C_6H_4N_4Cl_2$: C, 34.50; H, 1.99; N, 27.60. Found: C, 34.38; H, 2.01; N, 27.93.

2-Amino-3-cyano-5-acetoxymethyl-6-chloropyrazine (6). To a solution of 1.00 g of 2-amino-3-cyano-5-chloromethyl-6-chloropyrazine (**5**) in 25 ml of anhydrous DMF was added 1.00 g of anhydrous sodium acetate, and the reaction mixture was stirred for 16 hr. The resulting solution was then poured into 200 ml of water, and the mixture obtained was extracted with 3 × 200 ml of ethyl acetate. The combined extracts were dried over anhydrous $MgSO_4$, treated with animal carbon, and filtered. Removal of the solvent under reduced pressure then gave 0.98 g (88%) of **6** as an off-white solid. The analytical sample, recrystallized from cyclohexane–benzene, had mp 172–173°; NMR (DMSO-d_6) δ 2.05 (3, s, acetoxy), 5.06 (2, s, $-CH_2$), 7.86 (2, br s, $-NH_2$).

Anal. Calcd for $C_8H_7N_4O_2Cl$: C, 42.40; H, 3.11; N, 24.72. Found: C, 42.18; H, 2.96; N, 24.58.

2,4-Diamino-6-hydroxymethyl-7-methoxypteridine (7). To a methanolic solution of guanidine (made from 0.69 g of sodium in 20 ml of absolute methanol and 1.91 g of guanidine hydrochloride) was added 2.00 g of 2-amino-3-cyano-5-acetoxymethyl-6-chloropyrazine (**6**). Ethyl mercaptan (0.2 ml) was then added, and the reaction mixture was stirred under nitrogen in an oil bath at 65° for 8 hr. Cooling, followed by filtering and washing the collected solid with water and methanol, then gave 1.05 g (54%) of **7**. The analytical sample, recrystallized from methanol (pale yellow needles), had mp 280° dec; uv λ_{max} (0.1 *N* HCl) 378 nm (log ϵ 3.67), 338 (4.04), 333 (4.06), 326 (4.08), 247 (4.19), 224 (4.17).

Anal. Calcd for $C_8H_{10}N_6C_2$: C, 43.24; H, 4.54; N, 37.82. Found: C, 42.87; H, 4.63; N, 38.06.

2,4-Diamino-6-chloromethyl-8-hydroxy-7(8*H*)-pteridinone (10) Hydrochloride. To a solution of 2.0 g of chlorine in 40 ml of glacial acetic acid was added 1.0 g of 2,4-diamino-6-methylpteridine 8-oxide (**8**),[4b] and the resulting mixture was stirred in a small glass pressure device in an oil bath carefully maintained at 100–105°. Solution was generally complete within 15 min, and after heating for a total of 2 hr the bright orange solution was transferred to a 100-ml round-bottom flask and evaporated to complete dryness under reduced pressure (bath temperature 35°). The deep orange-red gum obtained was covered with an ice-cold solution of 1.0 g of dry HCl in 10 ml of anhydrous ethanol, and the resulting suspension was stirred for 3€ hr at room temperature (temperature must not exceed 25°). During this period, the reaction mixture slowly changed from a deep orange-red to a pale yellow, and 2,4-diamino-6-chloromethyl-8-hydroxy-7(8*H*)-pteridinone (**10**) hydrochloride precipitated. The product was collected by filtration, washed with ether, and dried to give 0.90 g (67%) of pale yellow **10** hydrochloride, which after crystallization from dioxane had mp >300° (some darkening over 200°); NMR (CF_3COOH) δ 4.23 (s, $-CH_2Cl$); uv λ_{max} (EtOH) 347 nm (log ϵ 4.11), 291 (3.69), 262 (4.09), 228 (sh, 4.22).

Anal. Calcd for $C_7H_8N_6O_2Cl_2$: C, 30.12; H, 2.89; N, 30.12; Cl, 25.41. Found: C, 29.93; H, 2.86; N, 29.85; Cl, 23.98.

2,4-Diamino-6-hydroxymethyl-7(8*H*)-pteridinone (3). Method A. A suspension of 0.70 g of 2,4-diamino-6-hydroxymethyl-7-methoxypteridine (**7**) in 50 ml of 5% aqueous NaOH was stirred at 100° until solution was complete. The deep brown solution was then treated with a small amount of Darco G-60 carbon and filtered through Celite to give a pale yellow solution. Addition of 12 *N* HCl to pH 7 resulted in the separation of a yellow, gelatinous precipitate. To the above suspension was added 570 ml of water and 30 ml of Beckman concentrated pH 7 buffer, and the resulting suspension was heated to 100° for 30 min, filtered, and cooled to give 0.30 g (46%) of **3** as a yellow, microcrystalline solid: uv λ_{max} (0.1 *N* NaOH) 370 nm (log ϵ 3.92), 350 (4.12), 340 (4.09), 274 (3.99), 257 (4.18), 223 (4.45).

Anal. Calcd for $C_7H_8N_6O_2$: C, 40.37; H, 3.87; N, 40.38. Found: C, 40.08; H, 4.01; N, 40.06.

Method B. 2,4-Diamino-6-chloromethyl-8-hydroxy-7(8*H*)-pteridinone (**10**) hydrochloride (500 mg) was suspended in a buffered solution prepared from 10 ml of Beckman concentrated pH 7 buffer and 242 ml of distilled water, and the resulting mixture was boiled with efficient stirring until all material had dissolved. The solution was then treated with a small amount of Darco G-60 car-

bon, allowed to boil an additional 5 min, and then filtered while hot. Sodium dithionite (400 mg) was added to the bright yellow filtrate, and stirring and boiling were continued for an additional 30 min. The mixture was then allowed to cool for several hours before filtering, washing thoroughly with water, and drying to give 250 mg (66%) of very pale yellow **3**, identical in all respects with authentic **3** prepared by method A.

2,4-Diamino-6-hydroxymethyl-8-methyl-7(8*H*)-pteridinone (11). 2,4-Diamino-6-hydroxymethyl-7(8*H*)-pteridinone (**3**, 100 mg) was dissolved in 10 ml of 0.1 *N* NaOH at room temperature. The resulting pale yellow solution was then cooled to 0° in an ice bath, and 0.3 ml of freshly distilled dimethyl sulfate was added in one portion. The reaction mixture was stirred for 3 hr while the temperature was maintained at 0–5°. During this time, a pale yellow precipitate gradually separated from the reaction mixture. After 3 hr, the reaction mixture was removed from the ice bath and allowed to warm slowly to room temperature. Stirring was then continued overnight, during which time the pH of the reaction mixture dropped to about 1 and all suspended material dissolved. The reaction mixture was then brought to pH 7 with solid sodium bicarbonate, allowed to stir for an additional 15 min at room temperature, and then cooled for 3 hr. Filtration followed by thorough washing with ice water then gave **11** as a bright yellow, amorphous solid. After drying to constant weight under high vacuum, the yield was 90 mg (84%) of chromatographically homogeneous material, analytically pure as obtained: mp >300°; NMR (CF_3COOH) δ 3.26 (3, s, NCH_3), 2.56 (2, s, CH_2OH); uv λ_{max} (0.1 *N* HCl) 338 nm (log ϵ 4.09), 302 (4.06), 222 (4.46).

Anal. Calcd for $C_8H_{10}N_6O_2$: C, 43.24; H, 4.54; N, 37.83. Found: C, 43.12; H, 4.48; N, 37.78.

2,4-Diamino-8-methyl-7(8*H*)-pteridinone (13). 2,4-Diamino-7(8*H*)-pteridinone (**12**,[5] 100 mg) was dissolved in 10 ml of 0.1 *N* NaOH at room temperature. The resulting pale yellow solution was then cooled to 0° in an ice bath, 0.3 ml of freshly distilled dimethyl sulfate was added in one portion, and the reaction mixture was stirred vigorously (0–5°) for 3 hr. It was then filtered, and the crystalline residue was washed with ethanol and dried to give 0.95 g (87%) of slightly off-white **13**. The analytical sample, prepared by dissolution in dilute HCl followed by precipitation with NH_4OH, had mp 280–300°; NMR (CF_3COOH) δ 3.45 (3, s, NCH_3), 8.16 (1, s, C_6 H); uv λ_{max} (0.1 *N* HCl) 338 nm (log ϵ 4.12), 2.99 (4.05), 223 (4.53).

Anal. Calcd for $C_7H_8N_6O$: C, 43.73; H, 4.20; N, 43.73. Found: C, 43.49; H, 4.05; N, 43.64.

2-Amino-4-methylamino-7(8*H*)-pteridinone (16). A suspension of 200 mg of 2,4-diamino-8-methyl-7(8*H*)-pteridinone (**13**) in 10 ml of 5% NaOH was stirred at reflux until all material had dissolved (ca. 35–40 min). The resulting solution was then cooled, adjusted to pH 5, and allowed to stir for an additional 2 hr at 5°. The separated material was collected, washed with ethanol, and dried overnight to yield 150 mg (75%) of very pale yellow **16**. A trace amount of isoxanthopterin (**15**) (determined chromatographically) was removed by crystallization from pH 7 buffered solution to give pure **16**: mp >300°; NMR (CF_3COOH) δ 3.93 (3, s, $NHCH_3$); mass spectrum *m/e* 192 ($M\cdot^+$), 177 ($M - CH_3$).

A solution of 50 mg of **16**, on refluxing for 24 hr in 10 ml of 10% NaOH, gave isoxanthopterin (85%), identical in all respects with authentic material.

2-Amino-4-methylamino-8-methyl-7(8*H*)-pteridinone (17). A solution of 30 mg of 2-amino-4-methylamino-7(8*H*)-pteridinone (**16**) in 5 ml of 0.1 *N* NaOH was stirred at 0–5° for 2 hr with 0.1 ml of freshly distilled dimethyl sulfate. The white precipitate which separated was then collected by filtration, washed with water followed by methanol, and dried to yield 25 mg (77%) of **17**, mp 260–280°. The material was analytically pure as obtained: uv λ_{max} (0.1 *N* HCl) 350 nm (log ϵ 4.16), 306 (4.07), 226 (4.53).

Anal. Calcd for $C_8H_{10}N_6O$: C, 46.59; H, 4.89; N, 40.76. Found: C, 46.55; H, 4.85; N, 40.77.

2-Amino-8-methyl-4,7(3*H*,8*H*)-pteridinedione (14). A solution of 50 mg of 2-amino-4-methylamino-8-methyl-7(8*H*)-pteridinone (**17**) in 5 ml of 10% NaOH was stirred under reflux for 24 hr. The resulting pale yellow solution was then diluted with 5 ml of water and adjusted to pH 7 with 6 *N* HCl to give a gelatinous precipitate. After standing overnight, the material was collected by filtration, washed thoroughly with water, and dried to yield 42 mg (90%) of **14**, identical in all respects with an authentic sample.[6]

2-Amino-6-hydroxymethyl-4,7(3*H*,8*H*)-pteridinedione (6-Hydroxymethylisoxanthopterin, 19). The basic hydrolysis of 2,4-diamino-6-hydroxymethyl-7(8*H*)-pteridinone (**3**) must be carried out under very exacting conditions if a successful conversion to **19**, free of isoxanthopterin-6-carboxylic acid (**22**), is to be realized. Of primary importance is the observation that the hydrolysis reaction must be maintained throughout under an inert atmosphere of nitrogen. Also, the use of highly concentrated alkaline solutions requires the use of alkali-resistant glass apparatus or suitable plastic labware. When these precautions are observed, however, excellent yields of pure **19** may be readily obtained.

2,4-Diamino-6-hydroxymethyl-7(8*H*)-pteridinone (**3**, 100 mg) was dissolved in 10 ml of 20% KOH which had previously been purged of oxygen by boiling under reduced pressure followed by flushing with a rapid stream of nitrogen. The resulting solution was heated with stirring by means of an oil bath at 80° (internal temperature 70–75°) in a reaction vessel fitted with an efficient condenser and nitrogen inlet. During the course of the reaction a steady stream of nitrogen was bubbled through the hydrolysis solution, which slowly turned dark yellow. After stirring for 48 hr under these conditions, a small amount of Darco G-60 carbon was added, and the mixture was filtered through Celite to give a bright yellow solution. The filtrate was diluted with an additional 10 ml of water and then brought to pH 7 by the dropwise addition of 6 *N* HCl. The title compound was then obtained as a bright yellow, globular precipitate, which (after stirring overnight) was collected by filtration and washed with water to yield 97 mg (97%) of crude **19**. This is sufficiently pure for most purposes. The crude material could be recrystallized from a solution of 95 ml of water and 5 ml of Beckman concentrated pH 7 buffer (Darco G-60) to give chromatographically homogeneous **19** (50% recovery) as a light yellow crystalline compound, mp >300°. The R_f on Whatman No. 1 paper (0.5% K_2CO_3) was 0.38; R_f of isoxanthopterin-6-carboxylic acid (**22**), 0.63; R_f of starting material (**3**), 0.18; uv λ_{max} (0.1 *N* NaOH) 342 nm (log ϵ 3.97), 278 (3.51), 255 (3.92).

Anal. Calcd for $C_7H_7N_5O_3\cdot H_2O$: C, 37.01; H, 3.99; N, 30.83. Found: C, 36.83; H, 4.12; N, 30.59.

Asperopterin B (2-Amino-6-hydroxymethyl-8-methyl-4,7(3*H*,8*H*)-pteridinedione, 1). A solution of 50 mg of **19** in 5 ml of 0.1 *N* NaOH was cooled to 0° in an ice–water bath. Freshly distilled dimethyl sulfate was then added dropwise with efficient stirring, the reaction progress being monitored after each successive 2–3 drops by paper chromatography (**19** has R_f 0.38 in 0.5% K_2CO_3; **1** has R_f 0.48) to avoid the addition of excess dimethyl sulfate. After all starting material had disappeared, the reaction mixture was stirred for an additional 3 hr at 0° and then allowed to warm to room temperature. The pH of the solution was adjusted to 5 with 6 *N* HCl, and after cooling overnight, the separated pale yellow crystalline solid was collected by filtration and washed with a small amount of ice water. The material obtained (38 mg, 72%) had identical uv and ir spectra with the spectra published for naturally occurring asperopterin B, as well as the same chromatographic behavior in three different solvent systems.[3]

Registry No.—**1**, 20041-66-1; **3**, 54643-27-5; **4**, 40127-89-7; **5**, 54643-28-6; **6**, 54677-78-0; **7**, 54643-29-7; **8**, 19994-63-9; **10** HCl, 54643-30-0; **11**, 54643-31-1; **12**, 26212-13-5; **13**, 54643-32-2; **16**, 54643-33-3; **17**, 54643-34-4; **19**, 54643-35-5; guanidine, 113-00-8.

References and Notes

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(2) This work was supported by a grant (CA-12876) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.

(3) Y. Keneko and M. Sanda, *Hakko Kogaku Zasshi*, **47**, 8 (1969).

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(5) E. C. Taylor, R. F. Abdulla, K. Tanaka, and P. A. Jacobi, *J. Org. Chem.*, **40**, 2341 (1975).

(6) We are indebted to Professor Wolfgang Pfleiderer of the University of Konstanz for the gift of an authentic sample of compound **14**.

(7) E. C. Taylor and R. F. Abdulla, *Tetrahedron Lett.*, 2093 (1973).

Pteridines. XXXVI. Syntheses of Xanthopterin and Isoxanthopterin. Application of *N*-Oxide Chemistry to Highly Functionalized Pyrazines and Pteridines[1,2]

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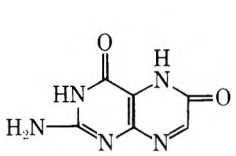
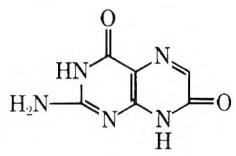
A number of new synthetic routes to xanthopterin (**1**) and isoxanthopterin (**2**) are described. Thus, **2** has been prepared from 2-amino-3-cyanopyrazine 1-oxide (**7**) by $POCl_3$ chlorination–deoxygenation to 2-amino-3-cyano-6-chloropyrazine (**10**), condensation with guanidine to give 2,4-diamino-7-methoxypteridine (**11**), and alkaline hydrolysis. Alternatively, **2** has been prepared from 2-amino-3-ethoxycarbonylpyrazine 1-oxide (**13**) by Ac_2O/AcOH rearrangement to 2-amino-3-ethoxycarbonyl-6(1*H*)-pyrazinone (**15**) followed by annelation of the pyrimidine ring with guanidine. Finally, **2** was readily prepared from 2,4-diaminopteridine 8-oxide (**25**) by reaction with pyrrolidine to give 2,4-diamino-7-(1-pyrrolidino)pteridine (**26**), followed by alkaline hydrolysis. Xanthopterin (**1**) has also been prepared by a number of new routes which use the *N*-oxide functionality for the selective positioning of appropriate substituents in the pyrazine ring. Thus, 2-amino-3-cyanopyrazine 4-oxide (**17**) (prepared from the isomeric 1-oxide by oxidation to the 1,4-dioxide **16** followed by selective monodeoxygenation with PCl_3) was converted to **1** by $POCl_3$/DMF deoxygenation–chlorination to give 2-amino-3-cyano-5-chloropyrazine (**19**), cyclization with guanidine to 2,4-diamino-6-methoxypteridine (**20**), and finally alkaline hydrolysis. The method of choice for the synthesis of pure xanthopterin (**1**), however, involves the selective, *quantitative* isomerization of pterin 8-oxide (**21**) with trifluoroacetic anhydride–trifluoroacetic acid. The mechanism of this remarkable *N*-oxide rearrangement is discussed, and experiments with a number of model pyrazines and pteridines are described.

The isolation, structural elucidation, and eventual synthesis of xanthopterin (**1**), isoxanthopterin (**2**), and their common oxidation product, leucopterin (**3**), constitute a



1



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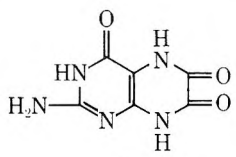


3

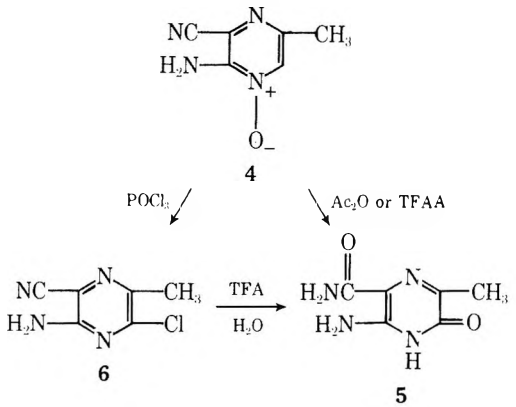
milestone in the early development of the field of pteridine chemistry.[3-5] These compounds are not only widespread insect pigments, but are also found in the skin and eyes of various fish and amphibia and have been identified as normal constituents of human urine.[6,7] The early suggestion that xanthopterin was in some way related to nutritional anemia has been well documented,[8] as has its growth-inhibiting effect on malignant tumors in mice.[9] Recent reports detailing antitumor activity of both xanthopterin and isoxanthopterin[10] and reconfirming the phenomenon of xanthopterin-stimulated renal mytosis[11] testify to the increasing attention now being directed to the importance of these naturally occurring pigments.

Both **1** and **2** have been synthesized previously by various adaptations of the conventional Isay-type synthesis of pteridines involving final construction of the pyrazine ring from preformed 2,4,5-triamino-6-hydroxypyrimidine. In every case, however, mixtures of products were obtained from which pure (?) **1** and **2** were available only with great difficulty. These conventional syntheses have been reviewed.[12] In view of the resurgence of interest in the physiological activity of these naturally occurring pigments, coupled with the deficiencies of available synthetic procedures, it is clear that simple, unequivocal synthetic routes leading to pure xanthopterin (**1**) and isoxanthopterin (**2**) would be of considerable contemporary interest and utility.

We have recently described a new synthetic approach to pteridines which involves the condensation of an α-aminonitrile with an α-oximinocarbonyl compound.[13-16] The resulting 2-aminopyrazine 1-oxides, substituted with a carboxamido, ester, or nitrile grouping at position 3, were then converted to pteridine 8-oxides by appropriate cyclization procedures. Since the ultimate objective in all of our previous syntheses was the unequivocal positioning of substituents at positions 6 and/or 7 in the final pteridine, the *N*-oxide grouping was of no intrinsic interest and was therefore removed by an appropriate deoxygenation procedure either at the pyrazine or pteridine stage. However, the widely exploited capability of the *N*-oxide grouping to facilitate both electrophilic substitution and nucleophilic displacement reactions in heterocycles,[17] coupled with the ready accessibility of both pyrazine and pteridine *N*-oxides by the above cyclization procedures, prompted us to examine the chemistry of these highly functionalized heterocyclic *N*-oxides in the hope that we could exploit them as synthetic intermediates for the facile and *regiospecific* introduction of substituents into the pyrazine and pteridine ring systems. The present paper describes the results of this investigation, which have led to several new syntheses of both xanthopterin (**1**) and isoxanthopterin (**2**) and have uncovered some novel *N*-oxide chemistry.

In order to examine the possible applicability of conventional *N*-oxide chemistry to highly functionalized pyrazine 1-oxides, the initial substrate chosen for study was the readily accessible 2-amino-3-cyano-5-methylpyrazine 1-oxide (**4**), available by condensation of aminomalononitrile tosylate with α-oximinoacetone.[14] Treatment of this pyrazine 1-oxide with a mixture of trifluoroacetic acid and trifluoroacetic anhydride (TFA–TFAA), or with acetic anhydride, resulted in a normal Katada rearrangement (oxygenation of the carbon α to the ring nitrogen with concomitant loss of the *N*-oxide group).[18] Conditions for the rearrangement were somewhat severe, however, and hydrolysis of the nitrile group also occurred, giving **5**. It was also possible to carry out the normal phosphorus oxychloride chlorination–

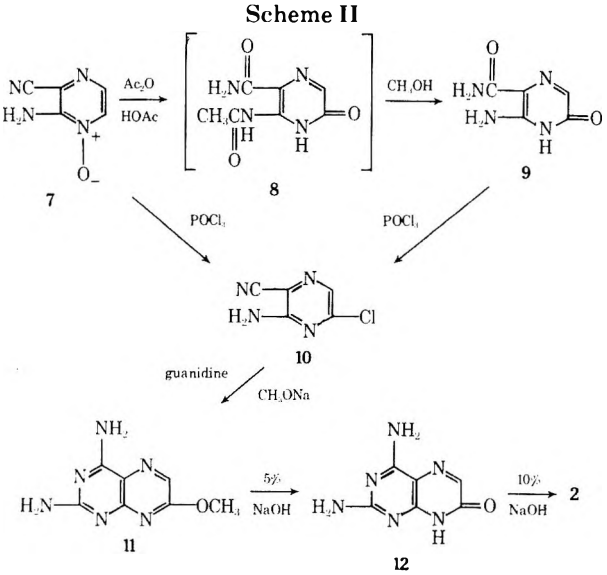
Scheme I



deoxygenation reaction on **4** to give 2-amino-3-cyano-5-methyl-6-chloropyrazine (**6**) in good yield. Hydrolysis of **6** with aqueous trifluoroacetic acid provided an alternate route to **5**. These reactions are summarized in Scheme I.

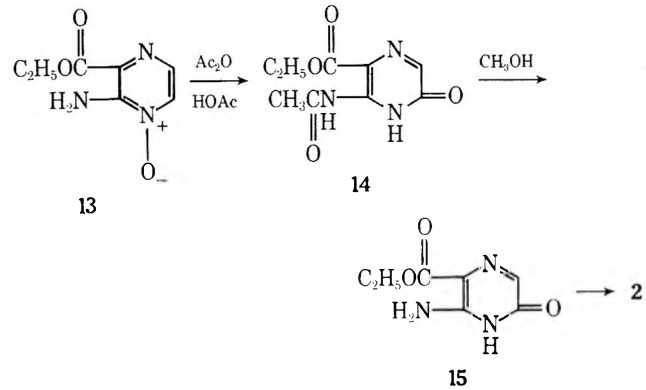
Encouraged by these preliminary results, attention was next turned to chemical transformations of 2-amino-3-cyanopyrazine 1-oxide (**7**)[14] in the hope that analogous conversions, if they could be effected, would lead to intermediates capable of cyclization to isoxanthopterin. These expectations were confirmed. Thus, treatment of **7** with acetic anhydride and acetic acid resulted in the formation of 2-acetamido-3-carbamoyl-6(1*H*)-pyrazinone (**8**), which was readily deacetylated to **9** by heating in methanol. Also, treatment of **7** with phosphorus oxychloride gave 2-amino-3-cyano-6-chloropyrazine (**10**), identical with the compound prepared from **9** with phosphorus oxychloride. The position of the chloro substituent in **10** was confirmed by its conversion to isoxanthopterin as follows. Treatment with guanidine in methanolic sodium methoxide gave 2,4-diamino-7-methoxypteridine (**11**) by simultaneous pyrimidine ring annelation and chloride displacement. Hydrolysis of **11** with 5% aqueous sodium hydroxide under reflux for 10 min then gave 2,4-diamino-7(8*H*)-pteridinone (**12**), which in turn could be hydrolyzed under more vigorous conditions (10% aqueous sodium hydroxide under reflux for 20 hr) to isoxanthopterin (**2**), identical with an authentic sample (see Scheme II).

Scheme II



An analogous Katada rearrangement was successfully effected with 2-amino-3-ethoxycarbonylpyrazine 1-oxide (**13**). Thus, treatment of **13** with a mixture of acetic anhydride and acetic acid gave 2-acetamido-3-ethoxycarbonyl-6(1*H*)-pyrazinone (**14**). Once again, the position of the new oxygen substituent on the pyrazine ring was confirmed by conversion of this compound to isoxanthopterin (**2**) by initial deacetylation to **15** with methanol, followed by cyclization with guanidine in refluxing DMF. These conversions are summarized in Scheme III.

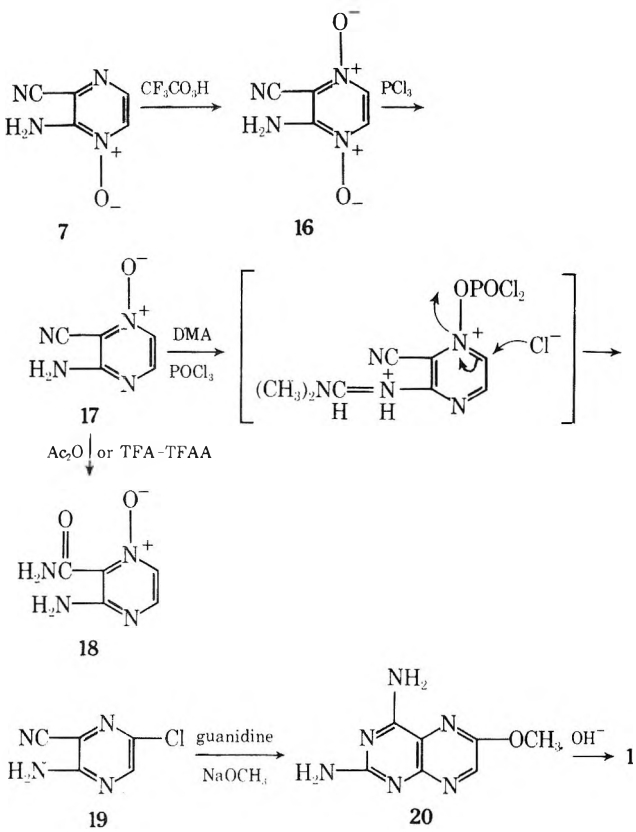
Scheme III



It would appear from the above results that conventional *N*-oxide chemistry is indeed applicable to these highly functionalized pyrazine 1-oxides, which may, as a consequence, be utilized for the introduction of substituents into the pyrazine ring α to the *N*-oxide grouping.

An extension of these rearrangement reactions to pyrazine 4-oxides should provide an attractive route to xanthopterin (**1**) and related 6-substituted pteridines. The requisite 2-amino-3-cyanopyrazine 4-oxide (**17**), although not available either by direct cyclization or by selective oxidation of 2-amino-3-cyanopyrazine, was successfully prepared by oxidation of **7** to the 1,4-dioxide **16** with pertrifluoroacetic acid, followed by selective monodeoxygenation with phosphorus trichloride. The chemical properties of this pyrazine *N*-oxide, however, proved to be strikingly different from those of its isomer (**8**). Thus, attempted rearrangement of **17** either with TFA–TFAA or with acetic anhydride, was unsuccessful; the only product isolated was the carboxamide **18** resulting from hydration of the nitrile substituent. The failure of the Katada rearrangement in this case, however, is not unreasonable, since the position of nucleophilic attack by acetate or trifluoroacetate anion is now para to the 2-amino substituent, whereas in the rearrangement of **7** to the 6-pyrazinone **9** the position of nucleophilic attack was activated by the para-situated nitrile (or carboxamide) grouping. This reasoning was reinforced by the observation that **17** could be smoothly converted to 2-amino-3-cyano-5-chloropyrazine (**19**) with phosphorus oxychloride in DMF. The success of this latter conversion presumably is due to the intermediate formation of a 2-dimethylaminomethylenamino derivative (a well-known reaction of heterocyclic amino groups with phosphorus oxychloride in DMF),[19] which, because of its greatly increased basicity, is undoubtedly protonated under the reaction conditions, thus activating the 5 position to nucleophilic addition. The product **19** was identical with an authentic sample prepared from 2-amino-3-ethoxycarbonylpyrazine by chlorination, aminolysis, and dehydration.[20] Compound **19** was then converted to xanthopterin (**1**) by reaction with guanidine in methanolic sodium methoxide to give 2,4-diamino-6-methoxypteridine (**20**) in a reaction analogous to that previously carried out on **10** (see Scheme II). Subsequent base hydrolysis of **20** then gave **1** in excellent yield. These reactions are summarized in Scheme IV.

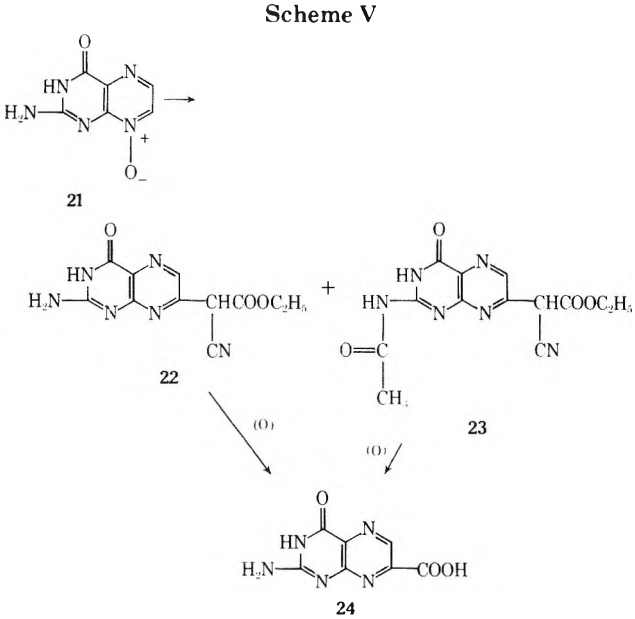
Scheme IV



Having thus achieved some measure of success in chemical transformations of these highly functionalized pyrazine *N*-oxides, attention was then turned to the possible synthetic utility of pteridine 8-oxides in the anticipation that analogous transformations leading to 7-substituted pteridines would be possible. Initial experiments, indeed, confirmed this expectation, but they also underscored the danger of direct extrapolation of results from one ring system to the other.

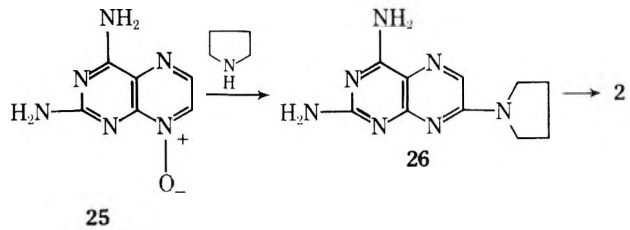
Treatment of a suspension of pterin 8-oxide (**21**) in anhydrous HMPA with acetic anhydride and ethyl cyanoacetate gave a mixture of **22** and **23** (see Scheme V). Attachment of the carbon side chain to position 7 of the pteridine nucleus was readily confirmed by the conversion of both **22** and **23** to pterin-7-carboxylic acid (**24**) by oxidation with potassium permanganate. This conversion of **21** to the 7-substituted pterins **22** and **23** thus corresponds to a normal *N*-oxide rearrangement utilizing an active methylene compound as the nucleophile, which results in the formation of a new carbon–carbon bond at a position α to the ring nitrogen.[21]

Scheme V



Similarly, it has also been possible to convert a pteridine 8-oxide into isoxanthopterin (**2**) as follows. 2,4-Diaminopteridine 8-oxide (**25**)[14] on treatment with neat pyrrolidine at 90° for 16 hr gave 2,4-diamino-7-(1-pyrrolidino)pteridine (**26**), which was then converted in a single step to **2** by hydrolysis with 10% aqueous sodium hydroxide (Scheme VI).

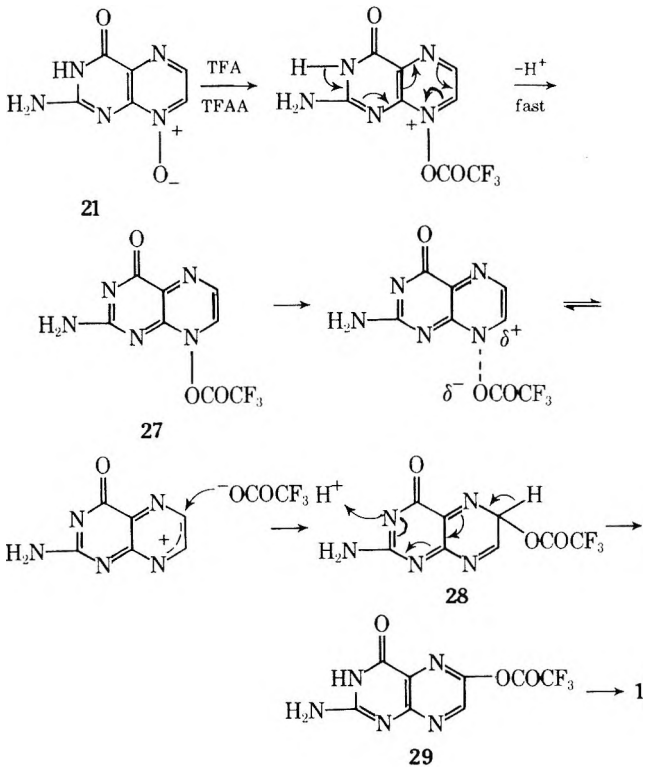
Scheme VI



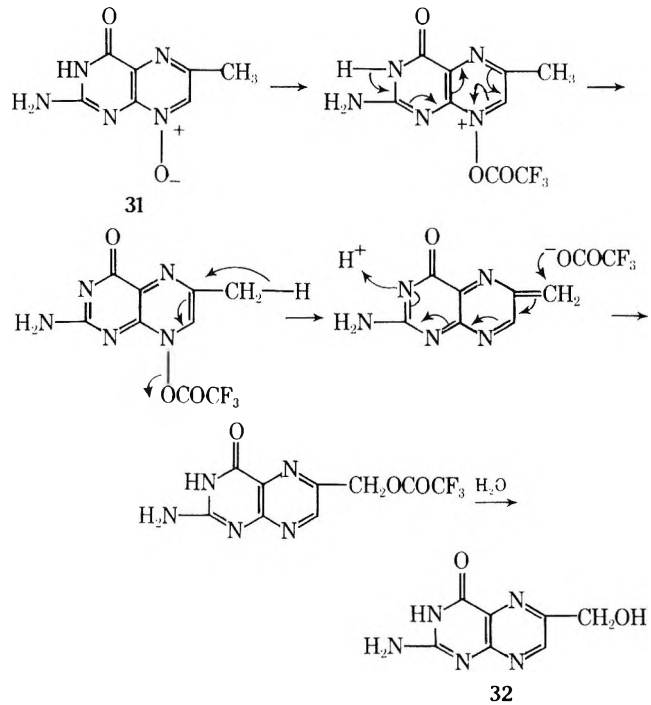
Until this point, it appeared that the chemistry of pteridine *N*-oxides was analogous to the conventional chemistry described above for the highly functionalized pyrazine *N*-oxides. It did not seem unreasonable, therefore, to expect that pterin 8-oxide (**21**) should undergo a normal Katada rearrangement with acetic anhydride (or related reagents) to give isoxanthopterin (**2**). However, this was not to be the case. No reaction of **21** either with acetic anhydride or with mixtures of acetic anhydride and acetic acid could be detected even upon prolonged (48 hr) reflux. Additionally, no reaction was observed with acetyl chloride, dichloroacetyl chloride, or benzoyl chloride in DMF or pyridine under a wide range of reaction conditions. However, **21** dissolved almost immediately in a 50:50 mixture of TFA–TFAA at 50° to give a bright yellow solution. The NMR spectrum of an aliquot of this yellow solution consisted of a single, sharp singlet at δ 8.60, and there was no trace of starting material (**21** exhibits two well-resolved doublets at δ 8.35 and 8.50, J = 4.5 Hz). When **21** was dissolved in TFA–TFAA at room temperature, the initial NMR spectrum of the reaction mixture showed both the resolved doublets of **21** and the above singlet. Over the course of 3–4 hr, however, the absorptions due to **21** slowly disappeared, with concurrent strengthening of the singlet at δ 8.60, until the final spectrum was identical with that obtained from the reaction of **21** with TFA–TFAA at 50°. The reaction mixture was worked up in the usual manner (evaporation of solvents followed by basic hydrolysis) to give, to our intense surprise, *xanthopterin* (**1**), not isoxanthopterin. *N*-Oxide rearrangements to a position β to the ring nitrogen are known in heterocyclic chemistry, although mixtures of the normal α-rearrangement products along with the abnormal β-rearrangement products are usually obtained.[22] The above conversion of **21** to **1**, which takes place in essentially quantitative yield, is most unusual in that it gives no trace of the "normal" product. It now represents the method of choice for the preparation of pure xanthopterin (**1**).

It seems probable that this unexpected conversion proceeds via intermediate **27**, which undergoes an allylic rearrangement of the trifluoroacetoxy group as shown (see Scheme VII). The extreme ease of this rearrangement may well be due to substantial *N*-trifluoroacetoxy bond heterolysis in the transition state leading from **27** to **28**, and its ir-

Scheme VII



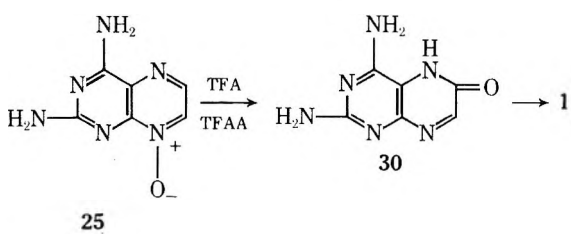
Scheme IX



reversibility may reasonably be attributed to the formation of a C–O bond at the expense of the much weaker N–O bond in **27**. Such a reaction pathway appears to be general in allylic rearrangements involving highly stabilized leaving groups, and an analogous pathway is well documented for other β-rearrangement reactions of heterocyclic *N*-oxides.[22]

2,4-Diaminopteridine 8-oxide (**25**) followed a parallel rearrangement pathway, but forcing conditions (refluxing TFA–TFAA, 5 hr) were required. The product of rearrangement was 2,4-diamino-6(5*H*)-pteridinone (**30**), alkaline hydrolysis of which provided an alternative although less satisfactory route to xanthopterin (**1**) (see Scheme VIII). Significantly, neither 2,4-diamino-6-methylpteridine

Scheme VIII



8-oxide nor 6-methylpterin 8-oxide (**31**) (in which the position β to the *N*-oxide is effectively blocked) could be induced to rearrange "normally" under any conditions; instead, they suffered mainly rapid decomposition to intractable tars. However, careful chromatography of the decomposition products from **31**, although revealing no trace of the product expected from a normal Katada rearrangement, did establish the presence of 6-hydroxymethylpterin (**32**).[23] The formation of this material is reasonably interpreted as shown in Scheme IX.

For reasons which are not clear at this point, 2,4-diaminopteridine 8-oxide (**25**), in contrast to its pyrazine precursor (**8**), proved to be completely unreactive toward phosphorus oxychloride–DMF. Similarly, 2,4-diamino-6-methylpteridine 8-oxide was also recovered unchanged under the same conditions. By contrast, however, 2,4-diamino-6-oximinomethylpteridine 8-oxide has been shown[15] to undergo a facile normal chlorination–deoxygenation reaction (accompanied by dehydration of the oximino grouping) to give 2,4-diamino-6-cyano-7-chloropteridine. It would appear that the presence of an electron-withdrawing group at position 6 is required for the phosphorus oxychloride chlorination–deoxygenation reaction of pteridine 8-oxides.

It is apparent from the above results that conventional *N*-oxide chemistry can be applied to highly functionalized pyrazine and pteridine *N*-oxides, but that subtle changes in structure, even at sites remote from the reaction center, can lead to drastic changes both in the rate and in the mode of the ensuing reactions. More detailed mechanistic studies of these transformations are in progress, and the inherent synthetic potentialities involved are currently under active exploration.

Experimental Section

2-Amino-3-carbamoyl-5-methyl-6(1*H*)-pyrazinone (5). Method A. Rearrangement of 2-Amino-3-cyano-5-methylpyrazine 1-Oxide (4) with Trifluoroacetic Acid–Trifluoroacetic Anhydride (TFA–TFAA). A solution of 1.0 g of **4** in 20 ml of TFA was treated with 5 ml of TFAA and stirred under reflux for 90 min. The reaction mixture was then cooled and poured into 150 ml of water at 0°, and the separated solid was collected by filtration to give 0.8 g (44%) of 2-trifluoroacetamido-3-carbamoyl-5-methyl-6(1*H*)-pyrazinone. The analytical sample was prepared by recrystallization from DMF–$CHCl_3$: mp 280–290° dec; NMR (CF_3COOH) δ 1.90 (3, s, C_5 CH_3).

Anal. Calcd for $C_8H_7F_3N_4O_3$: C, 36.37; H, 2.67; N, 21.21. Found: C, 36.39; H, 2.90; N, 20.94.

A suspension of the crude 2-trifluoroacetamido-3-carbamoyl-5-methyl-6(1*H*)-pyrazinone above was refluxed for 2 hr in 100 ml of methanol. Evaporation of the solvent to a small volume followed by cooling and subsequent filtration afforded 0.4 g (85%) of 2-amino-3-carbamoyl-5-methyl-6(1*H*)-pyrazinone (**5**): mp 276–278°; NMR (CF_3COOH) δ 1.96 (3, s, C_5 CH_3).

Anal. Calcd for $C_6H_8N_4O_2$: C, 42.85; H, 4.80; N, 33.32. Found: C, 42.72; H, 4.76; N, 33.55.

Method B. Rearrangement of 2-Amino-3-cyano-5-methylpyrazine 1-Oxide (4) with Acetic Acid–Acetic Anhydride. A solution of 0.5 g of **4** in 10 ml of acetic acid was treated with 7 ml of acetic anhydride and refluxed for 90 min. The reaction mixture

was then taken to dryness and any remaining acetic anhydride was destroyed by the addition of a small amount of ethanol and evaporation. The residue was recrystallized from ethanol to give 0.4 g (64%) of 2-acetamido-3-carbamoyl-5-methyl-6(1*H*)-pyrazinone: mp 238–239°; NMR (CF_3COOH) δ 2.01 (3, s, acetyl), 1.99 (3, s, C_5CH_3).

Anal. Calcd for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.80; N, 26.66. Found: C, 45.53; H, 4.76; N, 26.35.

A suspension of the crude 2-acetamido-3-carbamoyl-5-methyl-6(1*H*)-pyrazinone above in 30 ml of methanol was refluxed for 3 days. The resulting solution was cooled and the crystals which separated were collected by filtration to give 0.15 g (40%) of **5**, mp 275–276°, identical with the material prepared by method A above.

2-Amino-3-cyano-5-methyl-6-chloropyrazine (6). A suspension of 3.0 g of 2-amino-3-cyano-5-methylpyrazine 1-oxide (**4**) in 30 ml of DMF was treated dropwise with 6.0 ml of phosphorus oxychloride, maintaining the temperature between 80 and 90° (cold water bath). After addition was complete, the reaction mixture was stirred at 80–90° in a preheated oil bath for 10 min and then poured into 300 ml of water at 0°. The resulting solution was allowed to stand overnight before filtering and drying to give 3.0 g of crude product. Recrystallization from ethanol afforded 2.5 g (74%) of **6**: mp 228–229°; NMR (CF_3COOH) δ 2.07 (3, s, C_5CH_3).

Anal. Calcd for $C_6H_5N_4Cl$: C, 42.74; H, 2.99; N, 33.23; Cl, 21.03. Found: C, 42.87; H, 2.89; N, 33.44; Cl, 21.23.

2-Amino-3-carbamoyl-6(1*H*)-pyrazinone (9). A suspension of 5.0 g of 2-amino-3-cyanopyrazine 1-oxide (**7**)[14] in 100 ml of acetic acid and 68 ml of acetic anhydride was refluxed for 2 hr. The reaction mixture was then evaporated to dryness under reduced pressure and any remaining acetic anhydride was destroyed by the addition of a small volume of ethanol followed by evaporation to dryness. Recrystallization of the residue from methanol afforded 4.7 g (65%) of 2-acetamido-3-carbamoyl-6(1*H*)-pyrazinone (**8**), mp 257–259° dec. The analytical sample, recrystallized twice from ethanol, melted at 258–259° dec, NMR (CF_3COOH) δ 7.61 (1, s, H_5), 2.01 (3, s, acetyl).

Anal. Calcd for $C_7H_8N_4O_3$: C, 42.86; H, 4.11; N, 28.56. Found: C, 42.67; H, 4.02; N, 28.70.

A suspension of 3.50 g of the above 2-acetamido-3-carbamoyl-6(1*H*)-pyrazinone in 600 ml of methanol was heated under reflux for 4.5 days. The reaction mixture was then treated with animal carbon, filtered, and concentrated to a small volume to give 2.66 g (96.5%) of **9**: mp 338°; NMR (CF_3COOH) δ 7.22 (1, s, H_5).

Anal. Calcd for $C_5H_6N_4O_2$: C, 38.96; H, 3.92; N, 36.25. Found: C, 39.04; H, 4.02; N, 36.35.

2-Amino-3-cyano-6-chloropyrazine (10). Method A. A suspension of 3.0 g of 2-amino-3-cyanopyrazine 1-oxide (**7**)[14] in 30 ml of DMF was stirred in an ice–water bath while 6.0 ml of phosphorus oxychloride was added dropwise between 5 and 10°. After addition was complete the reaction mixture was stirred for a further 16 hr at room temperature and then poured into ice water. After standing for 24 hr, the aqueous suspension was filtered and the residue was recrystallized from ethyl acetate–petroleum ether (bp 60–80°) to give 1.8 g (52%) of **10**. The analytical sample, recrystallized from ethanol, melted at 194–196°, NMR (CF_3COOH) δ 7.59 (1, s, H_5).

Anal. Calcd for $C_5H_3N_4Cl$: C, 38.85; H, 1.95; N, 36.25; Cl, 22.94. Found: C, 38.70; H, 1.95; N, 36.50; Cl, 22.85.

Method B. A suspension of 0.3 g of 2-amino-3-carbamoyl-6(1*H*)-pyrazinone (**9**) in 50 ml of DMF was stirred in an ice–water bath while 0.6 ml of phosphorus oxychloride was added dropwise between 5 and 10°. After addition was complete the reaction mixture was stirred at 70–80° for 80 min, and then at room temperature overnight. A brown precipitate was produced which was recovered by filtration, washed with water, and dried. Recrystallization from ethyl acetate–petroleum ether afforded 0.07 g (23%) of **10**, mp 192–194°, which was identical in all respects with the sample prepared by method A above.

2,4-Diamino-7-methoxypteridine (11). To a methanolic solution of guanidine (prepared from 1.2 g of sodium in 80 ml of methanol and 1.9 g of guanidine hydrochloride) was added 1.4 g of 2-amino-3-cyano-6-chloropyrazine (**10**). The reaction mixture was refluxed for 17 hr, cooled, and filtered to give 1.4 g (74%) of **11** as a yellow solid. Recrystallization from methanol gave 1.3 g of colorless crystals: mp 240–250°; NMR (DMSO-d_6) δ 7.88 (1, s, H_6), 3.86 (3, s, $-OCH_3$); uv λ_{max} (0.1 *N* HCl) 336 nm (log ϵ 4.13), 332 (4.16), 325 (4.19), 248 (4.23), 221 (4.13).

Anal. Calcd for $C_7H_8N_6O$: C, 43.75; H, 4.20; N, 43.73. Found: C, 43.92; H, 4.32; N, 43.79.

2,4-Diamino-7(8*H*)-pteridinone (12). A suspension of 0.25 g of 2,4-diamino-7-methoxypteridine (**11**) in 20 ml of 5% aqueous sodium hydroxide was stirred under reflux for 10 min, after which time all material had dissolved. Cooling followed by neutralization with 6 *N* HCl afforded an off-white solid which was recovered by filtration, redissolved in dilute aqueous sodium hydroxide solution, filtered (animal carbon), and reprecipitated at pH 4 to give 0.23 g (99%) of **12**. The sample was analytically pure as obtained: mp >400°; NMR (CF_3COOH) δ 7.68 (1, s, H_6); uv λ_{max} (0.1 *N* NaOH) 357 nm (sh, log ϵ 4.06), 345 (4.10), 280 (sh, 3.94), 263 (4.18), 219 (4.52).

Anal. Calcd for $C_6H_6N_6O$: C, 40.45; H, 3.39; N, 47.18. Found: C, 40.21; H, 3.19; N, 47.06.

Isoxanthopterin (2) by Hydrolysis of 2,4-Diamino-7-methoxypteridine (12). A suspension of 0.30 g of **12** in 20 ml of 10% aqueous sodium hydroxide was stirred under reflux for 20 hr. The reaction mixture was then diluted with 30 ml of water, decolorized with animal carbon, filtered, and adjusted to pH 4 with 6 *N* hydrochloric acid to give a white, crystalline solid. A second recovery of the precipitated solid from dilute NaOH solution by addition of HCl to pH 4 afforded 0.23 g (82%) of analytically pure isoxanthopterin, mp >300°, identical in all respects with an authentic sample.

2-Amino-3-ethoxycarbonylpyrazine 1-Oxide (13). A suspension of 17.7 g of finely powdered glyoxime and 59.4 g of ethyl α-aminocyanoacetate tosyl salt in 355 ml of water was stirred at room temperature for 45 hr. The resulting solution was extracted several times with chloroform, and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to give a yellow, crystalline solid. Recrystallization from ethanol then gave 6.1 g (17%) of **13**: mp 194–195°; NMR (CF_3COOH) δ 8.37 (1, d), 7.82 (1, d, H_5, H_6), 4.23 (2, q), 1.02 (3, t, OC_2H_5).

Anal. Calcd for $C_7H_9N_3O_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 46.18; H, 5.07; N, 23.06.

2-Acetamido-3-ethoxycarbonyl-6(1*H*)-pyrazinone (14). A suspension of 5.0 g of 2-amino-3-ethoxycarbonylpyrazine 1-oxide (**13**) in 66 ml of acetic anhydride and 100 ml of acetic acid was refluxed with stirring for 1.5 hr. The reaction mixture was then taken to dryness and treated with ethanol in the usual manner to give a brown solid after evaporation. Recrystallization from ethanol gave 3.7 g (60%) of **14**, mp 157–159°. The analytical sample, mp 158–160°, was recrystallized from ethanol: NMR (CF_3COOH) δ 7.73 (1, s, H_5), 4.08 (2, q), 0.99 (3, t, $-OC_2H_5$), 2.01 (3, s, acetyl CH_3).

Anal. Calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 47.96; H, 4.93; N, 18.96.

2-Amino-3-ethoxycarbonyl-6(1*H*)-pyrazinone (15). A suspension of 0.48 g of 2-acetamido-3-ethoxycarbonyl-6(1*H*)-pyrazinone (**14**) in 50 ml of ethanol was refluxed for 18 hr. The reaction mixture was then treated with animal carbon, filtered, and evaporated to dryness. Recrystallization of the residue from ethanol afforded 0.32 g (82%) of **15**, mp 226–228°. The analytical sample, recrystallized from ethanol, melted at 228–230°: NMR (CF_3COOH) δ 7.15 (1, s, H_5), 4.11 (2, q), 0.98 (3, t, $-OC_2H_5$).

Anal. Calcd for $C_7H_9N_3O_3$: C, 45.09; H, 4.95; N, 22.94. Found: C, 45.94; H, 4.87; N, 23.12.

Isoxanthopterin (2) by Cyclization of 2-Amino-3-ethoxycarbonyl-6(1*H*)-pyrazinone (15). To a methanolic solution of guanidine (prepared from 0.11 g of sodium in 20 ml of methanol and 0.48 g of guanidine hydrochloride) was added 0.30 g of **15** and the reaction mixture was refluxed with stirring for 1 hr. The solvent was then removed under reduced pressure and 10 ml of DMF was added to the residue. Refluxing for an additional 4.5 hr gave crude isoxanthopterin as an off-white precipitate. This was purified by precipitation from an alkaline solution with HCl in the usual manner to give 0.04 g (14%) of **2**, identical in all respects with an authentic sample.

2-Amino-3-cyanopyrazine 1,4-Dioxide (16). To a stirred, ice-cold solution of 12 ml of 30% hydrogen peroxide in 100 ml of trifluoroacetic acid was added 5.0 g of 2-amino-3-cyanopyrazine 1-oxide (**7**). Stirring at room temperature was then continued until the solution showed a negative starch–iodide reaction (ca. 18 hr). A further 8 ml of 30% hydrogen peroxide was then added at 0°, and stirring was continued a further 24 hr (starch–iodide test positive). The solvent was removed under reduced pressure below 40° to give a yellow, semicrystalline solid which was triturated with ice-cold ethanol and filtered after overnight refrigeration to give 2.9 g of crude **16**: mp 255° dec; NMR (CF_3COOH) δ 8.07 (1, d), 7.44 (1, d, H_5, H_6).

Anal. Calcd for $C_5H_4N_4O_2$: C, 39.48; H, 2.65; N, 36.84. Found: C, 39.57; H, 2.58; N, 37.00.

2-Amino-3-cyanopyrazine 4-Oxide (17). To an ice-cold suspension of 1.0 g of 2-amino-3-cyanopyrazine 1,4-dioxide (**16**) in 30 ml of tetrahydrofuran was added 1.4 g of phosphorus trichloride in 10 ml of tetrahydrofuran. The reaction mixture was stirred at 25° for 3.5 hr, the solvent was removed by evaporation under reduced pressure, and the residue was triturated with 50 ml of water. Filtration afforded crude **17**, mp 258–260°. The analytical sample was recrystallized from methanol to give 0.6 g (67%) of **17**: mp 262–263°; NMR (CF_3COOH) δ 7.79 (1, d), 7.37 (1, d, H_5, H_6).

Anal. Calcd for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.17. Found: C, 44.33; H, 2.89; N, 40.90.

2-Amino-3-carbamoylpyrazine 4-Oxide (18). A solution of 0.3 g of 2-amino-3-cyanopyrazine 4-oxide (**17**) in 1.5 ml of TFAA and 7.5 ml of TFA was stirred under reflux for 5 hr. The reaction mixture was then cooled and poured into water, and the aqueous solution was taken to dryness under reduced pressure. Ethanol was added to the residue and again removed by evaporation. The semicrystalline solid thus obtained was recrystallized from methanol to give 0.07 g (21%) of 2-amino-3-carbamoylpyrazine 4-oxide (**18**), mp 230–232°. The analytical sample, mp 230–232°, was recrystallized from methanol: NMR (CF_3COOH) δ 7.53 (1, d), 7.29 (1, d, H_5, H_6).

Anal. Calcd for $C_5H_6N_4O_2$: C, 38.96; H, 3.92; N, 36.35. Found: C, 38.79; H, 3.92; N, 36.65.

2-Amino-3-cyano-5-chloropyrazine (19).[20] To a stirred suspension of 1.0 g of 2-amino-3-cyanopyrazine 4-oxide (**17**) in 10 ml of DMF (held at 5–10°) was added 2.0 ml of phosphorus oxychloride. After addition was complete, the reaction mixture was stirred at 80–90° for 10 min, cooled, and poured into 10 ml of water at 0°. The aqueous mixture was stirred at room temperature for an additional 16 hr and cooled to give a crystalline precipitate of crude **19** which was collected by filtration. A further crop of crystals could be recovered from the filtrate by extraction with ethyl acetate, drying (Na_2SO_4), and removal of the solvent under reduced pressure. The combined materials were crystallized from ethyl acetate–petroleum ether to give 0.70 g (61%) of **19**: mp 152–154°; NMR (CF_3COOH) δ 7.81 (1, s, H_6).

Anal. Calcd for $C_5H_3N_4Cl$: C, 38.83; H, 1.96; N, 36.91; Cl, 22.22. Found: C, 38.89; H, 1.90; N, 36.63; Cl, 22.24.

2,4-Diamino-6-methoxypteridine (20). To a methanolic solution of guanidine (prepared from 0.35 g of sodium in 25 ml of methanol and 0.36 g of guanidine hydrochloride) was added 0.50 g of 2-amino-3-cyano-5-chloropyrazine (**19**). The suspension was stirred under reflux for 5 hr, cooled, and filtered, and the crude product was recrystallized from DMF–methanol to give 0.39 g (62%) of bright yellow **20**: mp >300°; NMR (CF_3COOH) δ 8.07 (1, s, H_7), 3.67 (3, s, $-OCH_3$); uv λ_{max} (0.1 *N* HCl) 362 nm (log ϵ 3.92), 353 (3.97), 274 (3.87), 248 (4.30).

Anal. Calcd for $C_7H_8N_6O$: C, 43.75; H, 4.20; N, 43.73. Found: C, 44.00; H, 4.16; N, 44.06.

Xanthopterin (1) by Hydrolysis of 2,4-Diamino-6-methoxypteridine (20). A suspension of 0.30 g of **20** in 20 ml of 10% aqueous sodium hydroxide was refluxed with stirring for 21 hr. The reaction mixture was then diluted with water, treated with animal carbon, and filtered. The pH of the filtrate was adjusted to 4 with acetic acid to give 0.26 g (93%) of bright yellow **1**. One precipitation from aqueous ammonia with dilute hydrochloric acid gave 0.24 g (86%) of xanthopterin monohydrate, mp >300°, identical in all respects with an authentic sample.

Pterin 8-Oxide (21). A suspension of 1.00 g of 2,4-diaminopteridine 8-oxide (**25**)[14] in 100 ml of 5% NaOH was heated under reflux until complete solution was achieved, and then for additional 5 min (total heating time 30 min). The yellow solution was then brought to pH 3 with 6 *N* HCl and allowed to stand for 30 min before filtering, washing thoroughly with water, and drying to yield 0.98 g (98%) of bright yellow **21**, identical with an authentic sample prepared by pertrifluoroacetic acid oxidation of pterin.[24]

Ethyl α-(Pterin-7-yl)-α-cyanoacetate (22). To a suspension of 0.15 g of pterin 8-oxide (**21**) in 15 ml of anhydrous HMPA was added 5.0 ml of ethyl cyanoacetate followed by 2 ml of acetic anhydride, and the mixture was stirred for 12 hr at 85–90°. Filtration afforded 0.01 g of unreacted **21**. The filtrate was diluted to 100 ml with absolute ethanol and stirred for 1 hr at 25° to give 0.05 g (30%) of **22** as a yellow, crystalline solid. The analytical sample crystallized from DMF as bright yellow needles: mp >300°; ir (KBr) $\bar{\nu}$ 2200 (CN), 1684, 1700 cm^{-1}; mass spectrum *m/e* 274 ($M^{\cdot+}$), 202 ($M - COOC_2H_5$); uv λ_{max} (EtOH) 402 nm (log ϵ 4.07), 317 (3.91), 267 (3.99), 232 (3.94).

Anal. Calcd for $C_{11}H_{10}N_6O_3$: C, 48.17; H, 3.68; N, 30.65. Found: C, 48.03; H, 3.82; N, 30.75.

Ethyl α-(2-Acetylpterin-7-yl)-α-cyanoacetate (23). Overnight refrigeration of the filtrate from **22** gave 0.03 g (15%) of **23** as a bright canary yellow solid. The analytical sample, which recrystallized from DMF in the form of elongated needles, had mp >300°; ir (KBr) $\bar{\nu}$ 2220 (CN), 1660, 1700 cm^{-1}; mass spectrum *m/e* 316 ($M^{\cdot+}$), 274 ($M - COCH_3$); uv λ_{max} (EtOH) 400 nm (log ϵ 4.42), 273 (4.43), 215 (4.26).

Anal. Calcd for $C_{13}H_{12}N_6O_4$: C, 49.37; H, 3.82; N. 26.57. Found: C, 49.11; H, 3.79; N, 26.28.

Oxidation of 22 or 23 to Pterin-7-carboxylic Acid (24). To a suspension of 0.60 g of **22** or **23** in 10 ml of water was added 0.10 g of sodium hydroxide, followed by the dropwise addition of 6.0 ml of 2 *M* potassium permanganate solution with stirring over a period of 2.5 hr at 80°. The excess potassium permanganate was destroyed with sodium sulfite, and the reaction mixture was then treated with animal carbon and filtered. The pH of the filtrate was adjusted to 2 to give a yellow microcrystalline solid. After the solution was stirred at 90° for 2 hr the crystals were collected by filtration, washed with water, and dried (0.4 Torr, 110°, 24 hr) to give 0.01 g of pterin-7-carboxylic acid (**24**), identical chromatographically and spectroscopically with an authentic sample.

2,4-Diamino-7-(1-pyrrolidino)pteridine (26). A suspension of 0.20 g of 2,4-diaminopteridine 8-oxide (**25**) in 15 ml of pyrrolidine was stirred for 16 hr at 95°. After removal of the solvent on a rotary evaporator, the yellow residue was triturated with 10 ml of absolute ethanol and refrigerated at 5° for 2 hr. Filtration afforded 0.17 g (62%) of **26** as a yellow powder. The analytical sample, prepared by recrystallizing a portion of the title compound twice from ethanol, had mp >300°; NMR (DMSO-d_6) δ 7.65 (1, s, H_6), 6.83 (2, br, $-NH_2$), 5.95 (2, br, $-NH_2$), 3.45 (4, m, α-pyrrolidine), 1.86 (m, β-pyrrolidine); uv λ_{max} (0.1 *N* HCl) 364 nm (log ϵ 4.34), 287 (4.18), 263 (4.16), 220 (4.46).

Anal. Calcd for $C_{10}H_{13}N_7$: C, 51.94; H, 5.67; N, 42.40. Found: C, 51.78; H, 5.65; N, 42.34.

Isoxanthopterin (2) by Hydrolysis of 2,4-Diamino-7-(1-pyrrolidino)pteridine (26). A suspension of 0.10 g of **26** in 20 ml of 5% NaOH solution was heated under reflux at 110° for 96 hr, and the resulting solution was cooled to 0° in an ice bath. After the pH was adjusted to 4 with 12 *N* HCl and the solution was allowed to stand for 12 hr, the solution had deposited 0.05 g (85%) of a yellowish-brown powder, which, following purification in the usual manner, gave isoxanthopterin (**2**), identical with an authentic sample.

Xanthopterin (1) by Rearrangement of Pterin 8-Oxide (21) with TFA–TFAA. A suspension of 1.0 g of pterin 8-oxide (**21**) in 5 ml of TFA and 5 ml of TFAA was stirred in an oil bath at 50°. After 20 min a homogeneous solution (bright yellow) was obtained, an aliquot of which showed only one aromatic proton (NMR). After stirring for a total of 1 hr the solution was evaporated to dryness at room temperature (10 Torr), and the residual solvent was removed under high vacuum (0.1 Torr) to give a bright yellow solid. Fifty milliliters of 10% ammonium hydroxide was added, and the resulting suspension was stirred for an additional 15 min at 50° and then dissolved by the slow addition of 1 *N* sodium hydroxide. After solution was complete, 500 mg of Darco G-60 carbon was added, and stirring was continued for an additional 20 min at 50°. Filtration through a small pad of Celite than gave a bright yellow solution, which on acidification with 6 *N* HCl to pH 3 gave the title compound as a yellow, microcrystalline precipitate. The product was collected, washed well with water and methanol, and dried overnight under high vacuum (0.1 Torr, P_2O_5) to give **1** in nearly quantitative yield. The product was shown to be pure **1** by virtue of its identical ir, uv, and paper chromatographic behavior with an authentic sample. The same rearrangement could be effected at room temperature, again in quantitative yield, but a total reaction time of 4 hr was required.

Xanthopterin (1) from 2,4-Diaminopteridine 8-Oxide (25). A suspension of 100 mg of **25** in a solution of 0.5 ml of TFAA and 3 ml of TFA was brought to reflux in an oil bath heated to 65° and stirred under these conditions for 5 hr. During this time the suspended solid slowly dissolved to give a deep red-brown solution. All solvents were then removed under reduced pressure to give 2,4-diamino-6(5*H*)-pteridinone (**30**) as a dark brown solid. This material was then dissolved in 10 ml of 5% NaOH, 100 mg of Darco G-60 carbon was added, and the mixture was heated for 24 hr in an oil bath at 100°. Filtration through a pad of Celite gave an orange-yellow solution, which upon acidification to pH 3 with 6 *N* HCl gave **1** as a gelatinous precipitate. The material was collected and

washed (water, then methanol) by centrifugation, and dried overnight under high vacuum to give 65 mg (65%) of **1**, identical with an authentic sample.

Registry No.—**1**, 119-44-8; **2**, 529-69-1; **4**, 19994-56-0; **5**, 54632-07-4; **6**, 54632-08-5; **7**, 42770-07-0; **8**, 54632-09-6; **9**, 54632-10-9; **10**, 54632-11-0; **11**, 54632-12-1; **12**, 26212-13-5; **13**, 54632-13-2; **14**, 54632-14-3; **15**, 54632-15-4; **16**, 54632-16-5; **17**, 54632-17-6; **18**, 54632-18-7; **19**, 17231-50-4; **20**, 26212-23-7; **21**, 42346-89-4; **22**, 54632-19-8; **23**, 54632-20-1; **24**, 31010-60-3; **25**, 42346-93-0; **26**, 54632-21-2; **30**, 26212-17-9; 2-trifluoroacetamido-3-carbamoyl-5-methyl-6(1*H*)-pyrazinone, 54632-22-3; 2-acetamido-3-carbamoyl-5-methyl-6(1*H*)-pyrazinone, 54632-23-4.

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Pteridines. XXXVIII. Synthesis of Some 2,4-Diamino-6-Substituted Methylpteridines. A New Route to Pteroic Acid[1,2]

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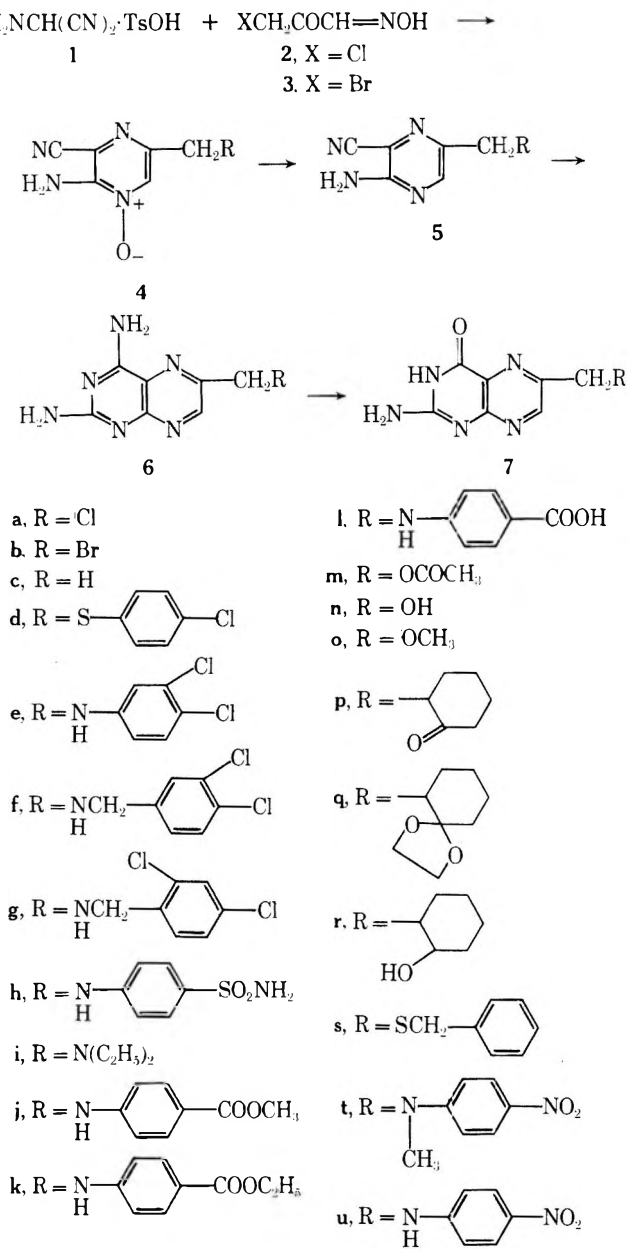
A versatile, flexible route to a variety of 6-substituted 2,4-diaminopteridines (**6**) and 6-substituted pterins (**7**) is described which involves the reaction of 2-amino-3-cyano-5-chloromethylpyrazine (**5**) with nucleophiles, followed by ring closure with guanidine (to give **6**), and final acid hydrolysis (to give **7**). Among the compounds conveniently prepared by this unequivocal route are 2,4-diamino-6-hydroxymethylpteridine, 6-hydroxymethylpterin, and pteroic acid. A three-component, one-pot (TCOP) condensation of aminomalononitrile tosylate, β-bromopyruvaldoxime, and added nucleophile has been developed which leads directly, in moderate yield but high purity, to 2-amino-3-cyano-5-substituted pyrazine 1-oxides (**4**).

Previous papers in this series have described a new, general, and unequivocal synthesis of 6- and/or 7-substituted pteridines from pyrazine 1-oxide intermediates, prepared by the condensation of α-aminonitriles with α-ketoaldoximes or α-oximino aldehydes.[3–5] The synthesis of 2,4-diaminopteridines substituted in position 6 with olefinic substituents suitable for final elaboration into multifunctional side chains characteristic of some of the naturally occurring pterins (i.e., biopterin, neopterin, urothion, etc.) involved (a) the preliminary formation of 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide (**4a**) by the condensation of aminomalononitrile tosylate (**1**) with β-chloropyruvaldoxime (**2**), (b) deoxygenation with phosphorus trichloride to 2-amino-3-cyano-5-chloromethylpyrazine (**5a**), (c) elaboration of the olefinic side chain by means of the Wittig reaction, and (d) terminal closure of the pyrimidine ring by cyclization with guanidine.[5] The present paper describes a number of nucleophilic displacement reactions on the chloromethyl substituent in **5a**, and the elaboration of the resulting substituted methylpyrazines to a variety of new 2,4-diaminopteridines and pterins. This paper also describes new and unequivocal syntheses of pteroic acid and of 6-hydroxymethylpterin, and a convenient three-component, one-pot (TCOP) synthesis of 2-amino-3-cyano-5-substituted methylpyrazine 1-oxides.

Although the primary chloro substituent in **5a** is reactive toward nucleophiles (we have previously described its displacement by methoxide ion and by triphenylphosphine[5]), conditions must be chosen with care because of the ease of nucleophilic addition to the 3-cyano grouping. Displacement by sodium 4-chlorothiophenolate occurred smoothly in methanol solution in high yield, without concomitant addition to the extremely reactive nitrile grouping, to give **5d**. Reaction of **5a** with aromatic amines, however, proved to be more critical, and optimum reaction conditions involved the use of acetonitrile as solvent, although DMSO at higher temperatures could also be employed. Thus, reaction of **5a** with 3,4-dichloroaniline, ethyl 4-aminobenzoate, or sulfanilamide in the presence of potassium carbonate led to the formation in high yield of the pyrazines **5e**, **5k**, and **5h**, respectively. Reaction of **5a** with 3,4-dichloro- and 2,4-dichlorobenzylamine, and with diethylamine, all occurred smoothly in 2-propanol solution to give the pyrazines **5f**, **5g**, and **5i**, respectively. Cyclization of these pyrazine o-aminonitriles to the corresponding 2,4-diaminopteridines (**6**) proceeded in the normal manner with guanidine in methanol in the presence of sodium methoxide.

The conversion of 2,4-diaminopteridines to pterins [2-amino-4(3*H*)-pteridinones] by selective hydrolysis of the 4-amino group has been exploited previously.[4,6–8] Thus, alkaline hydrolysis of **6k** gave pteroic acid (**7**), identical in every respect with an authentic sample.[9] This synthesis of pteroic acid is a five-step process utilizing readily available starting materials and involving crystalline intermediates

Scheme I



at all steps prior to the final cyclization to the penultimate 2,4-diaminopteridine, and it is completely unequivocal in that *only* the 6-substituted derivative is obtained. Extensions of this procedure to the preparation of related 6-substituted pteridines such as folic acid, aminopterin, and methotrexate will be described in forthcoming publications.

Condensation of 2-amino-3-cyano-5-chloromethylpyrazine (**5a**) with potassium acetate in 2-propanol resulted in smooth displacement of the primary halogen atom by an acetoxy group to give 2-amino-3-cyano-5-acetoxymethylpyrazine (**5m**). Cyclization of this latter compound with guanidine in the presence of sodium methoxide then gave 2,4-diamino-6-hydroxymethylpteridine (**6n**), which has recently been shown to be a valuable intermediate, via its conversion to 2,4-diamino-6-bromomethylpteridine, for the preparation of aminopterin and homologs.[10] Compound **6n** was previously prepared as a potential inhibitor of folic acid biosynthesis by Baugh and Shaw[8] by the classical Isay-type condensation of 2,4,5,6-tetraaminopyrimidine with dihydroxyacetone, but not only is this procedure intrinsically equivocal, but it leads to the simultaneous formation of 2,4-diamino-6-methylpteridine, which apparently cannot be separated from **6n**.[10] Since acid hydrolysis of **6n** readily gives 6-hydroxymethylpterin (**7n**),[8] this simple sequence of reactions makes this latter naturally occurring pteridine and biogenetic precursor to folic acid readily available in pure form.

The reaction of **5a** with enamines was briefly studied as a potential route to pteridine derivatives, functionalized at C-6 with hydroxyalkyl groups, which are of considerable interest as potential biopterin antagonists. Thus, the condensation of **5a** with 1-pyrrolidino-1-cyclohexene in refluxing THF, followed by in situ acid hydrolysis, led to 2-amino-3-cyano-5-(2-oxocyclohexylmethyl)pyrazine (**5p**), which was reduced with sodium borohydride to the corresponding cyclohexanol derivative **5r**. The ethylene ketal **5q** was prepared from **5p** by ketalization with ethylene glycol and acid. The pyrazine intermediates **5q** and **5r** were converted into the corresponding 2,4-diaminopteridines **6q** and **6r** by condensation with guanidine; acid hydrolysis of the former then gave 2,4-diamino-6-(2-oxocyclohexylmethyl)pteridine (**6p**). One may thus anticipate that the reaction of **5a** with cyclic as well as acyclic enamines should provide ready access to a diversity of related pteridines substituted at position 6 by multifunctional carbon substituents.

In an earlier publication we had described the preparation of 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide (**4a**) by condensation of β-chloropyruvaldoxime with aminomalononitrile in 2-propanol.[5] We had noted at the time that the use of methanol as solvent led to appreciable quantities of the 5-methoxymethylpyrazine 1-oxide **4o**. However, a subsequent observation that the conversion of **4a** to **4o** required 48 hr of reflux in methanol clearly indicated that the formation of **4o** in the above condensation reaction must have involved nucleophilic displacement of chlorine by methanol at some stage prior to ring closure to **4a**. This incidental observation suggests that condensation of a β-halopyruvaldoxime with aminomalononitrile in *the presence of an added nucleophile* should lead directly to 2-amino-3-cyano-5-substituted methylpyrazine 1-oxides (a three-component, one-pot or TCOP condensation). We have briefly explored this concept with some success. For example, a TCOP reaction involving aminomalononitrile tosylate, β-bromopyruvaldoxime (**3**), and benzyl mercaptan in 2-propanol solution led in moderate yield to pure 2-amino-3-cyano-5-(benzylthiomethyl)pyrazine 1-oxide (**4s**), which could be deoxygenated with phosphorus trichloride to **5s**, identical with an authentic sample prepared by the reaction of benzyl mercaptan with **5a**. In similar fashion, the pyrazine 1-oxides **4t** and **4u** were prepared by TCOP reactions. There appears to be a subtle dependence, however, upon a combination of nucleophilicity and basicity in the added nucleophile for success in these TCOP reactions. For example, potassium acetate, 4-chlorothiophenol, 2-nitro-4-chloroaniline, and 3,4-dichloroaniline all failed to give satisfactory TCOP reactions, apparently because they were either insufficiently nucleophilic (**4a** was isolated from each of these reaction mixtures), or too basic (leading to the tosyl salt of the added nucleophile). An attempted TCOP reaction utilizing triphenylphosphine as the added nucleophile led to reductive debromination and the formation of 2-amino-3-cyano-5-methylpyrazine 1-oxide (**4c**). This initially surprising result is, however, consistent with previous observations that α-bromocarbonyl compounds are reductively debrominated with triphenylphosphine in protic solvents.[11,12] Since 2-amino-3-cyano-5-bromomethylpyrazine 1-oxide (**4b**) reacts normally with triphenylphosphine in 2-propanol to give the phosphonium salt **4** [R = $^{+}P(C_6H_5)_3Br$], it seems reasonable to assume that the

formation of **4c** in the above TCOP reaction involves initial in situ formation of pyruvaldoxime from β-bromopyruvaldoxime (**3**) and triphenylphosphine, but attempts to confirm this by examination of the reaction of these two compounds in the absence of aminomalononitrile tosylate (**1**) were frustrated by extensive decomposition. As expected on the basis of earlier findings,[12] substitution of β-chloropyruvaldoxime (**2**) for **3** in the above TCOP reaction led to the phosphonium salt **4** (R = $^{+}P(C_6H_5)_3Cl^{-}$).

All of the pyrazine 1-oxides prepared by the TCOP procedure were deoxygenated to the respective pyrazines **5s, 5t,** and **5u,** which were then condensed with guanidine in the usual manner to give the 2,4-diaminopteridines **6s, 6t,** and **6u.**

The conversions described above are summarized in Scheme I.

Experimental Section[13]

2-Amino-3-cyano-5-(4-chlorophenylthiomethyl)pyrazine (5d). A mixture of 4.0 g of 2-amino-3-cyano-5-chloromethylpyrazine,[5] 3.5 g of 4-chlorothiophenol, and 1.3 g of sodium methoxide in 120 ml of methanol was stirred overnight at room temperature and then poured into 200 ml of ice water. The precipitated solid was collected by filtration and then heated under reflux with 50 ml of methanol for 30 min. Cooling and filtering then gave 6.1 g (94%) of **5d** as a colorless, microcrystalline solid, mp 161–162°. The analytical sample, mp 162–163°, was prepared by recrystallization from methanol.

Anal. Calcd for $C_{12}H_9N_4SCl$: C, 52.08; H, 3.26; N, 20.25; S, 11.57; Cl, 12.84. Found: C, 51.89; H, 3.20; N, 20.29; S, 11.21; Cl, 13.14.

2-Amino-3-cyano-5-(3,4-dichloroanilinomethyl)pyrazine (5e). A mixture of 1.68 g of 2-amino-3-cyano-5-chloromethylpyrazine, 8.10 g of 3,4-dichloroaniline, and 1.38 g of potassium carbonate in 50 ml of acetonitrile was stirred for 24 hr at room temperature. The precipitated product (contaminated by potassium salts) was collected by vacuum filtration and washed with a little cold acetonitrile. The product was then stirred with 50 ml of ether to remove excess aniline, collected again by filtration, washed with ether, and dried. Recrystallization of the product from ethyl acetate (charcoal) then gave 2.15 g (73%) of **5e** as a bright yellow powder, mp 198–199° dec. The analytical sample, mp 200–201° dec, was prepared by recrystallization from methanol.

Anal. Calcd for $C_{12}H_9N_5Cl_2$: C, 48.98; H, 3.06; N, 23.81; Cl, 24.15. Found: C, 48.78; H, 3.31; N, 24.04; Cl, 23.91.

2-Amino-3-cyano-5-(3,4-dichlorobenzylaminomethyl)pyrazine (5f). To 0.34 g of 2-amino-3-cyano-5-chloromethylpyrazine in 50 ml of 2-propanol was added 1.76 g of 3,4-dichlorobenzylamine. The reaction mixture was stirred for 24 hr at room temperature, after which time the light yellow precipitate which had separated was collected by filtration and dried, yield 0.54 g. To this crude product was added 50 ml of water, the pH was adjusted to 11 with 0.5 *N* NaOH, and the resulting precipitate was again collected by filtration. The yellow powder was added to a column of silica gel, and the column was then eluted with chloroform–ethyl acetate (1:3). The first two materials to be eluted from the column were the unreacted amine and the dialkylated amine (identified by NMR); the fractions containing **5f** then followed. Evaporation of the eluates gave 0.21 g (34%) of **5f.** Recrystallization from ethyl acetate gave a light yellow microcrystalline powder, mp 135–137°.

Anal. Calcd for $C_{13}H_{11}N_5Cl_2$: C, 50.67; H, 3.60; N, 22.73. Found: C, 50.74; H, 3.70; N, 22.50.

2-Amino-3-cyano-5-(2,4-dichlorobenzylaminomethyl)pyrazine (5g). This compound was prepared in 44% yield from 2-amino-3-cyano-5-chloromethylpyrazine and 2,4-dichlorobenzylamine as described above for the preparation of **5f,** mp (from diisopropyl ether) 136–138°.

Anal. Calcd for $C_{13}H_{11}N_5Cl_2$: C, 50.67; H, 3.60; N, 22.73. Found: C, 50.75; H, 3.58; N, 22.88.

2-Amino-3-cyano-5-(sulfanilamidomethyl)pyrazine (5h). A mixture of 0.84 g of 2-amino-3-cyano-5-chloromethylpyrazine, 4.30 g of sulfanilamide, and 0.69 g of potassium carbonate in 40 ml of acetonitrile was stirred for 24 hr at room temperature. Filtration then gave 0.71 g (47%) of an orange-yellow microcrystalline solid which was recrystallized from acetonitrile, mp 190–192°.

Anal. Calcd for $C_{12}H_{12}N_6O_2S$: C, 47.36; H, 3.97; N, 27.62. Found: C, 47.20; N, 3.94; N, 27.88.

2-Amino-3-cyano-5-(*N,N*-diethylaminomethyl)pyrazine (5i). A mixture of 1.68 g of 2-amino-3-cyano-5-chloromethylpyrazine, 1.63 g of diethylamine, and 50 ml of 2-propanol was stirred for 1.5 hr, during which time a mild exothermic reaction took place and then subsided. The reaction mixture was concentrated to dryness under reduced pressure and the residue was dissolved in water with addition of a few drops of 6 *N* HCl. The resulting acid solution was extracted with two 10-ml portions of ethyl acetate, and the pH was adjusted to 10 by addition of 40% NaOH. This basic solution was then extracted with three 15-ml portions of ethyl acetate, the ethyl acetate (from the latter extraction) was evaporated under reduced pressure, and the residual yellow plates were recrystallized from petroleum ether (bp 60–70°) to give 1.42 g (69%) of pale yellow, shining platelets, mp 90–92°.

Anal. Calcd for $C_{10}H_{15}N_5$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.69; H, 7.17; N, 33.77.

2-Amino-3-cyano-5-(4-carbethoxyanilinomethyl)pyrazine (5k). Under the same conditions as described for the preparation of **5e,** 2-amino-3-cyano-5-chloromethylpyrazine and ethyl 4-aminobenzoate were condensed in DMSO to give **5k** (64% yield) as a pale yellow crystalline solid, mp 184–185° (from ethanol).

Anal. Calcd for $C_{15}H_{15}N_5O_2$: C, 60.59; H, 5.09; N, 23.56. Found: C, 60.88; H, 5.08; N, 23.85.

2-Amino-3-cyano-5-acetoxymethylpyrazine (5m). A mixture of 10.0 g of 2-amino-3-cyano-5-chloromethylpyrazine and 8.9 g of potassium acetate in 400 ml of 2-propanol was stirred at 80–90° for 3 hr and then evaporated to dryness under reduced pressure. Trituration of the residue for 30 min in 100 ml of water followed by filtration gave a light gray solid which was dissolved in hot methanol, treated with Norite, and then evaporated to a small volume. Cooling then gave 8.3 g (73%) of **5m** as a colorless, crystalline solid, mp 140–141°.

Anal. Calcd for $C_8H_8N_4O_2$: C, 49.99; H, 4.20; N, 29.16. Found. C, 49.90; H, 4.14; N, 29.17.

2-Amino-3-cyano-5-(2-oxocyclohexylmethyl)pyrazine (5p). A solution of 5.0 g of 2-amino-3-cyano-5-chloromethylpyrazine and 4.9 g of 1-pyrrolidino-1-cyclohexene in 500 ml of tetrahydrofuran was heated under reflux overnight. Water (5 ml) was then added and refluxing was continued for an additional 1.5 hr. The reaction mixture was then evaporated to dryness under reduced pressure, the residue was dissolved in 800 ml of chloroform, and the resulting solution was washed with 100 ml of water. The chloroform solution was then evaporated to dryness, the residue was triturated with a small amount of cold methanol, and the colorless, microcrystalline solid was collected by filtration to give 5.1 g (74%) of **5p,** mp 171–172°. The analytical sample was prepared by recrystallization from methanol without change in the melting point.

Anal. Calcd for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.49; H, 6.07; N, 24.50.

2-Amino-3-cyano-5-(2-ethylenedioxycyclohexylmethyl)pyrazine (5q). A mixture of 2.6 g of 2-amino-3-cyano-5-(2-oxocyclohexylmethyl)pyrazine and 0.8 g of ethylene glycol in 70 ml of benzene containing 0.05 g of *p*-toluenesulfonic acid was heated under reflux for 3 hr. Excess solvent was removed by evaporation under reduced pressure, the solid residue was suspended in 50 ml of methanol and stirred at room temperature for 30 min, and the resulting solid was collected by filtration and recrystallized from methanol to give 2.0 g (65%) of fine colorless needles of **5q,** mp 169–170°.

Anal. Calcd for $C_{14}H_{18}N_4O_2$: C, 61.29; H, 6.61; N, 20.43. Found: C, 61.38; H, 6.69; N, 20.56.

2-Amino-3-cyano-5-(2-hydroxycyclohexylmethyl)pyrazine (5r). To a suspension of 2.0 g of 2-amino-3-cyano-5-(2-oxocyclohexylmethyl)pyrazine in 50 ml of cold methanol was added 0.17 g of sodium borohydride, and the resulting suspension was stirred for 10 min at 0° and then for an additional 30 min at room temperature. By this time the reaction mixture had become homogeneous. It was then evaporated under reduced pressure to dryness, and the residue was slurried for 10 min with 10 ml of 0.5 *N* HCl. The precipitated solid was collected by filtration, washed thoroughly with water, and recrystallized from methanol to give 1.4 g (70%) of light yellow crystals of **5r,** mp 151–155°. The NMR spectrum of this product (DMSO-d_6) indicated that a mixture of cis and trans isomers (~2:1) was formed in the reduction. No attempt was made to separate or further characterize this mixture, which was preserved in the subsequent guanidine cyclization to **6r** (vide infra).

Anal. Calcd for $C_{12}H_{16}N_4O$: C, 62.05; H, 6.94; N, 24.12. Found: C, 62.05; H, 6.98; N, 24.20.

2-Amino-3-cyano-5-(benzylthiomethyl)pyrazine 1-Oxide (4s). To a solution of 3.32 g of β-bromopyruvaldoxime and 2.48 g of benzyl mercaptan in 30 ml of 2-propanol was added 5.04 g of ami-

nomalononitrile tosylate, and the mixture was stirred at room temperature for 24 hr. The light yellow precipitate which had separated was collected by filtration (3.02 g, 55%) and recrystallized from ethanol to give a yellow, microcrystalline solid, mp 135–136° dec.

Anal. Calcd for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44; N, 20.57. Found: C, 57.41; H, 4.70; N, 20.76.

2-Amino-3-cyano-5-(*N*-methyl-4-nitroanilinomethyl)pyrazine 1-Oxide (4t). This compound was prepared in 56% yield from β-bromopyruvaldoxime, aminomalononitrile tosylate, and *N*-methyl-*p*-nitroaniline as described above for the preparation of **4s**, mp (from ethanol) 213–214° dec.

Anal. Calcd for $C_{13}H_{12}N_6O_3$: C, 52.00; H, 4.03; N, 27.99. Found: C, 51.84; H, 4.28; N, 28.15.

2-Amino-3-cyano-5-(*p*-nitroanilinomethyl)pyrazine 1-Oxide (4u). This compound was prepared in 29% yield from β-bromopyruvaldoxime, aminomalononitrile tosylate, and *p*-nitroaniline as described above for the preparation of **4s**, except that the initial precipitate proved to be the tosyl salt of **4u**. The free base was obtained as yellow needles, mp 143° dec, by suspending the salt in dilute sodium hydroxide, filtering, and recrystallizing the collected solid from methanol.

Anal. Calcd for $C_{12}H_{10}N_8O_3$: C, 50.35; H, 3.52; N, 29.36. Found: C, 50.36; H, 3.67; N, 29.31.

2-Amino-3-cyano-5-(benzylthiomethyl)pyrazine (5s). To a solution of 0.82 g of 2-amino-3-cyano-5-(benzylthiomethyl)pyrazine 1-oxide in 20 ml of tetrahydrofuran, cooled in an ice bath, was added 0.8 ml of phosphorus trichloride. The ice bath was then removed and the reaction mixture was allowed to warm to room temperature, with stirring, over a period of 45 min and then evaporated to a small volume under reduced pressure. The residual crystals were collected by filtration, washed with 10 ml of cold water, and recrystallized from benzene to give 0.49 g (64%) of light yellow platelets, mp 143–145° dec.

Anal. Calcd for $C_{13}H_{12}N_4S$: C, 60.92; H, 4.72; N, 21.86. Found: C, 60.88; H, 4.76; N, 21.41.

2-Amino-3-cyano-5-(*N*-methyl-*p*-nitroanilinomethyl]pyrazine (5t). This compound was prepared in 93% yield by deoxygenation of 2-amino-3-cyano-5-(*N*-methyl-*p*-nitroanilinomethyl)pyrazine 1-oxide with phosphorus trichloride as described above for the preparation of **5s**, mp (from methanol) 193–194° dec.

Anal. Calcd for $C_{13}H_{12}N_6O_2$: C, 54.93; H, 4.25; N, 29.56. Found: C, 54.74; H, 4.01; N, 29.73.

2-Amino-3-cyano-5-(*p*-nitroanilinomethyl)pyrazine (5u). This compound was prepared in 95% yield by deoxygenation of 2-amino-3-cyano-5-(*p*-nitroanilinomethyl)pyrazine 1-oxide with phosphorus trichloride as described above for the preparation of **5s**, mp (from acetonitrile) 238–239° dec.

Anal. Calcd for $C_{12}H_{10}N_6O_2$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.53; H, 3.78; N, 31.40.

2-Amino-3-cyano-5-methylpyrazine 1-Oxide (4c). A mixture of 1.66 g of β-bromopyruvaldoxime, 2.62 g of triphenylphosphine, and 2.53 g of aminomalononitrile tosylate in 20 ml of 2-propanol was stirred at room temperature for 5 hr. The yellow precipitate which had separated was collected by filtration (0.87 g, 57%) and recrystallized from ethanol to give pure **4c**, mp 186–187° (lit.[4] mp 187–188°), identical with an authentic sample.

2,4-Diamino-6-(4-chlorophenylthiomethyl)pteridine (6d). To a methanolic solution of guanidine (prepared by adding 2.7 g of guanidine hydrochloride to 200 ml of dry methanol containing 3.5 g of sodium methoxide, and removal of the precipitated sodium chloride by filtration) was added 5.0 g of 2-amino-3-cyano-5-(4-chlorophenylthiomethyl)pyrazine, and the resulting mixture was heated under reflux for 24 hr. The precipitate which had formed was collected by filtration and extracted for 30 min with hot methanol. Filtration then gave 5.3 g (93%) of **6d** as a pale yellow, microcrystalline solid, mp 286–287° dec.

Anal. Calcd for $C_{13}H_{11}N_6SCl$: C, 48.98; H, 3.46; N, 26.37; S, 10.05; Cl, 11.15. Found: C, 48.89; H, 3.57; N, 26.53; S, 9.99; Cl, 11.33.

The following compounds were similarly prepared from the appropriate 2-amino-3-cyanopyrazine precursor and guanidine.

2,4-Diamino-6-(3,4-dichloroanilinomethyl)pteridine (6e), 76% yield, mp (from DMF) 294–295° dec.

Anal. Calcd for $C_{13}H_{11}N_7Cl_2$: C, 46.43; H, 3.28; N, 29.17; Cl, 21.13. Found: C, 46.58; H, 3.47; N, 29.34; Cl, 20.99.

2,4-Diamino-6-(benzylthiomethyl)pteridine (6s), 85% yield, mp (from methanol) 152–154° dec.

Anal. Calcd for $C_{14}H_{14}N_6S$: C, 56.17; H, 5.05; N, 28.07. Found: C, 56.21; H, 4.76; N, 27.85.

2,4-Diamino-6-(*N*-methyl-4-nitroanilinomethyl)pteridine (6t), 85% yield, mp (from DMF) >350° dec.

Anal. Calcd for $C_{14}H_{14}N_8O_2$: C, 51.53; H, 4.32; N, 34.34. Found: C, 50.40; H, 4.38; N, 34.92.

2,4-Diamino-6-(3,4-dichlorobenzylaminomethyl)pteridine (6f), 66% yield, mp (from methanol–acetonitrile) 263–264° dec.

Anal. Calcd for $C_{14}H_{13}N_7Cl_2$: C, 48.01; H, 3.74; N, 28.00. Found: C, 47.94; H, 3.78; N, 28.08.

2,4-Diamino-6-(2,4-dichlorobenzylaminomethyl)pteridine (6g), 80% yield, mp (from methanol) 264–265° dec.

Anal. Calcd for $C_{14}H_{13}N_7Cl_2$: C, 48.01; H, 3.74; N, 28.00. Found: C, 47.92; H, 3.84; N, 28.00.

2,4-Diamino-6-(sulfanilamidomethyl)pteridine (6h), 87% yield, mp (after extraction of impurities with hot acetonitrile) >300° dec.

Anal. Calcd for $C_{13}H_{14}N_8O_2S$: C, 45.08; H, 4.07; N, 32.35. Found: C, 44.97; H, 4.21; N, 32.12.

2,4-Diamino-6-(*N,N*-diethylaminomethyl)pteridine (6i), 68% yield, mp (from ethanol) 271–272° dec.

Anal. Calcd for $C_{11}H_{17}N_7$: C, 53.42; H, 6.93; N, 39.65. Found: C, 53.40; H, 7.09; N, 39.64.

2,4-Diamino-6-(4-carbomethoxyanilinomethyl)pteridine (6j),[14] 66% yield, mp (from methanol–THF) 258–259° dec.

Anal. Calcd for $C_{15}H_{15}N_7O_2$: C, 55.38; H, 4.62; N, 30.15. Found: C, 55.49; H, 4.66; N, 30.25.

2,4-Diamino-6-(4-carbethoxyanilinomethyl)pteridine (6k),[15] 85% yield, mp (by extraction of impurities with hot methanol) 284–286° dec (lit.[16] mp 277° dec).

2,4-Diamino-6-hydroxymethylpteridine (6n), 84% yield, mp (from water) 333–334° dec.

Anal. Calcd for $C_7H_8N_6O$: C, 43.73; H, 4.20; N, 43.73. Found: C, 43.98; H, 4.12; N, 43.74.

2,4-Diamino-6-(2-ethylenedioxycyclohexylmethyl)pteridine (6q), 89% yield, mp (from methanol) 275–276° dec.

Anal. Calcd for $C_{15}H_{20}N_6O_2$: C, 56.95; H, 6.37; N, 26.57. Found: C, 57.04; H, 6.38; N, 26.30.

2,4-Diamino-6-(2-hydroxycyclohexylmethyl)pteridine (6r), 52% yield, mp (from methanol) 287–288° dec.

Anal. Calcd for $C_{13}H_{18}N_6O$: C, 56.92; H, 6.61; N, 30.64. Found: C, 56.89; H, 6.67; N, 30.84.

2-Amino-6-(4-carboxyanilinomethyl)-4(3*H*)-pteridinone (Pteroic Acid, 7l). A suspension of 0.5 g of 2,4-diamino-6-(4-carbethoxyanilinomethyl)pteridine in 160 ml of 0.2 *N* NaOH was heated under gentle reflux for 1.5 hr under an atmosphere of nitrogen. The resulting clear, colorless solution was cooled to 0° and the pH adjusted to 3–4 with dilute hydrochloric acid. The precipitate which separated was collected by centrifugation and suspended in 1 l. of boiling water and 1 *N* NaOH was added slowly until complete solution had been achieved (10 ml). The resulting solution was treated with Norite and filtered, and the pH of the filtrate was slowly adjusted to 3–4. The resulting fine yellow solid was collected by filtration and washed with water, methanol, and then ether, yield, 0.4 g (83%), mp >400°.

Anal. Calcd for $C_{14}H_{12}N_6O_3$: C, 53.84; H, 3.87; N, 26.91. Found: C, 54.04; H, 3.80; N, 27.11.

2,4-Diamino-6-(2-oxocyclohexylmethyl)pteridine (6p). To a solution of 1.0 g of 2,4-diamino-6-(2-ethylenedioxycyclohexylmethyl)pteridine in 1 ml of trifluoroacetic acid was added, under ice–salt bath cooling and stirring, 0.2 ml of concentrated H_2SO_4. The solution was stirred for 15 min at 0–5° and poured into ice water and the resulting slurry was stirred for an additional 15 min. The solid which was collected by filtration was triturated for 30 min with 50 ml of 2 *N* NaOH and filtered, and the collected solid was digested with 50 ml of refluxing methanol. Filtration then gave 0.7 g (81%) of **6p** as a yellow, microcrystalline solid, mp 282–283° dec. The analytical sample was recrystallized from a large volume of methanol without change in the melting point.

Anal. Calcd for $C_{13}H_{16}N_6O$: C, 57.34; H, 5.92; N, 30.86. Found: C, 57.09; H, 5.79; N, 30.70.

Registry No.—**1**, 5098-14-6; **3**, 37150-52-0; **4c**, 19994-56-0; **4s**, 54798-18-4; **4t**, 54798-19-5; **4u**, 54798-20-8; **5d**, 54798-21-9; **5e**, 54798-22-0; **5f**, 54798-23-1; **5g**, 54798-24-2; **5h**, 54798-25-3; **5i**, 54798-26-4; **5k**, 54798-27-5; **5m**, 54798-28-6; **5n**, 54798-29-7; **5p**, 54798-30-0; **5q**, 54798-31-1; *cis*-**5r**, 54798-32-2; *trans*-**5r**, 54798-33-3; **5s**, 54798-34-4; **5t**, 54832-63-2; **5u**, 54798-35-5; **6d**, 54798-36-6; **6e**, 54798-37-7; **6f**, 54798-38-8; **6g**, 54798-39-9; **6h**, 54798-40-2; **6i**, 54798-41-3; **6j**, 54798-42-4; **6k**, 23853-08-9; **6n**, 945-24-4; **6p**, 54798-43-5; **6q**, 54798-44-6; **6r**, 54798-45-7; **6s**, 54798-46-8; **6t**, 54798-47-9; **7l**, 119-24-4; 2-amino-3-cyano-5-chloromethylpyra-

zine, 40127-91-1; 4-chlorothiophenol, 106-54-7; 3,4-dichloroaniline, 95-76-1; 3,4-dichlorobenzylamine, 102-49-8; 2,4-dichlorobenzylamine, 95-00-1; sulfanilamide, 63-74-1; diethylamine, 109-89-7; ethyl 4-aminobenzoate, 94-09-7; potassium acetate, 127-08-2; 1-pyrrolidino-1-cyclohexene, 1125-99-1; ethylene glycol, 107-21-1; benzyl mercaptan, 100-53-8; *N*-methyl-*p*-nitroaniline, 100-15-2; *p*-nitroaniline, 100-01-6; guanidine, 113-00-8.

References and Notes

(1) For the previous paper in this series, see E. C. Taylor and P. A. Jacobi, *J. Am. Chem. Soc.*, submitted for publication.
(2) This work was supported by a grant (CA-12876) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.
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(13) All compounds were fully characterized by ir and NMR spectroscopy, and were shown to be homogeneous (except where otherwise noted) by TLC. Ir spectra were recorded on a Perkin-Elmer Model 237-B spectrophotometer, and NMR spectra on a Varian A-60A spectrophotometer using TMS as an internal standard in $DCCl_3$ and DMSO-d_6, and as an external standard in D_2O and TFA. All melting points are uncorrected and were determined on a Thomas-Hoover capillary apparatus.
(14) Prepared by cyclization of **5k** with guanidine in methanol in the presence of sodium methoxide; the methyl ester is formed by transesterification.
(15) Prepared by cyclization of **5k** with guanidine in ethanol in the presence of sodium ethoxide.
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Thallium in Organic Synthesis. XL. Preparation and Synthetic Utility of Diarylthallium Trifluoroacetates[1,2]

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Two methods are described for the preparation of diarylthallium trifluoroacetates: (1) the "disproportionation" of arylthallium ditrifluoroacetates by heating in acetone, and (2) the reaction of arylmagnesium bromides with thallium(III) trifluoroacetate (TTFA) to give diarylthallium bromides, conversion of the latter to diarylthallium hydroxides, and, finally, treatment with trifluoroacetic acid (TFA). Although it has been widely believed that diarylthallium(III) compounds are chemically inert, it is shown that these diarylthallium trifluoroacetates are useful, versatile intermediates for the synthesis of unsymmetrical biphenyls (by irradiation in benzene), aryl iodides (by heating with iodine in chloroform), and phenols (by reaction with lead tetraacetate–triphenylphosphine in TFA solution, followed by alkaline hydrolysis of the resulting aryl trifluoroacetates).

Diarylthallium(III) derivatives have been known for over 50 years, but the reported chemistry of these compounds is prosaic, perhaps as a result of a widespread belief that they are "amongst the most stable and least reactive organometallic compounds known".[3] We report that this reputed lack of reactivity is a myth, and that diarylthallium trifluoroacetates are useful and versatile intermediates for the preparation of unsymmetrical biphenyls, aryl iodides, and phenols.

Preparation of Diarylthallium Trifluoroacetates. Literature methods for the preparation of diarylthallium compounds involve the reaction of thallium(III) halides with arylboronic acids, with diarylmercury compounds, or with Grignard reagents.[4a-c] Two new methods for their preparation are described below.

Thallation of aromatic substrates with thallium(III) trifluoroacetate (TTFA) is now a well-known process[5a,b] in which the position taken by thallium with respect to substituents already present can often be controlled by a combination of kinetic, thermodynamic, and chelation factors.[6] We have reported previously on the "disproportionation" of the resulting arylthallium ditrifluoroacetates to give diarylthallium trifluoroacetates upon treatment with triethyl phosphite.[7] It was found in the course of this work that attempted recrystallization of the arylthallium ditrifluoroacetates from water or from acetone resulted in partial "disproportionation". We have now found that heating arylthallium ditrifluoroacetates in acetone for 1 hr, followed by addition of water, results in smooth conversion to diarylthallium trifluoroacetates in good to excellent yield (method A). This simple procedure thus supplements the triethyl phosphite "disproportionation" method utilized previously.[7] Representative compounds prepared by method A are listed, along with yield and melting point, in Table I.

Table I
Representative Diarylthallium Trifluoroacetates by Method A[a]

$$ArTl(OCOCF_3)_2 \xrightarrow[\text{water}]{\text{acetone}} Ar_2TlOCOF_3$$

$Ar_2TlOCOF_3$ registry no.	Ar	Yield, %	Mp, °C[b]
27675-18-9	4-$CH_3C_6H_4$	99	289–291
27675-21-4	3,4-$(CH_3)_2C_6H_3$	93	274–276
27675-19-0	2,4-$(CH_3)_2C_6H_3$	93	278–280
27675-20-3	2,5-$(CH_3)_2C_6H_3$	64	243–245
27675-22-5	2,4,6-$(CH_3)_3C_6H_2$	99	214–216
55073-42-2	2-Dibenzylfuranyl	47	286–287

[a] Melting points and elemental analyses were determined after one recrystallization of the diarylthallium trifluoroacetate from ethyl acetate. Satisfactory C, H analyses were reported for each compound listed in the table. [b] All of the compounds melted with decomposition.

Table II
Representative Diarylthallium Trifluoroacetates by Method B[a]

$$ArBr \xrightarrow[Et_2O]{Mg^0} ArMgBr \xrightarrow[Et_2O]{TTFA} Ar_2TlBr \xrightarrow[EtOH\text{-}H_2O]{KOH} Ar_2TlOH \xrightarrow[H_2O]{TFA} Ar_2TlOCOCF_3$$

$Ar_2TlOCOCF_3$ registry no.	Ar	Yield, %[b]	Mp, °C[c]	Molecular formula	Analysis, %, Found (calcd) C	H
55073-43-3	2-$CH_3C_6H_4$	71	244–246	$C_{16}H_{14}F_3O_2Tl$	38.57 (38.46)	2.76 (2.82)
55073-44-4	3-$CH_3C_6H_4$	50	247–249	$C_{16}H_{14}F_3O_2Tl$	38.77 (38.46)	2.83 (2.82)
55073-45-5	3-ClC_6H_4	70	267–270	$C_{14}H_8Cl_2F_3O_2Tl$	31.62 (31.11)	1.65 (1.49)
55073-46-6	3-BrC_6H_4	68	256–259	$C_{14}H_8Br_2F_3O_2Tl$	28.02 (26.72)	1.68 (1.28)
55073-47-7	3-$CH_3OC_6H_4$	43	250–251	$C_{16}H_{14}F_3O_4Tl$	34.53 (36.15)	2.69 (2.65)
55073-48-8	1-Naphthyl[d]	44[e]	247–248	$C_{22}H_{17}O_2Tl$	50.84 (51.03)	3.27 (3.31)
55073-49-9	2-Naphthyl[d]	55[f]	272–273	$C_{22}H_{17}O_2Tl$	50.58 (51.03)	3.47 (3.31)

[a] Melting points and elemental analyses were determined after one recrystallization or trituration of the diarylthallium trifluoroacetate or acetate with ethyl acetate. [b] Based on thallium(III) trifluoroacetate (TTFA). [c] All of the compounds melted with decomposition. [d] Since treatment of the diarylthallium hydroxide with aqueous TFA resulted in extensive decomposition, the corresponding acetate was prepared with HOAc. [e] Based on TTFA. The yield is 68% based on di(1-naphthyl)thallium hydroxide. [f] Based on TTFA.

A characteristic feature of the "disproportionation" procedure described above is its regiospecificity; no detectable scrambling of the aryl–thallium bond occurs, and the orientation of thallium with respect to ring substituents remains the same in the diarylthallium trifluoroacetates as it was in the starting arylthallium ditrifluoroacetates. A complementary route to diarylthallium trifluoroacetates which would provide access to derivatives with different orientations of substituents would be most useful. We have found such a procedure in the reaction of arylmagnesium bromides with TTFA. The initial product of the reaction, a diarylthallium bromide, was converted to the diarylthallium hydroxide by treatment with aqueous ethanolic potassium hydroxide, and the corresponding trifluoroacetate derivatives were then prepared by reaction with aqueous trifluoroacetic acid (TFA).[8] Representative compounds prepared by method B are listed in Table II, which also summarizes yield, melting point, and microanalytical data.

That methods A and B indeed yield the same compounds was confirmed by the synthesis of di-4-tolylthallium trifluoroacetate by both routes; the products were identical in all respects.

Synthesis of Unsymmetrical Biphenyls. We have reported previously that photolysis of arylthallium ditrifluoroacetates in benzene suspension results in replacement of the thallium substituent by a phenyl group (i.e., phenylation) to give unsymmetrical biphenyls in excellent yield.[9] We have now found that the same conversion can be effected in comparable yields utilizing diarylthallium trifluoroacetates as the organometallic precursors. Unsymmetrical biphenyls prepared by this photolysis route are listed in Table III.

We suggest that the initial photolytic reaction is homolysis of a C–Tl bond to give an aryl radical and the unstable thallium(II) species $ArTl(II)OCOCF_3$. The former serves as a precursor for 1 equiv of biaryl, while the latter disproportionates to give a second aryl radical and thallium(I) trifluoroacetate. This reaction sequence is thus analogous to that postulated previously for the photolysis of arylthallium ditrifluoroacetates in benzene to give unsymmetrical biphenyls.[9] The observed formation of small amounts (<5%) of biphenyl as well as symmetrical biaryls is in accord with the proposed mechanism.

Table III
Conversion of Diarylthallium Trifluoroacetates to Biphenyls

$$Ar_2TlOCOCF_3 \xrightarrow[C_6H_6]{h\nu} 2\ Ar\text{—}C_6H_5 + TlOCOCF_3$$

Ar	Yield, %[a]
C_6H_5[6,7]	95
4-$CH_3C_6H_4$	61[b]
2-$CH_3C_6H_4$	46[c]
3-BrC_6H_4	41[d]
3-ClC_6H_4	53[e]
3-$CH_3OC_6H_4$	67[f]
3,4-$(CH_3)_2C_6H_3$	65[g]

[a] Yields were determined by GLC analysis of the crude photolysis product. [b] Product contained 3% 4,4′-dimethylbiphenyl, 2% biphenyl, and <2% toluene. [c] Product contained 8% 2,2′-dimethylbiphenyl. [d] Product contained 9% biphenyl and 39% bromobenzene. [e] Product contained 4% biphenyl, 7% chlorobenzene, and 18% of an unidentified biaryl. [f] Product contained 2% biphenyl and 3% anisole. [g] Product contained 3% 3,3′,4,4′-tetramethylbiphenyl, 2% biphenyl, 3% o-xylene, and 14% of an unidentified biaryl.

This synthesis of unsymmetrical biphenyls complements and extends the related procedure which utilizes arylthallium ditrifluoroacetates,[9] since the substituent pattern possible with diarylthallium trifluoroacetates prepared by method B may be different from that accessible by method A (which must be identical with the pattern present in the arylthallium ditrifluoroacetate precursors).

Synthesis of Aryl Iodides. We have described previously a remarkably simple synthesis of aryl iodides which involves treatment of arylthallium ditrifluoroacetates with aqueous potassium iodide at room temperature. Reaction is complete in a matter of seconds, and the aryl iodide is formed in quantitative yield.[5b,10] We now report that diarylthallium trifluoroacetates, although stable to aqueous potassium iodide, may be converted to aryl iodides by reflux-

Table IV
Conversion of Diarylthallium Trifluoroacetates to Aryl Iodides

$$Ar_2TlOCOCF_3 \xrightarrow[HCCl_3]{I_2} 2\ ArI + TlOCOCF_3$$

Ar	Reaction time, hr[a]	Product	Yield, %[b]
C_6H_5[6,7]	16	Iodobenzene	80
2-$CH_3C_6H_4$	16	2-Iodotoluene	89
3-$CH_3C_6H_4$	16	3-Iodotoluene	74
4-$CH_3C_6H_4$	15	4-Iodotoluene	86
3,4-$(CH_3)_2C_6H_3$	19	4-Iodo-*o*-xylene	88
3-ClC_6H_4	18	3-Iodochlorobenzene	94
1-$C_{10}H_7$[c]	12	1-Iodonaphthalene	90
2-$C_{10}H_7$[c]	16	2-Iodonaphthalene	90
2-$C_{12}H_7O$	16	2-Iododibenzofuran	93

[a] All iodinations were done at the reflux temperature of chloroform (61°). [b] Yields were determined by GLC analysis of the crude organic products. [c] The corresponding acetate was used.

ing a solution in chloroform with an excess of molecular iodine. Representative aryl iodides prepared in this manner are listed in Table IV, along with appropriate experimental data.

The overall stoichiometry for the above conversion is given in eq 1. We suggest that the initial reaction is formation of an arylthallium trifluoroacetate iodide (eq 2) which spontaneously decomposes to give a second mole of aryl iodide and thallium(I) trifluoroacetate (eq 3). Support for

$$Ar_2TlOCOCF_3 + I_2 \longrightarrow 2ArI + TlOCOCF_3 \quad (1)$$

$$Ar_2TlOCOCF_3 + I_2 \longrightarrow ArI + ArTl(OCOCF_3)I \quad (2)$$

$$ArTl(OCOCF_3)I \longrightarrow ArI + TlOCOCF_3 \quad (3)$$

this interpretation comes from the observation that treatment of di-4-tolylthallium trifluoroacetate with 1 equiv of iodine resulted in the formation of 2 equiv of 4-tolyl iodide (91%) and thallium(I) trifluoroacetate (88% recovery); no thallium(I) iodide could be detected. Independent support for the spontaneous disproportionation of arylthallium trifluoroacetate iodides (eq 3) comes from the previously reported observation[5b] that treatment of phenylthallium ditrifluoroacetate with 1 equiv of potassium iodide resulted in instantaneous formation of iodobenzene in quantitative yield, with no concomitant formation of thallium(I) iodide.

The conversion of diarylthallium trifluoroacetates to aryl iodides by treatment with molecular iodine is thus analogous to the well-known conversion of diarylmercury derivatives with iodine to a mixture of the aryl iodide and an arylmercury iodide,[11] but it is much more effective as a synthetic tool because of the spontaneous decomposition to product of the arylthallium trifluoroacetate iodide intermediate (corresponding to the stable arylmercury iodide). The present route constitutes a practical synthetic procedure for the ultimate conversion of aryl Grignard reagents to aryl iodides.

Synthesis of Phenols. We also report that phenols may be prepared from diarylthallium trifluoroacetates in the same manner as previously reported for the conversion of arylthallium ditrifluoroacetates to phenols,[12] i.e., by treatment with lead tetraacetate in TFA followed by addition of triphenylphosphine. The resulting aryl trifluoroacetates are hydrolyzed to the phenols with aqueous base. Representative conversions and experimental details are given in Table V.

As was observed for the analogous phenol synthesis from arylthallium ditrifluoroacetates,[13] a bright yellow solid separated from the TFA reaction mixture after addition of lead tetraacetate, but before addition of triphenylphosphine. Examination of this yellow solid showed it to be identical with the intermediate complex prepared from arylthallium ditrifluoroacetates and lead tetraacetate in TFA solution.[13] It thus appears that the reaction of lead tetra(trifluoroacetate) (formed in situ from lead tetraacetate and TFA[14a]) with diarylthallium trifluoroacetates proceeds as shown in Scheme I. The yellow intermediate (presumed

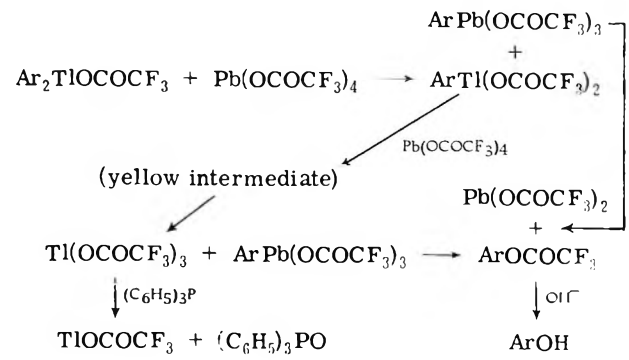
Table V
Conversion of Diarylthallium Trifluoroacetates to Phenols

$$Ar_2TlOCOCF_3 \xrightarrow[2.\ Ph_3P]{1.\ 2Pb(IV)} 2ArOCOCF_3 \xrightarrow{OH^-} 2ArOH$$

Ar	Reaction conditions[a] Temp, °C	Time, hr	Phenol	Yield, %[b]
C_6H_5[6,7]	41	1.0	Phenol	39
4-$CH_3C_6H_4$	22	0.1	*p*-Cresol	58
3-$CH_3C_6H_4$	22	1.0	*m*-Cresol	50
2-$CH_3C_6H_5$	22	1.0	*o*-Cresol	55
3,4-$(CH_3)_2C_6H_3$	22	0.5	*o*-4-Xylenol[c]	69
2,5-$(CH_3)_2C_6H_3$	22	0.5	*p*-2-Xylenol	67
2,4,6-$(CH_3)_3C_6H_2$	22	0.5	2,4,6-Mesitol	21
3-ClC_6H_4	73	0.5	3-Chlorophenol	55
3-BrC_6H_4	73	1.2	3-Bromophenol	44
3-$CH_3OC_6H_4$[d]	22	0.4	3-Methoxyphenol	29

[a] These conditions refer to the period after the Pb(IV) addition and before the Ph_3P addition. [b] Yields were determined by GLC analysis of the crude product. [c] Product contained 1% o-3-xylenol. [d] Ph_3P was omitted.

Scheme I



to be a thallium–lead complex[13]) is formed by reaction of the arylthallium ditrifluoroacetate with the second equivalent of lead tetra(trifluoroacetate). Aryllead tri(trifluoroacetates) are known to decompose spontaneously to lead ditrifluoroacetates and aryl trifluoroacetates.[14a,b] In further support of this proposed reaction course, we have observed that treatment of di-4-tolylthallium acetate with lead tetraacetate in glacial acetic acid gave 4-tolylthallium diacetate and 4-tolyllead triacetate.

The reason for the effectiveness of triphenylphosphine addition remains uncertain, although oxidation to triphenylphosphine oxide, presumably by TTFA released in the metal–metal exchange reaction between the arylthallium ditrifluoroacetate and lead tetra(trifluoroacetate), has been confirmed.[13]

It should be mentioned that while it was not directly determined whether complete metathesis of lead tetraacetate to lead tetra(trifluoroacetate) in TFA solution occurred in our experiments,[14a] the following evidence suggests that

this metathesis process was probably complete. When a solution of lead tetraacetate in TFA was added to a TFA solution of phenylthallium ditrifluoroacetate,[7] phenyl trifluoroacetate was the only ester detected; no phenyl acetate was formed.[15] Furthermore, dissolution of 4-tolyllead triacetate in TFA results only in the formation of 4-tolyl trifluoroacetate.[14a,b,15]

This phenol synthesis from diarylthallium trifluoroacetates complements the corresponding synthesis from arylthallium ditrifluoroacetates. Yields are only moderate, but the procedure represents a viable conversion of aryl Grignard reagents to phenols. There is clearly no advantage, however, in employing the present method for phenol synthesis from arylthallium ditrifluoroacetate precursors utilizing method A (initial "disproportionation"), since the latter organothallium compounds can be converted directly to phenols.[12]

It thus appears that diarylthallium trifluoroacetates (and presumably other diarylthallium derivatives as well) are not exceptionally stable substances, and may be utilized under appropriate reaction conditions as intermediates in a variety of useful aromatic substitution reactions.

Experimental Section[16]

Synthesis of Diarylthallium Trifluoroacetates. Method A. By Disproportionation of Arylthallium Ditrifluoroacetates. The general procedure is illustrated by the disproportionation of 3,4-dimethylphenylthallium ditrifluoroacetate to di(3,4-dimethylphenyl)thallium trifluoroacetate. A solution of 8.00 g (0.015 mol) of 3,4-dimethylphenylthallium ditrifluoroacetate in 15 ml of acetone was heated under reflux for 30 min and cooled, and 40 ml of water was added. The white crystalline solid which separated was collected by filtration, washed with water, and dried to give 3.66 g (93%) of white silky crystals, mp 269–275° dec. The analytical sample, mp 274–276° dec, was recrystallized from ethyl acetate.

Data for other diarylthallium trifluoroacetates obtained in the same manner from arylthallium ditrifluoroacetates are summarized in Table I.

Method B. By Reaction of Aryl Grignard Reagents with Thallium(III) Trifluoroacetate (TTFA). The general procedure is illustrated by the conversion of 2-bromotoluene to di-2-tolylthallium trifluoroacetate. Thus, 17.10 g (0.10 mol) of 2-bromotoluene was converted to the corresponding Grignard reagent in the normal fashion. To a solution of this Grignard reagent in diethyl ether, under nitrogen, was added by means of a dropping funnel a solution of 10.86 g (0.02 mol) of dry TTFA in 30 ml of anhydrous ether. The rate of addition was adjusted so that the exothermic reaction was maintained under control. The resulting stirred heterogeneous reaction mixture was heated gently under reflux for 15 min and then cooled to 0°. Excess Grignard reagent was destroyed by addition of 50 ml of water, and the resulting precipitate was collected by filtration, suspended in 50 ml of pyridine, and heated under reflux for 2 hr. The suspended solids were removed by filtration and the filtrate was evaporated under reduced pressure to give a residual solid (di-2-tolylthallium bromide) to which was added 20 ml of 3 *M* potassium hydroxide and 20 ml of ethanol. The resulting suspension was heated under reflux for 18 hr, and the white solid was collected by filtration, washed with distilled water, and dried in vacuo for 2 hr at 50° to give 6.64 g (82%) of di-2-tolylthallium hydroxide.

A suspension of 4.00 g of the above material in 40 ml of TFA and 40 ml of water was stirred for 15 min, an additional 80 ml of water was added, and the resulting solid was collected by filtration to give 4.33 g (87%) of di-2-tolylthallium trifluoroacetate as a white, microcrystalline solid, mp 244–246° dec. The microanalytical sample was prepared by recrystallization from ethyl acetate (see Table II). Representative data for other diarylthallium trifluoroacetates prepared by method B are summarized in Table II.

Di(1-naphthyl)thallium Acetate. Di(1-naphthyl)thallium hydroxide was prepared from 1-bromonaphthalene by the general procedure described above. A solution of 4.90 g (0.01 mol) of di(1-naphthyl)thallium hydroxide was dissolved in 25 ml of pyridine and 25 ml of acetic anhydride, and the resulting solution was heated on a steam bath for 20 min and then cooled to approximately 2°. Addition of 50 ml of water resulted in precipitation of a solid which was collected by filtration, washed well with water, and dried to give 3.62 g (68%) of di(1-naphthyl)thallium acetate. The analytical sample was prepared by trituration with boiling ethyl acetate, and melted at 247–248° dec (see Table II).

Preparation of Unsymmetrical Biphenyls. The general procedure for the photochemical synthesis of unsymmetrical biphenyls is illustrated by the conversion of di-4-tolylthallium trifluoroacetate to 4-methylbiphenyl. Thus, a suspension of 1.25 g (0.0025 mol) of di-4-tolylthallium trifluoroacetate in 300 ml of benzene was placed in a 500-ml quartz tube fitted with a reflux condenser. The stirred reaction suspension was purged with nitrogen for 15 min and then irradiated, with continuous stirring, for a period of 18 hr with 300-nm light in a Rayonet photochemical reactor. The benzene solvent was then removed by distillation under reduced pressure, and the residue was taken up in 100 ml of *n*-hexane–ether (1:1). The latter solution was extracted with 30 ml of water, the aqueous layer was extracted again with 25 ml of *n*-hexane–ether (1:1), and the organic extracts were combined and passed through 10 g (200 mesh, <0.08 mm) of silica gel. The combined eluates were dried ($MgSO_4$) and evaporated under reduced pressure to give 0.55 g of crude product. GLC analysis of this crude product showed that it contained 0.50 g of 4-methylbiphenyl (61%), as well as 4,4′-dimethylbiphenyl (3%), biphenyl (2%), toluene (<2%), and 2-methylbiphenyl (2%).

Other unsymmetrical biphenyls prepared in analogous fashion are listed in Table III. All compounds were identified by ir spectral comparison or by a comparison of GLC retention times with those of authentic samples.

Synthesis of Aryl Iodides. The general procedure for the synthesis of aryl iodides is illustrated by the conversion of di-2-tolylthallium trifluoroacetate to 2-iodotoluene. Thus, a stirred mixture of 0.50 g (0.001 mol) of di-2-tolylthallium trifluoroacetate and 0.51 g (0.002 mol) of iodine in 20 ml of chloroform was heated under reflux, protected from light, for 16 hr. To the cooled reaction mixture was added a solution of 2.00 g (0.01 mol) of $Na_2S_2O_5$ in 25 ml of water, and the two-phase solution was vigorously stirred until the purple color of iodine had been completely discharged. The heavy yellow precipitate of thallium(I) iodide was removed by filtration through Celite, the chloroform layer in the filtrate was separated, and the aqueous layer was extracted with an additional 25-ml portion of chloroform. The combined chloroform extracts were washed with water, dried ($MgSO_4$), and evaporated to give 0.39 g (89%) of GLC-pure 2-iodotoluene.

Representative data for the conversion of other diarylthallium trifluoroacetates to aryl iodides are given in Table IV.

Reaction of Di-4-tolylthallium Trifluoroacetate with 1 Equiv of Iodine. A mixture of 0.50 g (0.001 mol) of di-4-tolylthallium trifluoroacetate and 0.25 g (0.001 mol) of iodine in 20 ml of chloroform was heated under reflux for 18 hr, by which time the purple iodine color had been completely discharged. The cooled reaction mixture was concentrated to half volume under reduced pressure, cooled, and then filtered to give 0.27 g of thallium(I) trifluoroacetate. Addition of petroleum ether to the chloroform filtrate and cooling yielded an additional 0.01 g of thallium(I) trifluoroacetate, combined yield 0.028 g (88%(= MP [[5–[[7°/ Evaporation of the filtrates then gave 0.40 g (91%) of 4-iodotoluene, identical with an authentic sample.

Synthesis of Phenols. The general procedure is illustrated by the conversion of di-2-tolylthallium trifluoroacetate to o-cresol. Thus, to a cooled (2°), stirred suspension of 2.50 g (0.005 mol) of di-2-tolylthallium trifluoroacetate in 10 ml of TFA was added by means of a dropping funnel a solution of 4.61 g (0.01 mol) of lead tetraacetate in 10 ml of TFA. After addition was complete, the reaction mixture was allowed to warm to room temperature, stirred for an additional 60 min, and cooled again to 2°, and a solution of 2.62 g (0.01 mol) of triphenylphosphine in 10 ml of TFA was added rapidly. Excess TFA was then removed under reduced pressure, 25 ml of 6 *N* hydrochloric acid was added, and lead(II) and thallium(I) chlorides were removed by filtration. The filtrate was extracted with two 25-ml portions of methylene chloride, the extracts were combined, and 50 ml of 2 *N* sodium hydroxide was added. The two-phase solution was stirred for 30 min at room temperature, the methylene chloride layer was separated and extracted with an additional 25-ml portion of 2 *N* sodium hydroxide, and the combined aqueous alkaline layers were acidified with hydrochloric acid. The acidic aqueous solution was then extracted with three 25-ml portions of methylene chloride, the combined extracts were washed with 25 ml of saturated sodium bicarbonate solution to remove residual TFA, the basic washings were extracted in turn with 25 ml of methylene chloride, and the combined organic ex-

tracts were washed with water, dried ($MgSO_4$), and evaporated to give 0.59 (55%) of GLC-pure *o*-cresol, identical with an authentic sample.

Representative experimental data for the synthesis of other phenols from diarylthallium trifluoroacetates are given in Table V.

Reaction of Di-4-tolylthallium Acetate with Lead Tetraacetate. To a stirred suspension of 2.00 g (0.004 mol) of di-4-tolylthallium trifluoroacetate in 15 ml of aqueous ethanol (1:1) was added 0.4 g (0.01 mol) of sodium hydroxide. The heterogeneous mixture was stirred for 30 min at room temperature, and the precipitated white solid was collected by filtration, washed well with water, and dried to give 1.61 g (>99%) of di-4-tolylthallium hydroxide. This material was dissolved in 10 ml of glacial acetic acid and the solution was stirred for 30 min at room temperature. Removal of the acetic acid under reduced pressure then gave 1.35 g (76%) of di-4-tolylthallium acetate as a colorless, crystalline solid, mp 264–265° dec.

Anal. Calcd for $C_{16}H_{17}O_2Tl \cdot 0.5\ H_2O$: C, 42.26; H, 3.99. Found: C, 42.54; H, 3.95.

A suspension of 1.25 g (0.0028 mol) of di-4-tolylthallium acetate hemihydrate (prepared as described above) and 1.15 g (0.0025 mol) of lead tetraacetate in 20 ml of glacial acetic acid was stirred for 18 hr at room temperature. The initially opaque mixture became clear after ~45 min. Excess acetic acid was removed by evaporation under reduced pressure, the residue was stirred with 30 ml of benzene, and the suspended colorless solid was collected by filtration and dried, yield 1.14 g (98%), mp 223–225° dec. The ir spectrum of this compound was identical with that of authentic 4-tolylthallium diacetate (vide infra).

Addition of petroleum ether (bp 30–60°) to the filtrate and cooling resulted in the separation of 0.46 g (38%) of 4-tolyllead triacetate monohydrate, mp 98–101° dec (lit.[17] mp 86–88°).

Anal. Calcd for $C_{13}H_{16}O_6Pb \cdot H_2O$: C, 31.64; H, 3.68. Found: C, 32.04; H, 3.96.

4-Tolylthallium Diacetate. To a solution of 5.21 g of 4-tolylthallium ditrifluoroacetate in 20 ml of acetonitrile was added 10 ml of 5 *M* sodium hydroxide, and the yellow suspension which formed immediately was stirred at room temperature for 5 min. The yellow solid (4-tolylthallium oxide) was then collected by filtration, washed thoroughly with water, and dried (3.11 g, >99%). A suspension of 0.80 g of 4-tolylthallium oxide in 10 ml of chloroform containing 0.45 g of glacial acetic acid was stirred for 1 hr at room temperature, the resulting solution was evaporated to dryness under reduced pressure, and the residual white solid (1.01 g, 95%) was recrystallized from 1,2-dichloroethane, mp 222–223° dec.

Anal. Calcd for $C_{11}H_{13}O_4Tl$: C, 31.94; H, 3.17. Found: C, 32.18; H, 3.21.

Behavior of 4-Tolyl Acetate in Trifluoroacetic Acid. A solution of 0.15 g of 4-tolyl acetate in 20 ml of TFA was stirred at room temperature for 20 min and then evaporated under reduced pressure. The residual oil was partitioned between 10 ml of methylene chloride and 10 ml of 6 *N* HCl by stirring for 10 min. After the methylene chloride layer was separated, the aqueous acid layer was extracted with 3 × 40 ml of methylene chloride, and the extracts were combined with the methylene chloride layer above and washed with saturated sodium bicarbonate solution, then with water, dried ($MgSO_4$), and evaporated under reduced pressure. Mass spectral analysis of the residual oil showed *only* the presence of 4-tolyl acetate; no evidence for 4-tolyl trifluoroacetate could be found. In addition, the NMR spectrum of the residual oil showed two methyl group resonances (δ 2.23 and 2.32) of equal intensity.

Conversion of 4-Tolyllead Triacetate to 4-Tolyl Trifluoroacetate in TFA. A solution of 0.24 g of 4-tolyllead triacetate monohydrate in 10 ml of TFA was stirred for 20 min at room temperature and then evaporated under reduced pressure. The residual oil (which possessed a strong phenolic odor) was stirred vigorously with 5 ml of dichloromethane and 5 ml of 6 *N* HCl, the precipitated lead dichloride was separated by filtration, the aqueous layer was extracted with three 20-ml portions of dichloromethane, and the combined dichloromethane extracts were washed with saturated aqueous sodium bicarbonate and then with water and dried ($MgSO_4$). Evaporation then gave 0.07 g (70%) of 4-tolyl trifluoroacetate, identified by comparison (GLC, NMR, ir) with authentic material.

Registry No.—4-Tolylthallium ditrifluoroacetate, 23586-55-2; 3,4-dimethylphenylthallium ditrifluoroacetate, 23586-56-3; 2,4-dimethylphenylthallium ditrifluoroacetate, 34202-98-7; 2,5-dimethylphenylthallium ditrifluoroacetate, 34202-99-8; 2,4,6-trimethylphenylthallium ditrifluoroacetate, 23586-57-4; 2-dibenzofuranylthallium ditrifluoroacetate, 55073-50-2; 2-bromotoluene, 95-46-5; 3-bromotoluene, 591-17-3; 3-bromochlorobenzene, 108-37-2; 1,3-dibromobenzene, 108-36-1; 3-bromoanisole, 2398-37-0; 1-bromonaphthalene, 90-11-9; 2-bromonaphthalene, 580-13-2; di-2-tolylthallium bromide, 55073-51-3; di-3-tolylthallium bromide, 55073-52-4; di(3-chlorophenyl)thallium bromide, 55073-53-5; di(3-bromophenyl)thallium bromide, 55073-54-6; di(3-methoxyphenyl)thallium bromide, 55073-55-7; di(1-naphthyl)thallium bromide, 55073-56-8; di(2-naphthyl)thallium bromide, 55073-57-9; di-2-tolylthallium hydroxide, 55073-58-0; di-3-tolylthallium hydroxide, 55073-59-1; di(3-chlorophenyl)thallium hydroxide, 55073-60-4; di(3-bromophenyl)thallium hydroxide, 55073-61-5; di(3-methoxyphenyl)thallium hydroxide, 55073-62-6; di(1-naphthyl)thallium hydroxide, 55073-63-7; di(2-naphthyl)thallium hydroxide, 55073-64-8; di-4-tolylthallium hydroxide, 55073-65-9; di-4-tolylthallium acetate, 50795-46-5; 4-tolylthallium diacetate, 55073-66-0; 4-tolyllead triacetate, 3076-56-0.

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Addition of *p*-Toluenesulfonyl Isocyanate to Imino Ethers. Isolation of a Stable 1,4-Dipolar Intermediate

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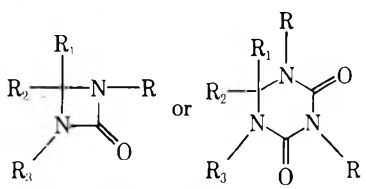
The reaction between *p*-toluenesulfonyl isocyanate and methyl *N*-*tert*-butylformimidate (**1**) forms a 2:1 cycloadduct (**2**). The azetines **3–5** form analogous 2:1 cycloadducts (**6–8**) under identical conditions. With an excess of **3**, the 1,4-dipolar intermediate **10** can be isolated. It is characterized by conversion to **6** with *p*-toluenesulfonyl isocyanate and by hydrolysis to the urea **11**.

In connection with studies on cycloaddition reactions of imino ethers,[1] we have investigated the addition reactions of isocyanates. The reactions with 2-alkoxy-1-azetines are of special interest because they have permitted the isolation of a stable 1,4-dipolar intermediate.

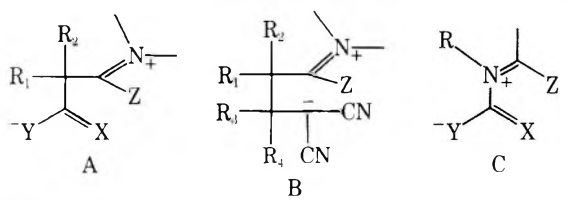
Isocyanates have been found to add to carbon–nitrogen double bonds to give 1:1 1,3-diazetidinone adducts in many

$$R_1R_2C{=}NR_3 + RN{=}C{=}O \longrightarrow$$



cases.[2–12] When there are abstractable hydrogens α to the C=N bond, 1:1 ene-type adducts are often formed.[13–21] There have also been many cases in which 2:1 adducts have been formed by addition of a second molecule of isocyanate to a hypothetical 1,4-dipolar intermediate.[3,4b,22–34] In the case of unhindered imines, 1:2 adducts incorporating two molecules of imine are sometimes found.[12,25,35–37]

The intermediacy of 1,4-dipolar ions has been suggested[2d] to account for these reactions. Such intermediates appear to be trapped as 2:1 adducts, 1:2 adducts, and, in a few cases, 1:1:1 adducts with a third component.[22,25,33,34,38] Gompper has isolated and characterized a number of stable 1,4 (or 1,5) unconjugated dipolar ions of type A from reactions of ketene *N,S*-acetals and enamines with heterocumulenes,[29–42] or of type B with electron-deficient ole-

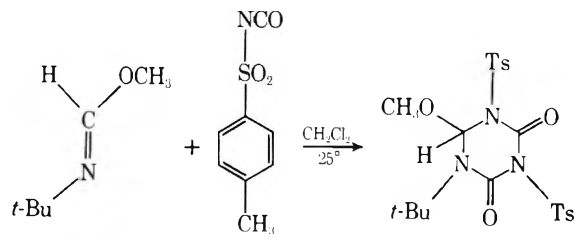


A B C

fins.[43] The cross-conjugated dipolar ions of type C, however, have not been previously isolated and characterized,[44,45] although they appear to have been trapped in additions of ketenes to imines with added water, methanol, and sulfur dioxide.[44b,46] We report here additions of *p*-toluenesulfonyl isocyanate to 2-alkoxy-1-azetines,[47] which give an isolable and characterizable cross-conjugated 1,4-dipolar ion of type C for the first time.

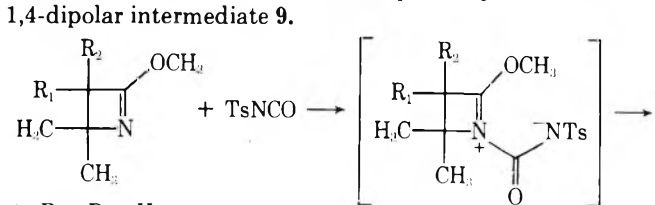
Results and Discussion

Treatment of the somewhat hindered aliphatic imino ether **1** with 2 equiv of *p*-toluenesulfonyl isocyanate results in an 86% yield of 1,3-di-*p*-toluenesulfonyl-5-*tert*-butyl-6-methoxytriazine-2,4-dione (**2**), a normal 2:1 cycloadduct. This is analogous to the reactions of other imines and isocyanates.[5–7,9,12] The 2-alkoxy-1-azetines **3–5** give similar



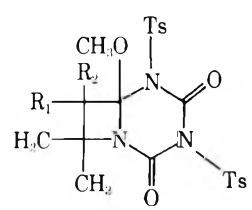
1 Ts = $-SO_2C_6H_4CH_3$ **2**

2:1 cycloadducts **6–8** in high yields on treatment with 2 equiv of *p*-toluenesulfonyl isocyanate. These crystalline adducts are well characterized by their spectral data but decompose readily on melting or standing. They are typical of 1,4-dipolar additions[2d] and are probably formed via a 1,4-dipolar intermediate **9**.



3. $R_1 = R_2 = H$
4. $R_1 = R_2 = CH_3$
5. $R_1 = H$; $R_2 = CH_3$

9



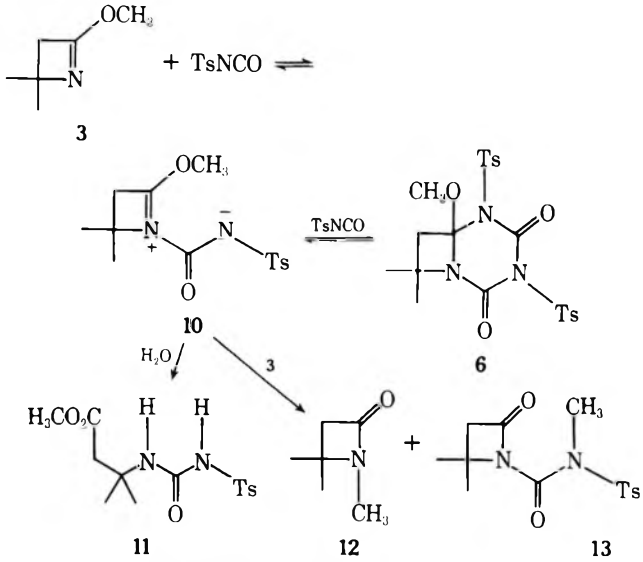
6. $R_1 = R_2 = H$
7. $R_1 = R_2 = CH_3$
8. $R_1 = H$; $R_2 = CH_3$

Upon treatment of *p*-toluenesulfonyl isocyanate with excess azetine **3** at 0°, a white solid precipitates. The white solid is an amorphous powder which decomposes on melting and is quite insoluble in organic solvents. The mass spectrum of the solid indicates only peaks from **3** and *p*-toluenesulfonyl isocyanate, to which the solid decomposes thermally. The infrared spectrum (in Nujol) shows two peaks of medium intensity at 1690 and 1645 cm^{-1}. Other 1,4-dipoles have also shown peaks in the 1600–1700-cm^{-1} range.[39–43] There were no infrared peaks in the region expected for a 1,3-diazetidinone. This white powder has been assigned the 1,4-dipolar ion structure **10** on the basis of these physical properties and the chemical interconversions that follow below.

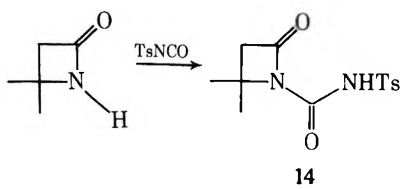
To confirm the structure of **10** and the 1,4-dipolar mechanism for the formation of **6** from **3**, *p*-toluenesulfonyl isocyanate was added to **10** and the 2:1 cycloadduct **6** isolated in 96% yield. The zwitterion **10** is moisture sensitive and readily adds water in the expected fashion. The ester urea

11 is isolated in 97% yield from addition of water to 10 or exposure of 10 to moist air, providing strong evidence for the dipolar structure 10. The azetine 3 is stable to aqueous hydrolysis under the experimental conditions and the p-toluenesulfonyl isocyanate hydrolyzes to p-toluenesulfonamide, a minor side product in these reactions.

The 2:1 adduct 6 also reacts with water to give the urea 11 and p-toluenesulfonamide. This demonstrates that 6



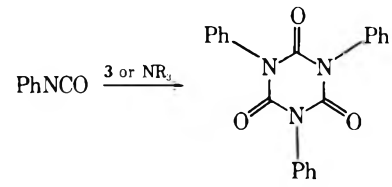
can equilibrate with the 1,4-dipolar ion 10 and isocyanate. The dipolar ion 10 decomposes on attempted dissolution in dichloromethane to a complex mixture containing 12% of 3, some p-toluenesulfonyl isocyanate, 37% of 6, 27% of 12, 12% of 13, and traces of urea 11 (8%) and p-toluenesulfonamide (~2%) from water hydrolysis. The composition of this mixture further supports the 1:1 composition assigned to 10 and clearly demonstrates that the dipolar ion 10 can readily equilibrate with imino ether 3 and isocyanate. The two amides 12 and 13 are formed under a variety of conditions in variable ratios. They appear to be formed in a Lewis acid catalyzed intermolecular alkylation mechanism.[48] The p-toluenesulfonyl isocyanate probably acts as the catalyst in these reactions via 10 as the initial alkylating agent. The structure of 13 is supported by its spectral similarities with the related urea 14 formed from addition



of p-toluenesulfonyl isocyanate to 4,4-dimethylazetidin-2-one.

In an attempt to produce a 1:2 cycloadduct composed of two molecules of azetine 3 and one of p-toluenesulfonyl isocyanate, analogous to other imines,[12,35-37] 3 was added to 10. The only products detected and isolated were the amides 12 and 13, in about a 1:1 ratio. With the low concentration of p-toluenesulfonyl isocyanate no 2:1 adduct 6 was observed, but no 1:2 adduct was seen either. Similarly, a 2:1 mixture of imino ether 3 and isocyanate give a 1:1 mixture of 12 and 13. In an attempt to prepare a 1:1:1 cycloadduct, phenyl isocyanate was added to 10, but the only products found were the 2:1 cycloadduct 6 and amide 12.

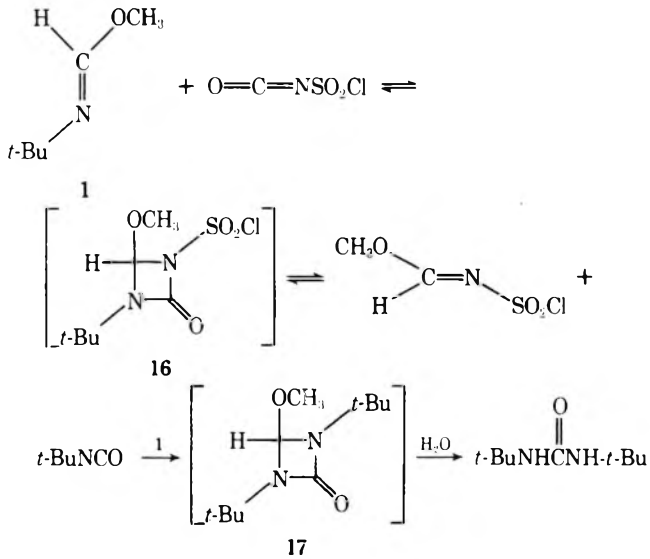
To test the generality of these reactions with p-toluenesulfonyl isocyanate, the reaction between the less reactive phenyl isocyanate and 3 was tried. It gave only a white solid precipitate within minutes at 25°. The crystalline product was determined by NMR to be the trimer of phenyl isocyanate 15[2,3] complexed with ca. two molecules of



15

acetonitrile.[49,50] No adducts with 3 could be detected. From control experiments, no trimerization of phenyl isocyanate occurs in pure acetonitrile, but upon the addition of a tertiary amine, trimerization takes place overnight at 25°. The azetine 3 is therefore acting as a catalyst[22] for the trimerization process.

Finally, the very reactive chlorosulfonyl isocyanate was added to imino ether 1. Imino ether 1 was used because it most closely resembles the anils that have been added to chlorosulfonyl isocyanate to give 2:1 cycloadducts.[28] The two reagents were mixed in dichloromethane at −70°; work-up gave only a small amount (1.4%) of a solid identified as N,N′-di-tert-butylurea by comparison of spectral data with the literature.[51,52] The product can be rationalized as originating from a disproportionation sequence proceeding through a reactive 1:1 cycloadduct 16. Analogous disproportionations have been shown to occur in other systems.[2,10] Subsequent reaction with 1 and hydrolysis could give the urea. The cycloadduct 17 is postulated to give rise to the urea. The aliphatic tert-butyl isocyanate adds to 1, since it does not form dimers or trimers in base like phenyl isocyanate.



Experimental Section

All boiling points and melting points are uncorrected. Ir spectra were obtained in solution with a matched reference cell on a Perkin-Elmer 337 grating infrared spectrophotometer. NMR spectra were obtained on a 60-MHz Varian Associates T-60 spectrometer. Mass spectra were obtained on a MS-902 spectrometer.

Materials. The phenyl isocyanate and chlorosulfonyl isocyanate (CSI) were purchased from Aldrich Chemical Co. The p-toluenesulfonyl isocyanate was purchased from Eastman Chemical Co. and distilled before using. The imino ethers were made by alkylation of the corresponding amide or lactam with trimethyloxonium fluoroborate.[1,47]

Reaction of p-Toluenesulfonyl Isocyanate with 1. To a mixture of 990 mg (5.02 mmol) of p-toluenesulfonyl isocyanate, 4 ml of dichloromethane, and 50 mg of potassium carbonate at −20° was added a solution of 260 mg (2.26 mmol) of 1 in 1 ml of dichloromethane. The reaction was allowed to come to room temperature over a 2-hr period. After filtering off the potassium carbonate, the

organic solution was washed with aqueous sodium bicarbonate and dried over anhydrous potassium carbonate. Evaporation of the solvent in vacuo resulted in a solid. Recrystallization in carbon tetrachloride gave 1.07 g (86%) of 1,3-di-*p*-toluenesulfonyl-5-*tert*-butyl-6-methoxy-1,3,5-triazine-2,4-dione (**2**): mp 135–137° dec; ir (CH_2Cl_2) 2920, 1760 (sh), 1730 (s), 1605, 1380, 1340 cm^{-1}; NMR (CH_2Cl_2) δ 1.48 (s, 9 H), 2.45 (s, 6 H), 3.44 (s, 3 H), 6.51 (s, 1 H), 7.40 (m, 4 H), 8.10 (m, 4 H). The mass spectrum showed only peaks from decomposition to *p*-toluenesulfonyl isocyanate and **1** because **2** is thermally unstable and decomposes before vaporization.

Reaction of *p*-Toluenesulfonyl Isocyanate with 4. Following the procedure for **2**, treatment of 64 mg (0.45 mmol) of **4** with 172 mg (0.87 mmol) of *p*-toluenesulfonyl isocyanate gives a near quantitative yield of a 2:1 adduct by NMR analysis. The adduct decomposed upon aqueous bicarbonate treatment. The spectral data fit 3,5-di-*p*-toluenesulfonyl-6-methoxy-7,7,8,8-tetramethyl-1,3,5-triazabicyclo[4.2.0]octa-2,4-dione (**7**): ir (CH_2Cl_2) 2960, 1745, 1720, 1600, 1385 cm^{-1}; NMR (CH_2Cl_2) δ 1.18 (s, 3 H), 1.35 (s, 3 H), 1.40 (s, 3 H), 1.43 (s, 3 H), 2.44 (m, 6 H), 3.18 (s, 3 H), 7.40 (m, 4 H), 8.05 (m, 4 H).

Reaction of *p*-Toluenesulfonyl Isocyanate with 5. Following the procedure for **1**, treatment of 70 mg (0.55 mmol) of **5** and 221 mg (1.12 mmol) of *p*-toluenesulfonyl isocyanate gives a near quantitative yield of an adduct by NMR analysis. Crystallization from carbon tetrachloride gave 102 mg (36%) of an unstable adduct, 3,5-di-*p*-toluenesulfonyl-6-methoxy-7,8,8-trimethyl-1,3,5-triazabicyclo[4.2.0]octa-2,4-dione (**8**): mp 135–143° dec; ir (CCl_4) 2950, 1755 (sh), 1730 (s), 1600, 1390, 1350 cm^{-1}; NMR (CCl_4) δ 1.17 (d, J = 7 Hz, 3 H), 1.33 (s, 3 H), 1.47 (s, 3 H), 2.43 (s, 6 H), 3.18 (s, 3 H), 7.40 (m, 4 H), 8.00 (m, 4 H) (the methine hydrogen was not detected). The mass spectrum showed only peaks from decomposition to *p*-toluenesulfonyl isocyanate and **5**, again because **8** is thermally unstable and decomposes before vaporization.

Reaction of *p*-Toluenesulfonyl Isocyanate with 3. To a solution of 326 mg (1.65 mmol) of *p*-toluenesulfonyl isocyanate in 4 ml of dichloromethane was added a solution of 92 mg (0.82 mmol) of **3** in 1 ml of dichloromethane at −20°. After reaching room temperature (ca. 1 hr), the solvent was removed in vacuo. Crystallization from carbon tetrachloride–dichloromethane–hexane gave 340 mg (82%) of 3,5-di-*p*-toluenesulfonyl-6-methoxy-8,8-dimethyl-1,3,5-triazabicyclo[4.2.0]octa-2,4-dione (**6**): mp >110° dec; ir (CCl_4) 2960, 1755, 1730, 1600, 1390 cm^{-1}; NMR (CCl_4) δ 1.63 (s, 6 H), 2.50 (s, 6 H), 2.75 and 3.13 (AB, J = 13.5 Hz, 2 H), 3.27 (s, 3 H), 7.40 (m, 4 H), 8.10 (m, 4 H). The mass spectrum showed only peaks from decomposition to *p*-toluenesulfonyl isocyanate and **3**, because **6** is thermally unstable and decomposes before vaporization.

Preparation of 1,4-Dipolar Adduct 10 from 3 and *p*-Toluenesulfonyl Isocyanate. To a solution of 426 mg (3.77 mmol) of **3** in 4 ml of dichloromethane at −40° was added a solution of 312 mg (1.58 mmol) of *p*-toluenesulfonyl isocyanate in 2 ml of dichloromethane. Upon warming the reaction mixture to ca. 0°, a white precipitate slowly came out of solution. Filtration or centrifugation at room temperature in an inert atmosphere followed by a dichloromethane rinse and drying in a stream of nitrogen resulted in 147 mg (30%) of an amorphous, white powder, **10**: mp 110–113° dec; ir (Nujol) 1690, 1645, 1420, 1270, 1240, 1140, 1080, 1065, 1015, 980, 905, 850, 825, 810, 790, 775, 705, 665 cm^{-1}; NMR (CH_2Cl_2) insoluble. The mass spectrum showed only peaks from decomposition to *p*-toluenesulfonyl isocyanate (*m/e* 197, 155, 91, 42) and **3** (*m/e* 113, 84, 56). The white powder **10** decomposes to a mixture of 37% of **6**, 8% of **11**, 27% of **12**, 12% of **13**, 12% of imino ether **3**, and some *p*-toluenesulfonyl isocyanate and/or *p*-toluenesulfonamide (due to traces of moisture) upon attempted solution in dichloromethane. The NMR integration of this decomposition mixture in dichloromethane solution indicates a 1:1 molar ratio of reactants **3** and *p*-toluenesulfonyl isocyanate in the adduct **10**. The infrared spectrum of the decomposed solution shows peaks at 2250 (*p*-toluenesulfonyl isocyanate), 1740 (broad band for 2:1 adduct **6**, amide **11**, and urea **13**), 1800, 1700 (amide **12**), and 1620 cm^{-1} (from **3**).

Reaction of 10 with *p*-Toluenesulfonyl Isocyanate. To 112 mg (0.36 mmol) of **10** in a round-bottom flask in a glove box was added 73 mg (0.37 mmol) of *p*-toluenesulfonyl isocyanate in 5 ml of dichloromethane. The heterogeneous mixture was kept at room temperature overnight. The solvent was removed in vacuo, leaving a solid. Crystallization from carbon tetrachloride–dichloromethane–hexane gave 176 mg (96%) of the 2:1 adduct **6**, mp 113° dec.

Reaction of 10 with 3. To 31 mg of **10** in an NMR tube was added ca. 100 mg of **3** in dichloromethane. After several hours at room temperature, the NMR spectrum showed only amides **12** and **13** in equal proportions along with excess **3**. The amides **12** and **13** were isolated from reactions containing excess **3** after standing at room temperature for several days. The solid **13** was separated from the liquid **12**. Distillation of the oil gave 1,4,4-trimethylazetidinone (**12**): bp 100° (2 mm); ir (CCl_4) 2960, 1750, 1280 cm^{-1}; NMR (CH_2Cl_2) δ 1.37 (s, 6 H), 2.65 (s, 5 H, NCH_3 and $-CH_2-$) [lit. NMR ($CDCl_3$) 1.35 (s, 6 H), 2.65 (s, 5 H)].[47a] Recrystallization of the crude crystals above gave 1-*N*-methyl-*N*-*p*-toluenesulfonylaminocarbonyl-4,4-dimethylazetidinone (**13**): mp 133–135° (recrystallized from carbon tetrachloride–dichloromethane–hexane); ir (CH_2Cl_2) 2950, 1800, 1705, 1275 cm^{-1}; NMR (CH_2Cl_2) δ 1.53 (s, 6 H), 2.40 (s, 3 H), 2.80 (s, 2 H), 3.15 (s, 3 H), 7.62 (AA'BB', 4 H); mass spectrum (90 eV) *m/e* 246.1377 ($M^+ - SO_2$, calcd for $C_{14}H_{18}N_2O_2$, 246.1368); *m/e* (rel intensity) 246 ($M^+ - SO_2$, 34), 191 (9), 155 (46), 139 (34), 121 (11), 119 (14), 117 (14), 97 (23), 92 (14), 91 (100), 84 (83), 83 (71), 70 (11), 65 (26), 58 (26), 57 (23), 56 (69), 55 (31), 51 (11), 44 (20), 43 (86), 42 (60), 41 (60), 39 (29).

Reaction of 10 with Water. To 142 mg (0.46 mmol) of **10** was added 73 mg (4 mmol) of water in 1 ml of acetonitrile. Evaporation of the solvent gave 146 mg (97%) of methyl 3-methyl-*N*-*p*-toluenesulfonylaminecarbonyl-3-aminobutanoate (**11**): mp 116–119° (from carbon tetrachloride–dichloromethane); ir (KBr) 3400 (br d), 3370 (sh), 2970, 2820, 1740, 1695, 1550, 1450, 1350 cm^{-1}; NMR (CCl_4) δ 1.37 (s, 6 H), 2.44 (s, 3 H), 2.65 (s, 2 H), 3.66 (s, 3 H), 7.23 (m, 2 H), 7.75 (m, 2 H), ca. 8.3 (NH); mass spectrum (70 eV) *m/e* 313.0857 ($M^+ - CH_3$, calcd for $C_{13}H_{17}N_2O_5S$, 313.0858); *m/e* (rel intensity) 328 (M^+, 0.17), 313 ($M^+ - CH_3$, 2), 297 (4), 264 (5), 256 (2), 255 (13), 232 (2), 217 (2), 215 (3), 198 (2), 197 (15), 171 (3), 157 (8), 156 (3), 155 (35), 117 (3), 116 (42), 115 (4), 114 (3), 108 (12), 107 (8), 92 (6), 91 (78), 84 (14), 83 (4), 74 (3), 73 (7), 65 (13), 63 (3), 59 (6), 58 (100), 57 (4), 56 (6), 55 (4), 51 (3), 43 (6), 42 (17), 41 (7), 39 (8).

Attempted Reaction of 10 with Phenyl Isocyanate. To 41 mg (0.13 mmol) of **10** was added 15 mg (0.31 mmol) of phenyl isocyanate in 1 ml of dichloromethane in an NMR tube. After 10 hr at room temperature, the NMR spectrum indicated only the formation of the 2:1 adduct **6** (ca. 70%) and amide **12** (ca. 25%) and no apparent reaction with phenyl isocyanate.

Reaction of 2:1 Cycloadduct 6 with Water. A solution composed of 40 mg (0.08 mmol) of **6**, 14 mg (0.8 mmol) of water, 0.5 ml of dichloromethane, and enough acetone to make it homogeneous was heated for ca. 10 min in a steam cone. The NMR spectrum showed complete decomposition. Removal of volatiles left a solid behind. The solid was identified as *p*-toluenesulfonamide by comparison of NMR and ir spectra of an authentic sample. The volatiles contained the azetine **3** by comparison of NMR and ir spectra. The only other decomposed material in the NMR and ir spectra was the urea **11** (ir 1740 cm^{-1} w). Upon standing in moist air, **6** decomposes to a 50:50 mixture of urea **11** and *p*-toluenesulfonamide as analyzed by NMR and ir.

Reaction of *p*-Toluenesulfonyl Isocyanate with 4,4-Dimethylazetidinone. To a solution of 190 mg (0.96 mmol) of *p*-toluenesulfonyl isocyanate in 0.5 ml of dichloromethane was added 98 mg (0.99 mmol) of 4,4-dimethylazetidinone in 0.5 ml of dichloromethane. The addition produced an exothermic reaction. NMR analysis showed clean conversion to **14** in 24 hr. Crystallization from carbon tetrachloride–dichloromethane–hexane gave 51 mg (18%) of *N*-*p*-toluenesulfonylaminocarbonyl-4,4-dimethylazetidinone (**14**): mp 138–140°; ir (CH_2Cl_2) 3250, 1775, 1730 cm^{-1}; NMR (CH_2Cl_2) δ 1.53 (s, 6 H), 2.42 (s, 3 H), 2.87 (s, 2 H), 7.40 (m, 2 H), 8.00 (m, 2 H), ca. 9.1 (broad s, 1 H, NH); mass spectrum (70 eV) *m/e* 232.1204 (calcd for $C_{13}H_{16}N_2O_2$, 232.1212) ($M^+ - SO_2$); *m/e* (rel intensity) 296 (M^+, 0.1), 232 (15), 171 (30), 155 (35), 109 (5), 108 (55), 107 (13), 106 (4), 92 (8), 91 (100), 90 (5), 89 (8), 84 (8), 83 (6), 65 (25), 56 (20), 42 (10), 41 (12), 39 (15).

Attempted Reaction between 3 and Phenyl Isocyanate. To 165 mg (1.38 mmol) of phenyl isocyanate was added 156 mg (1.38 mmol) of **3** in 0.5 ml of acetonitrile. The reaction tube was freeze degassed and sealed under vacuum (<0.1 mm). White crystals separated out within minutes (temperature ≤25°). The crystals were filtered, washed with acetonitrile, and dried in a vacuum desiccator. This resulted in 85 mg (ca. 50%) of trimer **15**: mp 268–271° (lit. mp 285°);[2] ir (CH_2Cl_2) 3050, 2250 (from CH_3CN), 1710, 1495, 1415 cm^{-1}; NMR (CH_2Cl_2) δ 1.97 (s, variable integration in different runs from 5.4 to 7.5 H from ca. 2 CH_3CN per mole of trimer) and 7.50 (m, 15 H); mass spectrum (70 eV) *m/e* 357.1126 (calcd for $C_{21}H_{15}N_3O_3$, 357.1113); *m/e* (rel intensity) 357 (M^+, 36), 305 (1), 282 (0.5), 238 (3), 218 (1), 212 (1), 167 (1), 149 (2), 145 (3), 120 (8), 119 (100), 93 (6), 91 (15), 77 (5), 64 (7), 57 (5), 55 (5), 43 (12), 41 (13). The white crystals are composed of the trimer of phenyl isocyanate, **15**, complexed with ca. two acetonitrile molecules.[49,50]

Reaction of Phenyl Isocyanate with Base. To 210 mg (1.76 mmol) of phenyl isocyanate was added 183 mg of acetonitrile. After 4 days with no apparent change, several drops of methyldiethylamine were added. After 1 day at 25°, 200 mg (ca. 95%) of white crystals was isolated. Recrystallization from dichloromethane afforded the trimer of phenyl isocyanate, **15**, mp 271.5–272.5°. The NMR still showed a trace of acetonitrile present (δ 1.97).

Reaction of Chlorosulfonyl Isocyanate with 1. A solution of 290 mg (2.52 mmol) of **1** in 0.5 ml of dichloromethane was added to a solution of 400 mg (2.82 mmol) of chlorosulfonyl isocyanate in 0.5 ml of dichloromethane at −70°. The solution was allowed to come to room temperature, then poured into water. The organic layer was separated, washed with aqueous sodium sulfite–sodium hydroxide solution, and dried over potassium carbonate. Removal of solvent and all volatile material left 6 mg (1.4%) of a solid residue characterized as *N,N'*-di-*tert*-butylurea: mp 177–184° (sublimes) (lit. mp 245°);[51] ir (CH_2Cl_2) 3400, 2950, 1680 cm^{-1}; NMR (CH_2Cl_2) δ 1.27 (s), NH not seen; mass spectrum (70 eV) *m/e* 172.1582 (calcd for $C_9H_{20}N_2O$, 172.1575); *m/e* (rel intensity) 172 (M^+, 4), 157.1346 ($M^+ - CH_3$, 7), 84 (7), 61 (7), 58 (100), 57 (13), 56 (9), 44 (16), 41 (20).

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Registry No.—**1**, 49680-36-6; **2**, 55222-40-7; **3**, 23974-38-1; **4**, 49680-46-8; **5**, 52856-04-9; **6**, 55254-58-5; **7**, 55222-41-8; **8**, 55222-42-9; **10**, 55222-43-0; **11**, 55222-44-1; **12**, 23974-51-8; **13**, 55254-60-9; **14**, 55254-59-6; **15**, 1785-02-0; *p*-toluenesulfonyl isocyanate 4083-64-1; phenyl isocyanate, 103-71-9; 4,4-dimethylazetidinone, 4879-95-2; acetonitrile, 75-05-8; chlorosulfonyl isocyanate, 1189-71-5; *N,N'*-di-*tert*-butylurea, 5336-24-3.

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Addition of Dimethyl Acetylenedicarboxylate to Imino Ethers. Trapping of a 1,4-Dipolar Intermediate

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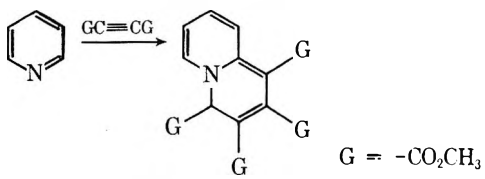
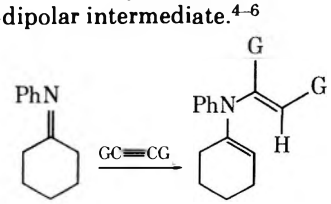
The *O*-alkylformimidates **1a** and **1b** react with dimethyl acetylenedicarboxylate (DMAD) to form 2:1 cycloadducts **2a** and **2b**. The 2-alkoxyazetines **6** (and **12**) react with DMAD to form 1:1 linear fumarate **7** (**13**) and maleate **8** (**14**) adducts via 1,4-dipolar ions like **9**. These 1,4-dipolar ions can also dimerize in nonpolar solvents to give the eight-membered ring 2:2 adducts **16** and **17**. The 1,4-dipolar ions postulated as intermediates in these reactions can be trapped with added water to give products **18**, **24–28**, and **31**.

The addition of electron-deficient acetylenes to carbon–nitrogen double bonds was first studied by Diels and Alder.[1] They found that aromatic heterocycles such as pyridine add dimethyl acetylenedicarboxylate (DMAD) to give a 2:1 adduct.[1–5] This reaction was later recognized by Huisgen to be one of a large class of reactions which are thought to proceed via 1,4-dipolar intermediates.[2–5] Analogous adducts have been found to incorporate two molecules of imine to one of DMAD; and 1:1:1 adducts of imine, DMAD, and phenyl isocyanate have been observed.[4,6]

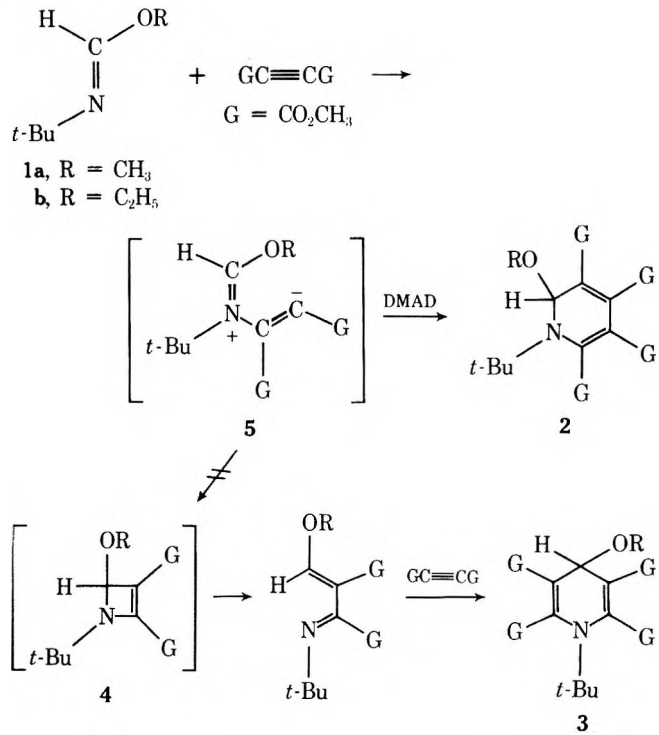


We report here the addition reactions of DMAD with a variety of imino ethers. Imino ethers are readily available by alkylation of amides and lactams[7] and might prove to be useful intermediates in heterocycle synthesis involving 1,4-dipolar additions. Of particular interest are the strained 1-azetines[7–11] derived from alkylation of β-lactams,[7,8] since they might give 1:1 adducts in the 1-azabicyclo[2.2.0]hexane system. Of the additions to imines studied,[12–20] only in the cases of additions of ynamines and enamines to C=N bonds have such cyclic 1:1 adducts been found,[16–20] although the 2-azetines formed in some cases ring open at low temperatures.[18,19] In a case of DMAD addition to an imine, a 1:1 type adduct was obtained, presumably via a 1,4-dipolar intermediate.[4–6]



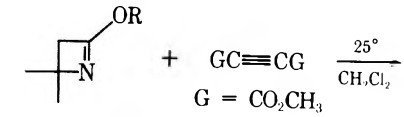
Results and Discussion

Additions of dimethyl acetylenedicarboxylate (DMAD) to the *N*-*tert*-butyl formimidates **1a** and **1b** give no 1:1 adducts, but 2:1 adducts **2a** and **2b** are formed in fair yields in boiling dioxane. The structures of the 2:1 adducts **2** are apparent from their spectral data. The asymmetric center to which the ethoxy group is attached in **2b** gives rise to an ABX_3 pattern for the diastereotopic methylene hydrogens of the ethoxy group instead of a simple quartet.[21] This rules out the structure **3** derived from ring opening of the 2-azetine **4**[13–15,22–26] followed by Diels–Alder reaction with DMAD.[25] The formation of **2** is most conveniently accounted for by capture of a 1,4-dipolar intermediate **5** by DMAD. The adducts **2a** and **2b** were the only products isolated regardless of the molar ratio of reagents.

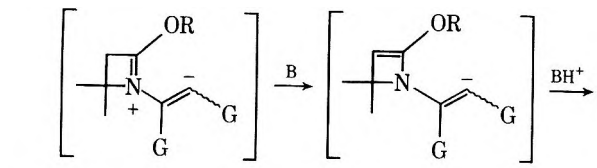


In contrast to the additions to **1**, the azetines **6a** and **6b** give primarily 1:1 adducts on addition of DMAD in dichloromethane solution. The reaction occurs readily under much milder conditions to give approximately a 50:50 mixture of the fumarate and maleate esters **7** and **8** in greater than 50% yield. The structures of **7** and **8** are apparent from their NMR spectra; the two different vinyl singlets and two different vinyl heptets (A part of an AX_3Y_3) are well accommodated by this assignment. These products are formed in dichloromethane independent of the molar ratio or order of addition of the reagents. No evidence was found for formation of the 1:1 adduct **11** or the 2:1 adduct analogous to **2**. Apparently **7** and **8** are formed by proton abstraction from the 1,4-dipole **9** and ring opening of 2-azetine **10**. The formation of **10** is analogous to the known ene-type reactions of DMAD and imines with abstractable hydrogens.[4–6] The geometry of **9** and the formation of both products **7** and **8** eliminate the possibility of an intramolecular proton abstraction. 2-Azetines are known to ring open readily.[13–15,22–24,26] Analogously to **6**, the azetine **12** gives esters **13** and **14** in 26% yield. The low yield can be attributed to steric hindrance by the 3-methyl substituent in the proton abstraction. A tertiary amine base was added to facilitate proton removal.

Since there are no abstractable hydrogens in the tetramethylazetines **15a** or **15b**, they cannot give 1:1 adducts analogous to **7** and **8**. Instead, on reaction with DMAD at



6a, R = CH_3
b, R = C_2H_5



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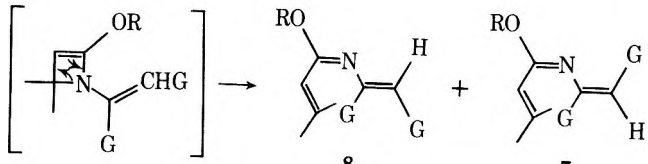
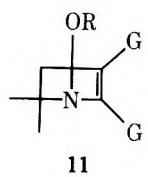


10 **8** **7**



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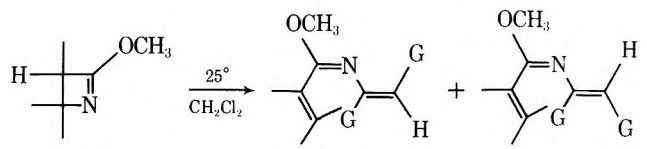
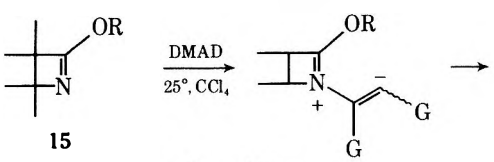


12 **13** **14**

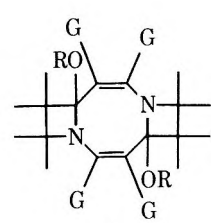
+
$GC{\equiv}CG$

25° in methylene chloride, they give only polymers and recovered azetine. In carbon tetrachloride solvent, however, a new high molecular weight product **16b** (from **15b**) is



15

a, R = CH_3
b, R = C_2H_5



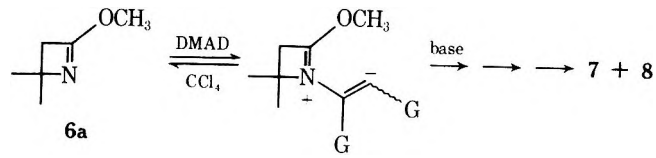
16

formed in 88% yield after distillation. This product and the related methoxy derivative **16a** have NMR spectra consistent with a 1:1 ratio of reactants but the boiling points and mass spectra are those expected for a 2:2 adduct. From the symmetry of the NMR spectra, the eight-membered ring structure **16a,b** is indicated, but a distinction between syn and anti fusions of the azetidine rings is not possible. They have a twofold axis and center of inversion, respectively, and should show the same symmetry in their NMR spectra. The asymmetry of the centers of ethoxyl group attachment is indicated by a complicated pattern for the diastereotopic methylene hydrogens of the ethoxyl in **16b**. This product appears to be formed simply by dimerization of a 1,4-dipolar intermediate. There is little precedent for these sorts of dimers in 1,4-dipolar ion chemistry.[27]

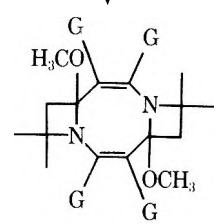
Table I
Ratios of 1:1 and 2:2 Products from 6a

[6a], *M*	[DMAD], *M*	Solvent	Ratio of [7] + [8]:[17]
0.82	1.16	CCl_4	0.7
0.41	0.58	CCl_4	0.7
0.13	0.13	CCl_4	1.3
0.34	0.48	1.6 *M* *N*-methylpiperidine in CCl_4	4
0.082	0.116	CH_2Cl_2	>10

Although no 2:2 dimer could be detected from **6a** in dichloromethane solvent, the dimer **17** was found to form in 35% yield along with 35% of a 1:1 mixture of **7** and **8** in carbon tetrachloride solution. Again the boiling point and mass spectrum indicated a 2:2 adduct, while the NMR spectrum has the symmetry expected of an eight-membered ring dimer **17**.



6a **9a** 7 + 8

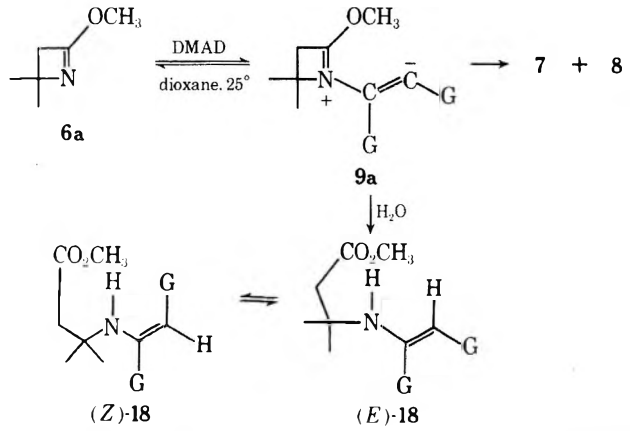


17

The variation in the ratio of 1:1 products **7** and **8** to the 2:2 product **17** with different reaction conditions is shown in Table I. The most dramatic effect is the lack of any observable 2:2 adduct in dichloromethane solvent. This can be explained as a consequence of the competition between the charge destroying dimerization step, **9a** → **17**, and a more polar transition state for proton abstraction by base in forming **7** and **8**. The 2:2 adducts **16a,b** are also strongly favored in nonpolar solvent. Interestingly, the rate of reaction of **6a** in dichloromethane is essentially identical with that in carbon tetrachloride, suggesting that the rate-determining step in these reactions is not simply the formation of the 1,4-dipolar ion, since such a reaction should be strongly accelerated in polar solvents.[28]

Normally the imino ether **6a** must act as the base in the hydrogen abstraction step, but in the presence of 1.6 *M* *N*-methylpiperidine the rate of formation of **7** and **8** increases relative to the rate of dimerization of **9a** in accord with the postulated mechanism. Increased reagent concentrations favor the 2:2 adduct over the 1:1 adduct as expected from a mechanism overall fourth order for **17** and third order for **7** and **8** (using **6a** as the base). This effect may not appear as large as expected because of the competing solvent polarity effect at high reagent concentrations. The rates of these reactions were followed approximately by NMR and showed the expected increases at high reagent concentrations. The data in Table I thus appear consistent with a mechanism involving a common 1,4-dipolar intermediate for the products **7**, **8**, and **17**.

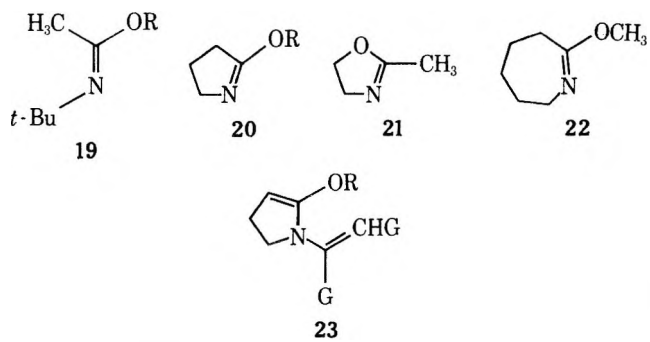
To confirm the presence of a 1,4-dipolar ion **9a** in these reactions, the addition of DMAD to **6a** was carried out in dioxane at 25° in the presence of water. A mixture was iso-

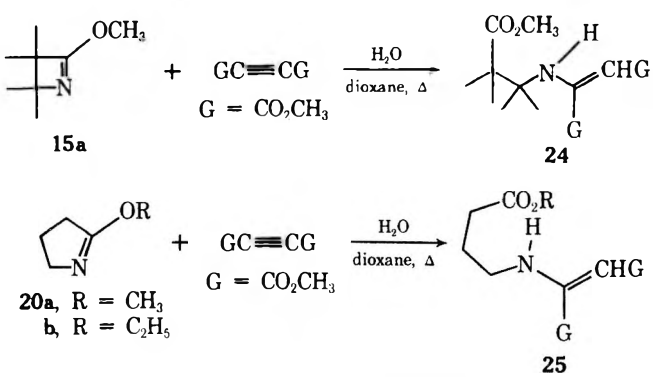


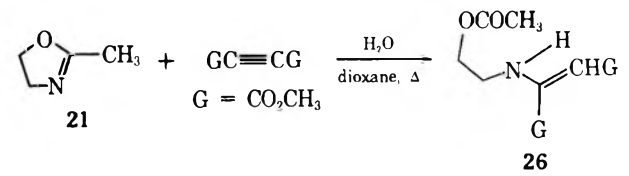
lated containing 75% of a trapping product **18** along with 17% of **7** and 8% of **8** by NMR analysis. Product **18** is initially formed as a 2:1 mixture of isomers (*E*)-**18**, with maleate configuration, and (*Z*)-**18**, with the fumarate configuration. On work-up and distillation the maleate isomer isomerizes to favor (*Z*)-**18** by 10:1. These configurational assignments were made on the basis of the usual preference in amine additions to DMAD[29] for the fumarate isomer at equilibrium. The chemical shifts of the vinyl hydrogens at δ 4.78 for (*E*)-**18** and δ 4.81 for (*Z*)-**18** are ambiguous,[29,30] however, and the configurational assignments are only tentative.

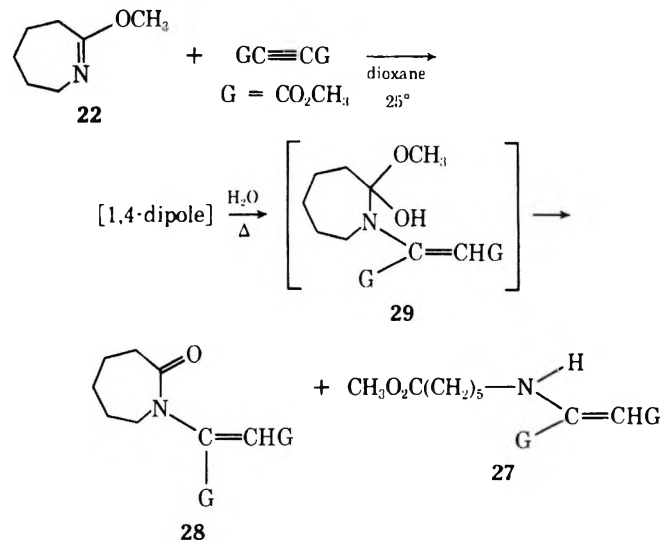
Under identical conditions, but with no DMAD present, no hydrolysis of **6b** occurs. This eliminates the possibility that **18** might have been formed by reaction of an amino ester from hydrolysis of **6a** with DMAD,[31,32] and further implicates the 1,4-dipole **9a** as an intermediate in these reactions.

Attempted additions of DMAD to the imino ethers **19–22** produced only polymeric and high boiling products, perhaps via hydrogen abstraction reactions to enamines like **23** followed by further condensation reactions with DMAD. In the reactions of imino ethers **15a** and **20a,b** with DMAD in boiling aqueous dioxane, however, the water trapping products **24** and **25** are isolated in moderate yields. In the reaction of imino ether **21** and DMAD in the presence of water, approximately 40% of product **26** is isolated. These structures follow from spectral data and comparison of analogous products (**18, 24, 25**).[33] When water is added to the reaction mixture of **22** and DMAD at 100°, a mixture of products is obtained. The mixture is composed of ca. 50% of the ester enamine **27** and ca. 50% of the caprolactam **28** as analyzed by NMR. It is curious that only imino ether **22** gave an amide product **28**. This product **28** could not have come from the addition of caprolactam and DMAD, because amides and lactams add only under drastic conditions.[34] The amide **28** could come from the initial water trapping product **29** of the 1,4-dipole. Cyclization of **27** to **28** was shown not to occur under the reaction conditions.

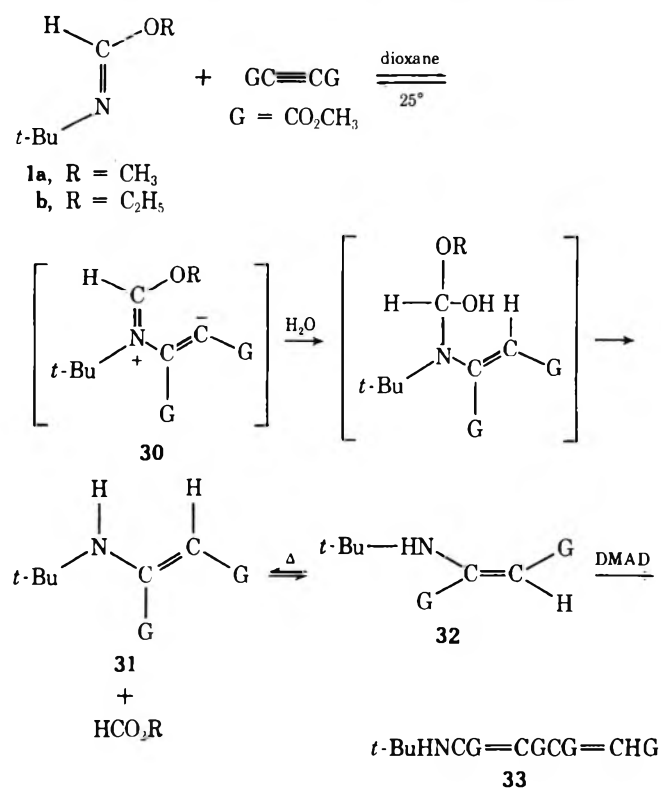








With the acyclic imino ethers **1a** and **1b**, heating to 100° with dioxane, DMAD, and water gives 59% of product **31**.



With excess DMAD under identical conditions, 29% of product **33** is isolated. Performing the reaction at room temperature, 46% of product **31** is isolated. Under the same conditions, but without added DMAD, no hydrolysis of imino ether **1b** occurs. Product **31** must come from water trapping of the 1,4-dipole **30** derived from imino ether **1** and DMAD at room temperature (analogous to azetine **6**). With excess DMAD, product **32** probably cycloadds to DMAD and ring expands to give product **33** (analogous to reactions of other enamines with DMAD).[24]

The imino ethers **1b** and **6b** were shown not to hydrolyze at 25° in dioxane–water,[35] confirming that these water trapping experiments involve interception of a 1,4-dipolar intermediate rather than hydrolysis followed by DMAD addition.[29] Reactions of iminosulfuranes with DMAD in the presence of water have been postulated to involve trapping of a 1,4-dipolar intermediate,[22] but no control experiments were run to test the possibility of hydrolysis of the iminosulfuranes.[36]

The rate of disappearance of **1b** increases tenfold on addition of water to the reaction mixture in dioxane at 25°. This suggests that the rate-limiting step in the 1,4-dipolar reaction of **1b** to give **2** is not the addition of DMAD to **1b** to give **30**, but the addition of **30** to DMAD.

Experimental Section

All boiling points and melting points are uncorrected. Ir spectra were obtained neat or in solution with a matched reference cell on a Perkin-Elmer 337 grating infrared spectrophotometer. Uv spectra were recorded on a Cary 15 Spectrophotometer. NMR spectra were obtained on a 60-MHz Varian Associates T-60 or a Jeolco C-60H spectrometer. Where indicated, 100-MHz spectra were obtained on a Varian HA-100 spectrometer. Mass spectra were obtained on a MS-902 spectrometer or on a Finnigan 1015 quadrupole spectrometer where indicated.

Materials. The dimethyl acetylenedicarboxylate (DMAD) was purchased from Aldrich Chemical Co. and freshly distilled before use. The imino ethers were either purchased from Aldrich Chemical Co. or made by alkylation of the corresponding amide with a trialkyloxonium fluoroborate.[37]

***O*-Ethyl *N*-*tert*-butylformimidate (1b)** was prepared by standard procedures[37] from *N*-*tert*-butylformamide and triethyloxonium fluoroborate in 73% yield: bp 118–122°; ir (neat) 2950, 1650, 1380 cm^{-1}; NMR (CCl_4) δ 1.10 (s, 9 H), 1.18 (t, J = 7.1 Hz, 3 H), 3.94 (q, J = 7.1 Hz, 2 H), 7.23 (s, 1 H); mass spectrum (70 eV) *m/e* 129.1156 (calcd for $C_7H_{15}NO$, 129.1154); *m/e* (rel intensity) 129 (M^+, 28), 114 (100), 101 (17), 87 (2), 86 (56), 85 (9), 84 (2), 73 (5), 72 (4), 71 (3), 69 (3), 59 (3), 58 (95), 57 (95), 56 (22), 55 (7), 46 (46), 45 (19), 44 (5), 43 (7), 42 (29), 41 (53), 40 (4), 39 (17).

Reaction of DMAD with 1a. A solution composed of 316 mg (2.75 mmol) of **1a** and 780 mg (5.50 mmol) of DMAD in 20 ml of 1,2-dichloroethane was refluxed for 24 hr. The solvent was removed in vacuo leaving a viscous residue. Upon addition of ether to the residue, a white solid precipitated out of solution. Recrystallization from methanol gave 548 mg (50%) of **2a**: mp 144.5–146.5°; ir ($CHCl_3$) 2950, 1750, 1725, 1600 cm^{-1}; uv (ethanol) 215 nm (ϵ 13,500), 278 (14,000), 345 (10,200); NMR (CCl_4) δ 1.50 (s, 9 H), 3.58 (s, 3 H), 3.67 (s, 6 H), 3.92 (s, 3 H), 5.43 (s, 1 H); mass spectrum (70 eV) *m/e* 399.1526 (calcd for $C_{18}H_{25}NO_9$, 399.1529); *m/e* (rel intensity) 399 (M^+, 3), 369 (1), 368 (3), 354 (1), 241 (3, 240 (16, 313 (3, 298 (3), 286 (2), 285 (9), 284 (77), 266 (4), 253 (2), 252 (12), 251 (100), 237 (5), 224 (1), 205 (2), 194 (1), 178 (2), 167 (1), 166 (1), 151 (1), 137 (1), 135 (2), 79 (1), 77 (1), 59 (5), 58 (1), 57 (30), 56 (2), 55 (2), 45 (2), 44 (2), 42 (3), 41 (11), 39 (2).

Reaction of DMAD with 1b. Following the procedure for **1a** above, 392 mg (3.04 mmol) of **1b** and 470 mg (3.30 mmol) of DMAD in 10 ml of dichloromethane resulted in 460 mg (67%) of **2b**: mp 155.5–156.5°; ir ($CHCl_3$) 2950, 1740, 1680, 1595 cm^{-1}; NMR (100 MHz) ($CDCl_3$) δ 1.46 (t, $J_{AX} = J_{BX}$ = 7.0 Hz, 3 H) (X part of ABX_3), 1.54 (s, 9 H), 3.66 (s, 6 H), 3.71 (s, 3 H), 3.86 (s, 3 H), 4.07 (dq, J_{BX} = 7.0, J_{AB} = 9.5 Hz, 1 H) (B part of ABX_3), 4.53 (dq, J_{AX} = 7.0, J_{AB} = 9.5 Hz, 1 H) (A part of ABX_3, AB spectrum obtained from time averaged computer technique), 5.66 (s, 1 H); mass spectrum (70 eV) *m/e* 413.1689 (calcd for $C_{19}H_{27}NO_9$, 413.1686); *m/e* (rel intensity) 413 (M^+, 10), 382 (12), 355 (8), 354 (47), 326 (12), 299 (17), 298 (100), 267 (32), 266 (100), 238 (83), 206 (33), 178 (25), 59 (25), 57 (83), 41 (42).

Reaction of DMAD with 6a. A mixture of 279 mg (2.46 mmol) of **6a** and 348 mg (2.45 mmol) of DMAD in 10 ml of dichloromethane was left at room temperature for 24 hr. Evaporation of solvent in vacuo left an oil residue. The residue was chromatographed on alumina using carbon tetrachloride and vacuum distilled, yielding 338 mg (54%), bp 100–110° (0.1 mm), of a mixture composed of approximately equal amounts of fumarate (**7a**) and maleate (**8a**) isomers. The fumarate isomer **7a** could be enriched in early short-path distillation fractions. The spectral data are listed: ir (CCl_4) 2950, 1740 (sh), 1725, 1670, 1630, 1440 cm^{-1}; NMR (100 MHz, CCl_4) for **7a** δ 1.79 (d, J = 1.4 Hz, 3 H), 1.90 (d, J = 1.4 Hz, 3 H), 3.60 (s, 3 H), 3.74 (s, 6 H), 5.35 (heptet, J = 1.4 Hz, 1 H), 6.01 (s, 1 H) (assigned fumarate isomer);[38] for **8a**, δ 1.92 (d, J = 1.4 Hz, 3 H), 1.98 (d, J = 1.4 Hz, 3 H), 3.64 (s, 3 H), 3.76 (s, 3 H), 3.82 (s, 3 H), 5.08 (s, 1 H), 5.78 (heptet, J = 1.4 Hz, 1 H) (assigned maleate isomer);[38] mass spectrum (70 eV) *m/e* 255.1113 (calcd for $C_{12}H_{17}NO_5$, 255.1107); *m/e* (rel intensity) 255 (M^+, 2), 224 (2), 196 (80), 164 (100), 136 (30), 115 (20), 114 (20), 113 (30), 85 (20), 83 (50), 82 (20), 59 (40), 55 (40), 53 (20), 41 (20), 39 (30).

Reaction of DMAD with 6b. Following the procedure for **6a**, 73 mg (0.58 mmol) of **6b** and 92 mg (0.65 mmol) of DMAD yielded 78 mg (50%) of a 1:1 mixture of fumarate (**7b**) and maleate (**8b**) isomers: bp 114° (0.2 mm); ir (neat) 2950, 1740 (sh), 1730, 1670, 1630, 1440 cm^{-1}; uv (ethanol) 220 nm (ϵ 15,000), 226 (11,000); NMR (CCl_4) for **7b** δ 1.39 (t, J = 9.7 Hz, 3 H), 1.75 (d, J = 1.3 Hz, 3 H), 1.80 (d, J = 1.3 Hz, 3 H), 3.57 (s, 3 H), 3.71 (s, 3 H), 4.14 (q, J = 9.7 Hz, 2 H), 5.26 (m, $J \simeq$ 1.3 Hz, 1 H), 5.92 (s, 1 H) (assigned fumarate isomer);[38] for **8b** δ 1.33 (t, J = 9.7 Hz, 3 H), 1.88 (d, J = 1.3 Hz, 3 H), 1.95 (d, J = 1.3 Hz, 3 H), 3.61 (s, 3 H), 3.71 (s, 3 H), 4.24 (q, J = 9.7 Hz, 2 H), 4.99 (s, 1 H), 5.69 m, $J \simeq$ 1.3 Hz, 1 H) (assigned maleate isomer);[38] mass spectrum (Finnigan) (70 eV) *m/e* (rel intensity) 270 (1.3), 269 (M^+, 1.3), 254 (0.5), 238 (8), 237 (1.7), 224 (1.5), 211 (8), 210 (57), 178 (94), 150 (60), 128 (25), 122 (33), 101 (15), 100 (17), 97 (20), 96 (17), 94 (19), 84 (24), 83 (100), 82 (100), 69 (22), 68 (31), 67 (23), 59 (18), 55 (80), 54 (33), 53 (67), 43 (17), 42 (17), 41 (35), 39 (81).

Reaction of DMAD with 12. Following the procedure for **6a** with the addition of 1 drop of ethyldiisopropylamine, 105 mg (0.83 mmol) of **12** and 120 mg (0.84 mmol) of DMAD yielded 58 mg (26%) of a 1:1 mixture of fumarate (**13**) and maleate (**14**) isomers: bp 100–110° (10^{-3} mm); ir (CCl_4) 2970, 1740 (sh), 1725, 1640, 1620, 1440 cm^{-1}; NMR (CCl_4) for **13** δ 1.60 (s, 6 H), 1.68 (s, 3 H), 3.58 (s, 3 H), 3.68 (s, 6 H), 5.90 (s, 1 H) (assigned as fumarate isomer);[38] for **14** δ 1.60 (s, 6 H), 1.68 (s, 3H), 3.60 (s, 3 H), 3.74 (s, 3 H), 3.80 (s, 3 H), 5.13 (s, 1 H) (assigned as maleate isomer);[38] mass spectrum (70 eV) *m/e* 269.1256 (calcd for $C_{13}H_{19}NO_5$, 269.1263); *m/e* (rel intensity) 269 (M^+, 10), 254 (3), 239 (12), 222 (3), 210 (67), 194 (5), 183 (7), 179 (10), 178 (100), 151 (12), 150 (20), 97 (5), 96 (7), 95 (8), 69 (12), 68 (13), 67 (13), 59 (8), 55 (10), 53 (18), 44 (12), 43 (5), 42 (8), 41 (47), 40 (3), 39 (13).

Reaction of 6a with DMAD in Carbon Tetrachloride. A mixture of 147 mg (1.30 mmol) of **6a** and 184 mg (1.29 mmol) of DMAD in 10 ml of carbon tetrachloride was left at 25° for 24 hr. A mixture composed of 35% yield each of the 1:1 isomers **7** and **8** and 2:2 adduct was found by NMR. Vacuum distillation afforded two fractions: 184 mg (53%), bp <140° (10^{-3} mm), containing mostly isomers **7a** and **8a**, and 143 mg (47%), bp 140–180° (10^{-3} mm). The higher boiling fraction was chromatographed on alumina with dichloromethane elution and redistilled, giving **17**: bp 150° (10^{-3} mm); ir (CCl_4) 2950, 1745, 1730 (sh), 1555, 1435 cm^{-1}; NMR (CCl_4) δ 1.58 (s, 3 H), 1.73 (s, 3 H), 2.64 (s, 2 H), 3.47 (s, 3 H), 3.67 (s, 3 H), 3.72 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) no parent observable, 425 (0.4), 423 ($M^+ - C_4H_8 - OCH_3$,1), 421 (0.8), 411 (4), 409 (8), 407 (6), 380 (4), 378 (6), 376 (4), 304 (10), 292 (24), 290 (72), 258 (30), 235 (28), 233 (100), 174 (18), 166 (26), 160 (20), 73 (28), 59 (40), 55 (32), 41 (40).

Reaction of 15b with DMAD in Carbon Tetrachloride. Following the procedure for **6a** above with 1 ml of carbon tetrachloride, 144 mg (0.93 mmol) of **15b** and 134 mg (0.94 mmol) of DMAD gave a high-boiling oil. Chromatography on alumina with diethyl ether elution and redistillation gave 245 mg (88%) of high-boiling oil **16b**: bp 150–160° (0.07 mm); ir (CCl_4) 2950, 1750, 1735 (sh), 1570, 1440, 1270 cm^{-1}, nearly identical with that of **17**; NMR (CCl_4) δ 1.07 (t, J = 6.8 Hz, 3 H), 1.25 (s, 3 H), 1.37 (s, 3 H), 1.44 (S= 6 H), 3.48 (s, 3 H), 3.54 (s, 3 H), ca. 3.7 (m, 2 H). The mass spectrum (Finnigan) indicated peaks up to *m/e* 440 with a pattern similar to that of **17**. In dichloromethane solvent this reaction gave only recovered imino ether and polymer.

Reaction of 15a with DMAD in Carbon Tetrachloride. Following the procedure for **6a** above and using 1 ml of carbon tetrachloride, 271 mg (1.92 mmol) of **15a**, and 273 mg (1.92 mmol) of DMAD resulted in an exothermic reaction. Chromatography on alumina with dichloromethane elution and distillation gave a clear oil, **16a**: bp 140–160° (0.1 mm); ir (CCl_4) 2940, 1740, 1560 cm^{-1}, nearly identical with that of **17**; NMR (CCl_4) δ 1.22 (s), 1.36 (s), 1.40 (broad s), and 1.55 (s) (ca. 24 H), 3.62 (s), 3.70 (s), and 3.75 (s) (ca. 18 H); mass spectrum (Finnigan) *m/e* up to ca. 450 with a pattern similar to that of **16b**. In chloroform and dichloromethane solvent, this reaction gives only recovered imino ether and polymer.

Attempted Reaction of DMAD with Imino Ethers 19–22. Following the procedure of **1b**, equimolar amounts of the above imino ethers and DMAD resulted in the production of polymers, both with and without total consumption of the imino ether.

Reaction of DMAD with 6a in the Presence of Water. A solution of 334 mg (2.96 mmol) of **6a**, 422 mg (2.98 mmol) of DMAD, and 76 mg (4.22 mmol) of water in 10 ml of dioxane was left at 25° for 24 hr. The NMR spectrum of the crude reaction mixture showed 75% of product **18**, 17% of fumarate **7a**, and 8% of maleate **8a** on evaporation of the solvent. Chromatography on alumina with dichloromethane elution and vacuum distillation afforded 477 mg (59%) of product **18**: bp 110–120° (0.8 mm); ir (CCl_4) 3250, 2950, 1745, 1670, 1620, 1205 cm^{-1}; NMR (CCl_4) δ 1.42 (s, 6 H), 2.70 (s, 2 H), 3.65 (s, 6 H), 3.82 (s, 3 H), 4.81 (s, 1 H), 8.30 (s, 1 H, NH); mass spectrum (70 eV) *m/e* 273.1216 (calcd for $C_{12}H_{19}NO_6$, 273.1212); *m/e* (rel intensity) 273 (20), 245 (16), 242 (8), 214 (12), 200 (20), 196 (100), 185 (68), 172 (44), 164 (96), 160 (24), 159 (32), 140 (76), 136 (48), 128 (40), 115 (28), 112 (32), 100 (32), 87 (24), 83 (48), 82 (28), 73 (40), 68 (32), 59 (40), 55 (48), 43 (60). This sample was tentatively assigned the fumarate, (*Z*)-**18** configuration but contained a trace of (*E*)-**18** as indicated by a small peak at δ 4.78 in a 1:10 ratio to the peak at δ 4.81 for (*Z*)-**18**. The NMR spectrum of the crude reaction mixture showed a 2:1 ratio of isomers (*E*)-**18** to (*Z*)-**18**.

Reaction of DMAD with 15a in the Presence of Water. After a solution of 320 mg (2.27 mmol) of **15a**, 323 mg (2.27 mmol) of DMAD, and 43 mg (2.39 mmol) of water in 10 ml of dioxane was heated to 110° for 24 hr, 350 mg (51%) of **24** was isolated on distillation: bp 100° (3×10^{-3} mm); ir (CCl_4) 3350, 2940, 1740 cm^{-1}; NMR (CCl_4) δ 1.26 (s, 12 H), 3.60 (s, 3 H), 3.67 (s, 3 H), 3.77 (s, 3 H), 4.65 (s, 1 H), 8.50 (s, 1 H).

Reaction of DMAD with 20a in the Presence of Water. Following the preceding procedure for preparation of **24**, 5.31 mg (4.70 mmol) of **20a**, 673 mg (4.73 mmol) of DMAD, and 110 mg (6.10 mmol) of water gave 464 mg (38%) of product **25a**: bp 120–140° (0.1 mm); ir (CCl_4) 3300, 2950, 1745, 1670, 1620, 1445 cm^{-1}; NMR (CCl_4) δ 1.83 (m, 2 H), 2.32 (m, 2 H), 3.40 (m, 2 H), 3.68 (s, 6 H), 3.85 (s, 3 H), 5.00 (s, 1 H), 8.15 (br d, 1 H); mass spectrum (Finnigan) (50 eV) 260 (0.07), 259 (M^+, 0.2), 228 (0.6), 227 (0.6), 212 (0.3), 200 (0.5), 196 (4), 195 (5), 180 (1), 172 (6), 168 (2), 167 (2), 166 (1), 154 (9), 153 (3), 141 (6), 140 (31), 136 (2), 128 (4), 126 (7), 125 (3), 112 (26), 108 (23), 101 (43), 100 (7), 94 (5), 82 (16), 69 (23), 68 (23), 59 (100), 55 (18), 54 (10), 53 (13), 45 (28), 43 (10), 42 (15), 41 (43), 39 (10). The adduct **25a** was alternatively synthesized by treating the product from acidic methanolysis of 2-pyrrolidone with DMAD under basic conditions (added solid sodium bicarbonate).

Reaction of DMAD with 20b in the Presence of Water. Following the procedure for preparation of **24**, 228 mg (2.02 mmol) of **20b**, 287 mg (2.02 mmol) of DMAD, and 38 mg (2.10 mmol) of water gave 231 mg (42%) of **25b**: bp 130–150° (0.1 mm); ir (neat) 3300, 1750, 1670, 1620 cm^{-1}; NMR (HA-100) (CCl_4) δ 1.23 (t, J = 7.1 Hz, 3 H), 1.85 (m, 2 H), 2.25 (m, 2 H), 3.35 (m, 2 H), 3.64 (s, 3 H), 3.82 (s, 3 H), 4.07 (q, J = 7.1 Hz, 2 H), 5.00 (s, 1 H), 8.13 (s, 1 H, NH).

Reaction of DMAD with 21 in the Presence of Water. Following the preceding procedure for preparation of **24**, 292 mg (3.44 mmol) of **21**, 489 mg (3.44 mmol) of DMAD, and 76 mg (4.22 mmol) of water gave 315 mg (37%) of **26**; bp 114–124° (0.1 mm); ir (CCl_4) 3300, 2950, 1750, 1675, 1620, 1210 cm^{-1}; NMR (CCl_4) δ 2.02 (s, 3 H), 3.55 (t, $J \simeq 5$ Hz, 2 H), 3.60 (s, 3 H), 3.78 (s, 3 H), 4.10 (t, $J \simeq 5$ Hz, 2 H), 5.08 (s, 1 H), 8.12 (s, 1 H, NH); mass spectrum (70 eV) *m/e* 245.0908 (calcd for $C_{10}H_{15}NO_6$, 245.0899); *m/e* (rel intensity) 245 (M^+, 3.2) 214 (9), 185 (90), 172 (54), 153 (9), 140 (90), 126 (18), 125 (13), 112 (36), 94 (13), 87 (27), 68 (18), 59 (13), 45 (36), 44 (36), 43 (100), 42 (9).

Reaction of DMAD with 22 in the Presence of Water. Following the preceding procedure for preparation of **24**, 610 mg (4.80 mmol) of **22** and 683 mg (4.80 mmol) of DMAD with excess water gave a mixture composed of 70% **27** and 30% amide **28** by NMR analysis. Fractional distillation gave 477 mg (35%) of **27**: bp ~160° (0.15 mm); ir (CCl_4) 3450, 3280, 2950, 1745 (s), 1670, 1615, 1440 cm^{-1}; NMR (CCl_4) δ 1.50 (m, 6 H), 2.20 (m, 2 H), 3.35 (m, 2 H), 3.60 (s, 3 H), 3.80 (s, 3 H), 4.97 (s, 1 h), 8.10 (s, 1 H, NH); mass spectrum (70 eV) *m/e* 287.1356 (calcd for $C_{13}H_{21}NO_6$, 287.1369); *m/e* (rel intensity) 287 (M^+, 20), 272 (0.4), 256 (17), 255 (24), 228 (20), 224 (34), 223 (10), 197 (10), 196 (100), 184 (7), 173 (10), 172 (30), 168 (10), 167 (20), 164 (7), 154 (20), 141 (10), 140 (45), 129 (14), 128 (10), 126 (7), 114 (7), 113 (7), 112 (17), 100 (14), 97 (17), 87 (7), 82 (10), 69 (50), 68 (24), 67 (7), 59 (24), 55 (42), 54 (7), 53 (10), 45 (24), 44 (7), 43 (10), 42 (14), 41 (50), 39 (14). Subjecting the sample **27** to the experimental conditions (refluxing aqueous dioxane) for 8 hr results in decomposition of **27** with no formation of **28**.

Distillation of late fractions from chromatography on alumina with carbon tetrachloride elution gave 150 mg (15%) of amide **28**: bp 170° (0.3 mm); ir (CCl_4) 2950, 1740 (s), 1695, 1615, 1440, 1370 cm^{-1}; NMR (CCl_4) δ 3.62 (s, 3 H), 3.68 (s, 3 H), 5.52 (s, 1 H), and broad multiplets at 1.75 and 2.50; mass spectrum (70 eV) *m/e* (rel intensity) 255 (M^+, 4.5), 224 (3.5), 198 (3.5), 197 (16), 196 (100), 186 (3.5), 185 (16), 168 (4.5), 164 (8), 160 (3.5), 154 (7), 140 (3.5), 128 (6), 127 (6), 126 (35), 113 (3.5), 112 (7), 108 (6), 101 (4.5), 100 (7), 99 (3.5), 98 (28), 96 (6), 84 (6), 82 (3.5), 81 (4.5), 69 (7), 68 (6), 67 (6), 59 (6), 56 (6), 55 (14), 53 (4.5), 45 (4.5), 44 (6), 43 (3.5), 42 (19), 41 (29), 40 (4.5), 39 (8); mass spectrum (70 eV) *m/e* 255.1113 (calcd for $C_{12}H_{17}NO_5$, 255.1107).

The progress of a reaction mixture containing 127 mg of **22**, 142 mg of DMAD, and 730 μl of dioxane at 35° was followed by NMR. On addition of 70 μl of water, the rate of disappearance of **22** increased about tenfold and was complete within 3 hr. No **28** was formed under these conditions.

Formation of 31 from 1b and DMAD in the Presence of Water at 25°. A solution composed of 128 mg (0.85 mmol) of **1b**, 114 mg (0.80 mmol) of DMAD, and 14.5 mg (0.80 mmol) of water was left at room temperature for 11 hr. The NMR spectrum indicated complete consumption of imino ether **1b**. The sample was evaporated in vacuo and chromatographed on alumina with dichloromethane elution. Vacuum distillation gave 80 mg (46%) of product **31**: bp 90–100° (0.15 mm); ir (neat) 3330, 2940, 1745, 1665, 1600 cm^{-1}; NMR (CCl_4) δ 1.32 (s, 9 H), 3.57 (s, 3 H), 3.75 (s, 3 H), 4.65 (s, 1 H), 8.22 (br s, 1 H, NH) along with a minor (20%) isomer **32** δ 1.35 (s, 9 H), 3.54 (s, 3 H), 3.73 (s, 3 H), 4.69 (s, 1 H); mass spectrum (70 eV) *m/e* 215.1161 (calcd for $C_{10}H_{17}NO_4$, 215.1157); *m/e* (rel intensity) 215 (M^+, 42), 200 (33), 184 (16), 168 (25), 160 (25), 159 (83), 140 (25), 128 (100), 101 (42), 100 (83), 68 (66), 57 (100), 41 (92).

When the reaction was monitored by NMR at 35° on a mixture 0.82 *M* in **1b** and 1.16 *M* in DMAD in dioxane, the rate of disappearance of **1b** increased tenfold on addition of 10% water with complete disappearance occurring within 40 min.

The reaction of **1a** under identical conditions gave the same ratio of products with the same ir and NMR spectra. Products **31** and **32** were independently synthesized by treating DMAD with *tert*-butylamine in ether at room temperature[29a] and found to have identical ir and NMR spectra. The initial mixture at room temperature contained almost exclusively **31**, which was converted on heating at 80° in CCl_4 for 2 hr to a 10:1 mixture of **32** to **31** at equilibrium.

Formation of 31 from 1b and DMAD in the Presence of Water at 100°. A solution composed of 413 mg (3.20 mmol) of **1b** and 460 mg (3.24 mmol) of DMAD in 10 ml of 2% aqueous dioxane was refluxed for 24 hr. Vacuum distillation afforded 376 mg (59% yield) of a mixture of products **31** (80%) and **32** (20%), bp 70–80° (0.07 mm).

Following the procedure above, but with excess DMAD, 375 mg (2.90 mmol) of **1b** and 831 mg (5.85 mmol) of DMAD gave 254 mg (29%) of product **33**: bp 150–160° (0.3 mm); ir (neat and dilute CCl_4) 3220, 2940, 1745–1730, 1660, 1598 cm^{-1}; uv (ethanol) 229 nm (ϵ 8200); NMR (CCl_4) δ 1.35 (s, 9 H), 3.64 (s, 6 H), 3.68 (s, 3 H), 3.74 (s, 3 H), 6.61 (s, 1 H), 9.0 (s, 1 H, NH); mass spectrum (70 eV) *m/e* 357.1425 (calcd for $C_{16}H_{25}NO_8$, 357.1424); *m/e* (rel intensity) 358 (7), 357 (M^+, 40), 342 (5), 326 (7), 301 (14), 298 (3), 278 (5), 270 (7), 243 (10), 242 (100), 238 (18), 211 (8), 210 (82), 182 (5), 178 (15), 150 (7), 59 (12), 58 (3), 57 (25), 41 (18), 39 (3). Product **33** was independently synthesized by treating 210 mg (2.86 mmol) of *tert*-butylamine with 813 mg (5.70 mmol) of DMAD in dichloroethane at 90° for 16 hr. Chromatography on alumina using carbon tetrachloride elution and vacuum distillation (bp 106°, 0.1 mm) gave 840 mg (83%) of **33**.

Reaction of 32 and DMAD. A solution of 561 mg (2.61 mmol) of **32** and 372 mg (2.62 mmol) of DMAD was refluxed in dioxane for 24 hr and gave 658 mg (70%) of **33** after chromatography and vacuum distillation.

Attempted Reaction of Water and Adduct 2. Heating adduct **2** in aqueous dioxane for 24 hr produced no noticeable decomposition of **2** or formation of product **33.**

Attempted Reaction in Water and Imino Ether 6b. Heating imino ether **6b** in aqueous dioxane for 0.5 hr produced no noticeable reaction as ascertained by NMR. No reaction was detected on standing at room temperature for 2 days.

Hydrolysis of Imino Ether 1b. Heating 103 mg (0.80 mmol) of **1b** and 14.5 mg (0.80 mmol) of water in 1 ml of dioxane for 3 hr at 100° in a sealed NMR tube produced 42% of *N*-*tert*-butylformamide and 15% of *tert*-butylamine, with 42% unreacted **1b,** by NMR. No reaction was detected by NMR upon leaving imino ether **1b** with aqueous dioxane at room temperature for 16 hr.

Acknowledgment. We acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No.—**1a,** 49680-36-6; **1b,** 55236-60-7; **2a,** 55236-61-8; **2b,** 55236-62-9; **6a,** 23974-38-1; **6b,** 23974-43-8; **7a,** 55236-63-0; **7b,** 55236-64-1; **8a,** 55236-65-2; **8b,** 55267-65-7; **12,** 52856-04-9; **13,** 55236-66-3; **14,** 55236-67-4; **15a,** 49680-46-8; **15b,** 23974-48-3; **16a,** 55236-68-5; **16b,** 55236-69-6; **17,** 55236-70-9; (*Z*)-**18,** 55236-71-0; (*E*)-**18,** 55236-72-1; **20a,** 5264-35-7; **20b,** 5264-35-7; **21,** 1120-64-5; **22,** 2525-16-8; **24,** 55236-73-2; **25a,** 55236-74-3; **25b,** 55236-75-4; **26,** 55236-76-5; **27,** 55236-77-6; **28,** 55236-78-7; **31,** 24427-31-4; **32,** 55236-58-3; **33,** 55236-59-4; DMAD, 762-42-5.

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Aromatic *N*-Oxides. IX. Reaction of *N*-Alkoxy-2- (and 4-) alkylpyridinium Salts with Base[1]

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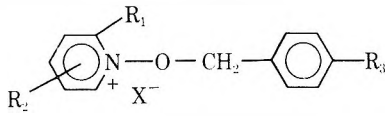
The preparation of a number of *N*-benzyloxy- and *N*-*p*-nitrobenzyloxy-2- and 4-alkylpyridinium bromides and perchlorates are described. When these salts were treated with base, the decomposition products were primarily the corresponding alkylpyridines and benzaldehyde or *p*-nitrobenzaldehyde and in the case of the *N*-alkoxy-2-methyl- or 4-methylpyridinium salts 1-aryl-2-(2- or 4-pyridyl)ethanols **16–18** (ca. 25%) were also formed. Evidence is offered that formation of alcohols **16–18** proceeds via anhydro base **20** and **23** intermediates.

The reaction of aromatic *N*-oxides (e.g., pyridine *N*-oxide) with alkyl halides, alkyl sulfonates, or alkyl sulfates to produce *N*-alkoxy ammonium salts (e.g., *N*-methoxypyridinium methosulfate) has appeared in numerous reports in the literature.[3–14] These salts are known to undergo several types of reactions,[10] one of which is an alkaline decomposition to yield the corresponding nitrogen heterocycle and an aldehyde.[4–7,11–13] The initial report of this reaction

Table I
***N*-Benzyloxy-2- and -4-alkylpyridinium Salts**

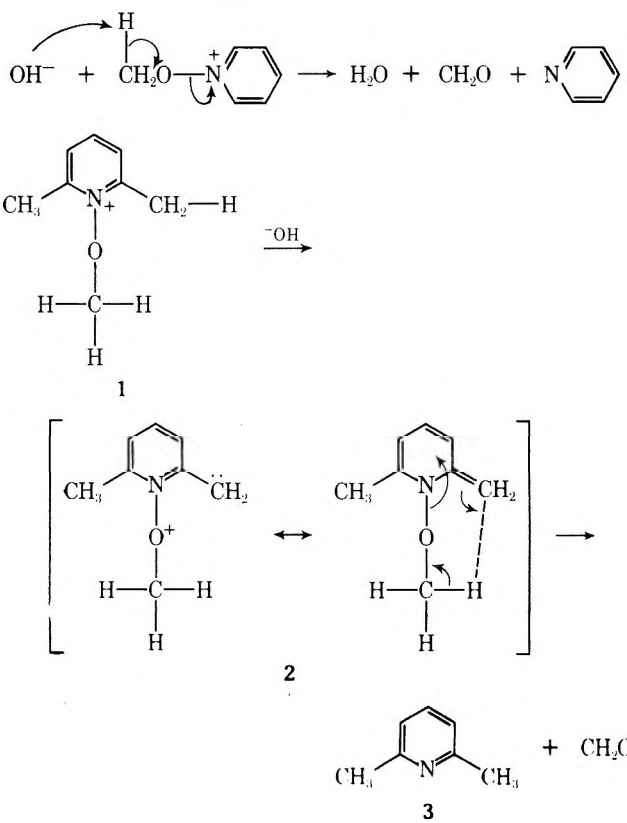


No.	Compd[a] R_1	R_2	R_3	X	Solvent[b]	Reaction conditions: Time, hr	Temp, °C	% yield
4	CH_3	H	H	Br	A	5	Reflux	96.5
5	CH_3	H	H	ClO_4				100
6	CH_3	H	NO_2	Br	B	0.5	100	53
7	C_2H_5	H	H	Br	A	1.5	*c*	83
8	C_2H_5	H	H	ClO_4				100
9	$C_6H_5CH_2$	H	H	Br	B	2.5	60–70	38
10	H	4-CH_3	H	Br	C	5	Reflux	76
11	H	4-CH_3	H	ClO_4				100
12	H	4-CH_3	NO_2	Br	B	1	70–75	75
13	H	4-$C_6H_5CH_2$	H	Br	B	1.5	60–70	85
14	CH_3	4-CH_3	H	Br	D	0.5	*c*	83
15	CH_3	6-CH_3	H	Br	A	1.5	*c*	75

[a] Analytical data (C and H) for compounds **4**, **5**, **6** (Br also), **8**, **11**, **14**, and **15** (N also) were all within 0.3%. [b] A = CH_3CN; B = CH_3NO_2; C = $CHCl_3$; D = $(C_2H_5)_2O$. [c] Room temperature.

by Henze[4] described the conversion of 1-methoxyquinolinium iodide by potassium hydroxide to quinoline and formaldehyde. Subsequently, Ochiai[5] and Katritzky[6] utilized this reaction as a method for nonreductive deoxygenation of pyridine *N*-oxide derivatives; and Feely, Lehn, and Boekelheide[7] applied this reaction as a method for the synthesis of aromatic aldehydes.

The mechanistic explanation of the alkaline decomposition of 1-methoxypyridinium methosulfate is generally viewed as a base-catalyzed E-2 type elimination.[7,10] How-

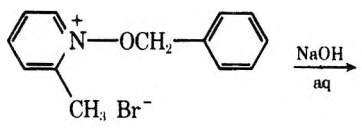


ever, Marmer and Swern[13] have shown that the reaction of 1-methoxy-2,6-dimethylpyridinium ion (**1**) (and most probably *N*-alkoxy-2-alkylpyridinium ions in general) and base proceed through the intermediate *N*-alkoxy anhydro base **2** to produce **3** and formaldehyde. We wish to report our results in this area which lend further support to Marmer and Swern's work and describe a new competing reaction.

The reaction of benzyl bromide or *p*-nitrobenzyl bromide and 2- or 4-alkylpyridine *N*-oxides was carried out in acetonitrile, nitromethane, chloroform, or ether under various conditions of temperature and time and gave *N*-benzyloxy-2- and 4-alkylpyridinium bromides in 53–96% yield (see Table I). The structures of the salts were established by their ir, NMR and mass spectra, and by elemental analysis. In the case of **4**, **7**, and **10** the bromide salts were converted to the corresponding perchlorates **5**, **8**, and **11** to facilitate elemental analyses. The mass spectra of the salts showed the molecular ion for the *N*-alkoxy cation in **4**, **9**, and **10**; however, the primary mode of fragmentation involved first reversal of the salt to the precursors benzyl bromide and the alkylpyridine *N*-oxide, then fragmentation of these latter two compounds. All of the *N*-benzyloxy salts exhibited molecular ion peaks at *m/e* 172 ($C_6H_5CH_2{}^{81}Br$) and 170 ($C_6H_5CH_2{}^{79}Br$) along with the characteristic tropylium ion at *m/e* 91 ($C_7H_7^+$),[15] while the fragmentation of the alkylpyridine *N*-oxide was identified by its M^+ and $(M - 16)^+$ peaks.

In general those salts with methyl or ethyl substituents on the pyridine ring were formed easily and in high yield, while considerable difficulty was encountered in the preparation of 2-benzylpyridinium salts regardless of the *N*-alkoxy group (e.g., methoxy, ethoxy, propoxy, butoxy, or benzyloxy). In the latter case inspection of models suggests that steric hindrance by the 2 substituent was probably a major inhibiting factor. In addition the 2- or 4-benzylpyridine salts **9** and **13** (an oil) reverted to starting materials on standing in solution (H_2O or D_2O); in contrast, **4** was stable in D_2O for periods up to at least 1 week.

The reaction of *N*-benzyloxy-2-methylpyridinium bromide (**4**) in aqueous sodium hydroxide gave 2-methylpyridine (68%) and benzaldehyde (70%) as previously reported by Boekelheide[7] but also produced a new product, 1-phenyl-2-(2-pyridyl)ethanol (**16**) (28% yield). 2-Methylpyridine and benzaldehyde were identified by comparison of their NMR spectra with those of an authentic sample and by preparation of known derivatives (picrate and 2,4-dinitrophenylhydrazone, respectively), while the known alcohol **16** was identified by its melting point and its ir and NMR



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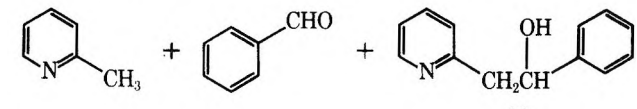

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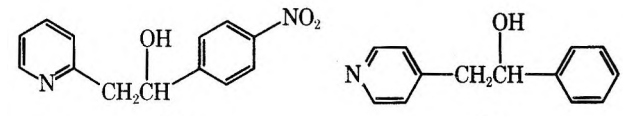
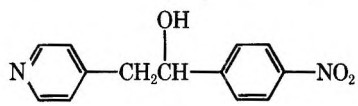


17 18



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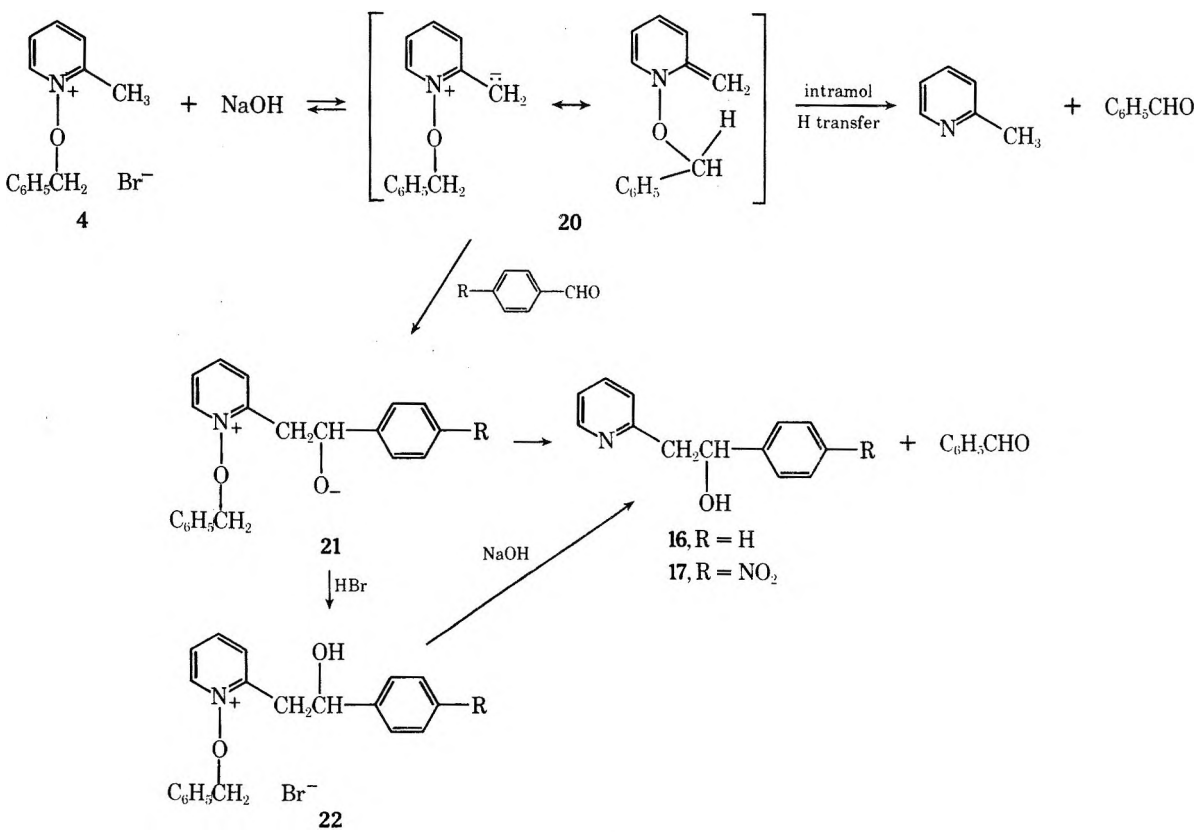
spectra. Inverse addition, namely salt solution added to sodium hydroxide solution, gave the same products in comparable yield, and variation of the reaction medium had little effect on the yield of alcohol **16** (23–30% yield) with the best alcohol yield obtained in dioxane–water (2:1).

Results for the alkaline decomposition of the other *N*-alkoxy salts are summarized in Table II. Condensation reactions were observed when a single methyl group was in the 2 or 4 position of the pyridine ring and gave alcohols **17**, **18**, and **19** identified by comparison of their melting points with literature values and by their ir and NMR spectra. *N*-Benzyloxy-2-ethyl-, 2,4-dimethyl-, and 2,6-dimethylpyridinium bromides produced only benzaldehyde and the corresponding alkylpyridine, while *N*-benzyloxy-2- and 4-benzylpyridinium bromides reverted to the corresponding benzylpyridine *N*-oxide.

Several reaction pathways were considered for the origin of the arylpyridylethanols **16–19**. First, the possibility of a base-catalyzed condensation of the products methylpyridine and benzaldehyde was excluded. The exposure of 2-methylpyridine and benzaldehyde or *p*-nitrobenzaldehyde to base under the same conditions as used in the alkaline decomposition of *N*-benzyloxy-2-methylpyridinium bromide did not produce alcohols **16** or **17** but gave near-quantitative yields of unreacted starting material. The preferred route in explaining the origin of alcohols **16–19** entails the formation of an intermediate anhydro base **20** which can condense with benzaldehyde, formed in a competing or subsequent reaction, to produce *N*-benzyloxy-2-(2-phenyl-2-hydroxyethyl)pyridinium salt (**21**). A base-catalyzed decomposition of **21** would form 1-phenyl-2-(2-pyridyl)ethanol (**16**) and benzaldehyde. Anhydro base **20** becomes especially attractive as an intermediate, since Marmer and Swern[13] have established that *N*-alkoxy anhydro bases are intermediates in the main reaction pathway leading to the alkylpyridine and aldehyde. Thus **20** may also undergo an intramolecular hydrogen transfer of a benzylic proton to the side chain methylene with elimination of benzaldehyde and formation of 2-methylpyridine. Therefore **20** can serve as a common intermediate, undergoing two competing reactions, which leads to the formation of all the observed reaction products.

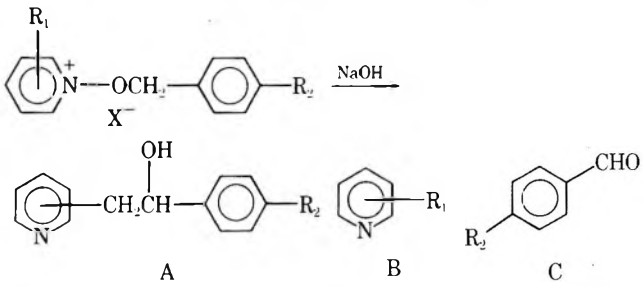
In an attempt to increase the yield of alcohol **16** the reaction of **4** and base was performed in the presence of added excess benzaldehyde; however, only a small increase of **16** was observed. When *p*-nitrobenzaldehyde was added to the reaction of **4** and base, *p*-nitrobenzaldehyde reacted, in preference to benzaldehyde, with intermediate **20** to form the dipolar ion **21**, R = NO_2, which proceeded to alcohol **17** (10% yield) as the only alcohol product. Other products isolated from this reaction were benzaldehyde (80%), 2-methylpyridine (58%), unreacted *p*-nitrobenzaldehyde (70%), and, a real bonus, *N*-benzyloxy-2-(2-*p*-nitrophenyl-2-hydroxyethyl)pyridinium bromide (**22**, R = NO_2)



4 20 21 22

16, R = H
17, R = NO_2

Table II
Reaction of *N*-Alkoxy-2- (and 4-) alkylpyridinium Salts with Sodium Hydroxide

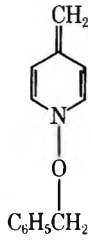


Compd	NaOH, (mmol)[a]	mmol	Solvent[b]	Time, hr	% yield A	B	C
4	(17.8)	18	A	1	29[k]	68[l]	70[m]
4	(17.8)[c]	18	A	1	26.5	67	60
4	(17.8)[d]	18	B	1	10	58	80[e,f]
4	(17.8)[d]	18	B	0.5			[g]
6	(4.6)	4.6	B	10	15[n]	62	60[o]
7	(10)	10	A	0.5		70[p]	100
9	(17.5)	19	A	1			[h]
10	(17.8)	18	A	1	18[q]	50[r]	59
12	(15.4)	16	B	1	23[s]	47	24[i]
13	(17.5)	19	A	1			[h]
14	(17.0)	18	A	1		84[t]	70
15	(6.8)	7.0	A	1		95[u]	98
22[v]	(4.5)	6.0	B	1	60		59[j]

[a] All reactions were carried out at room temperature. [b] A = H_2O; B = dioxane–H_2O (2:1). [c] This reaction was carried out by the addition of the salt 4 to NaOH. [d] The reaction was performed in the presence of *p*-nitrobenzaldehyde (17.8 mmol). [e] In addition to 80% benzaldehyde, 70% *p*-nitrobenzaldehyde, was recovered. [f] A new product, *N*-benzyloxy-2-(2-*p*-nitrophenyl-2-hydroxyethyl) pyridinium bromide (22), was formed in 13.5% yield. [g] The yield of 22 was 27.6%. Isolation of the other products was not attempted. [h] The corresponding *N*-oxide was recovered in near-quantitative yield. [i] Ca. 50% of the material was an unworkable tar. [j] Starting material, compound 22, was recovered in 36% yield. [k] Registry no., 2294-74-8. [l] Registry no., 109-06-8. [m] Registry no., 100-52-7. [n] Registry no., 20151-01-3. [o] Registry no., 555-16-8. [p] Registry no., 100-71-0. [q] Registry no., 20151-37-5. [r] Registry no., 108-89-4. [s] Registry no., 20151-33-1. [t] Registry no., 108-47-4. [u] Registry no., 108-48-5. [v] Registry no., 55400-85-6.

(13.5%). The yield of **22**, R = NO_2, was increased to 28% when the reaction time was cut in half. Identification of **22**, R = NO_2, followed from elemental analysis, ir, and mass spectral data. The reaction of **22**, R = NO_2, in base for 1 hr at room temperature gave 59% yield of benzaldehyde, 60% yield of 1-*p*-nitrophenyl-2-(2-pyridyl)ethanol, and 36% unreacted **22**, R = NO_2. These results clearly support the above proposed sequence **20** → **21** or **22** → **16** or **17** as a reasonable pathway to these alcohols. Furthermore, the isolation of **22**, R = NO_2, can be viewed as trapping the intermediate anhydro base **20**, thus lending additional support to the Marmer–Swern mechanism of initial anhydro base formation.

The formation of 1-phenyl-2-(4-pyridyl)ethanol (**18**) and the *p*-nitro alcohol **19** from the base-catalyzed reaction of *N*-benzyloxy- and *N*-*p*-nitrobenzyloxy-4-methylpyridinium bromides can be explained as above involving an anhydro base intermediate **23**. However, the intramolecular hydrogen transfer pathway available for the fragmentation of **20** to form 2-methylpyridine and benzaldehyde is not feasible for **23** to provide 4-methylpyridine and benzaldehyde. This leaves open the possibility of a base-catalyzed E-2 elimination reaction of the *N*-benzyl-4-methylpyridinium cation or of a bimolecular fragmentation of **23** initiated by either hydroxide ion or another molecule of anhydro base **23**. Deuterium-labeled experiments, similar to those used by Marmer and Swern, may shed some light on this point.



23

Experimental Section

***N*-Alkoxy-2- (and 4-) alkylpyridinium Salts.** An equimolar mixture of the 2- or 4-alkylpyridine *N*-oxide and benzyl bromide in the appropriate solvent (see Table I) was allowed to react for the specified time and temperature. The reaction mixture was cooled in an ice bath and the solid was filtered, washed with dry ether, and dried. In some cases the solvent of the reaction mixture was removed under reduced pressure and the residue was triturated or washed with ether, filtered, and dried.

The perchlorate salts were obtained by reaction of the *N*-benzyloxy-2- or 4-alkylpyridinium bromide in dilute hydrochloric acid with a saturated solution of sodium perchlorate. The resulting solution was filtered and dried.

Reactions of *N*-Alkoxy-2- (and 4-) alkylpyridinium Salts with Sodium Hydroxide. An appropriate volume of 1 *N* NaOH was added to a stirred solution of *N*-alkoxy-2- (or 4-) alkylpyridinium bromide (near equimolar quantities of salt and base were used, see Table II) in water or dioxane–water. The reaction mixture was stirred at room temperature for 1 hr and then acidified with 6 *N* HCl. After the acidified mixture was extracted with $CHCl_3$, the combined extracts were dried and the solvent was removed to give the aldehyde.

The acid aqueous phase was made slightly alkaline with solid $NaHCO_3$ and the precipitate was filtered and dried to give the 1-aryl-2-pyridylethanol.

The basic filtrate was extracted with $CHCl_3$, the extract was dried ($MgSO_4$) and filtered, and the solvent was removed to give the alkylpyridine.

Registry No.—**4**, 27371-06-8; **5**, 55400-75-4; **6**, 55400-76-5; **7**, 55400-77-6; **8**, 55400-78-7; **9**, 55400-79-8; **10**, 54531-19-0; **11**, 55400-81-2; **12**, 55492-94-9; **13**, 55400-82-3; **14**, 55400-83-4; **15**, 55400-84-5; 2-ethylpyidine *N*-oxide, 4833-24-3; 2-benzylpyridine *N*-oxide, 20531-86-6; 4-benzylpyridine *N*-oxide, 7259-53-2; 2,4-dimethylpyridine *N*-oxide, 1122-45-8; 2-methylpyridine *N*-oxide, 931-19-1; benzyl bromide, 100-39-0; sodium perchlorate, 7601-89-0; *p*-nitrobenzyl bromide, 100-11-8; 4-methylpyridine *N*-oxide, 1003-67-4; 2,6-dimethylpyridine *N*-oxide, 1073-23-0; 2,4-dinitrophenylhydrazone benzaldehyde, 1157-84-2.

Supplementary Material Available. The full experimental procedures for the preparation of **4–15**, their ir, NMR, and mass spectra data, and the reaction of these salts in base 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 $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2365.

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Dissociation Constants of the Amino-1,X-naphthyridines (X = 5, 6)

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The syntheses of 3-, 5-, and 8-amino-1,6-naphthyridines were accomplished. The second dissociation constants representing the transition from monocation to dication for 1,5- and 1,6-naphthyridine were determined. The first and second pK_a' values of the isomeric amino-1,5- and 1,6-naphthyridines were obtained by potentiometric and spectrophotometric methods. Only the 3-amino-1,5- and 3- and 8-amino-1,6-naphthyridines could be protonated a third time for which a third pK_a' value could be determined. The ultraviolet spectra of all the neutral molecules, mono-, di-, and, in the above-mentioned cases, trications, are presented.

The second dissociation constants of the aminoquinolines[3] and aminoisoquinolines[4] were determined previously. This was necessary in order to have a model with which the dissociation constants of the amino-1,5- and amino-1,6-naphthyridines could be correlated.

In the aminopyridines, aminoquinolines, and aminoisoquinolines, the first protonation occurs at the ring nitrogen. The pK_a' values for this process are most easily determined by potentiometric titration.[5] The second dissociation constants were obtained in highly acidic solutions. Therefore, ultraviolet spectroscopy is the method of choice[5] using the sulfuric acid–water H_0 scale[6,7] for solvent composition.

Amino-1,5-naphthyridines. Using the pK_a' values of aminopyridines and aminoquinolines as a basis, the possible position of the first protonation of the amino-1,5-naphthyridines can be advanced. The value for the first pK_a' of 1,5-naphthyridine in Table I is compared to the two values presently in the literature.[8,9] Our value (3.05 ± 0.02) was obtained by the same method that Albert and Phillips used. The pK_a' values for the amino isomers were calculated in the same manner and are also given in Table I. As in the cases of 4-aminopyridine[10] (Δ 4.02) and 4-aminoquinoline[11] (Δ 4.23), the basicity of the 4-amino-1,5-naphthyridine is enhanced (Δ 4.65) when all are compared to their parent ring systems. The 2-amino isomer (Δ 2.68) shows the same effect but to a lesser degree. The same trend is also seen with 2-aminopyridine[11] (Δ 1.63) and 2-aminoquinoline[11] (Δ 2.40). This similarity in basicity enhancement suggests that the first protonation occurs at the ring nitrogen of the substituted ring. In 3-amino-1,5-naphthyridine, the basicity is enhanced 1.85 pK units. This does not correlate with 3-aminopyridine[11] (Δ 0.75) and 3-aminoquinoline[11] (Δ 0.01), but does with 7-aminoquinoline[11] (Δ 1.71) and 3-aminoacridine[11] (Δ 2.44). This suggests that the site of the first protonation occurs at N-5—the nitrogen atom of the unsubstituted ring.

The second dissociation constants of 1,5-naphthyridine and its amino isomers appear in Table I. The antilogarithms of the individually calculated pK_a' values are averaged and converted back to a logarithm to obtain the particular pK_a' value. The maximum difference between this pK_a' value and the individually calculated values gives the "range". Albert[5] states that for a pK_a' value above 0, the range should not exceed ±0.06 units and below 0, ±0.1 units. Only in the 4-amino isomer could this satisfactory precision be obtained. Albert, Amarego, and Spinner[12] have observed similar results for the second dissociation constants of quinazoline (−5.5 ± 0.2), 4-methylquinazoline (−4.4 ± 0.2), and pyrimidine (6.3 ± 0.2). This discrepancy is probably due to the fact that the H_0 scale is based on primary aromatic amines as indicators and the function being protonated in our cases is most likely the second ring nitrogen. Arnett and Mach[13] have shown that aromatic tertiary amines do not follow the same H_0 scale as primary aromatic amines, but generate one of their own. A complete discussion of acidity functions and their abnormalities has been made by O'Conner[14] and references therein and Rochester.[15]

Only 3-amino-1,5-naphthyridine could be protonated a third time. The ultraviolet spectrum of the isolated trication at $H_0 = -10$ strongly resembles that of the dication of 1,5-naphthyridine. It has been shown with all of the aminoquinolines that the ultraviolet spectra of the isolated dications strongly resemble the quinolinium ion.[3] This would suggest that the primary amino group in 3-amino-1,5-naphthyridine is the final site of protonation. If the first protonation occurs at the 5 nitrogen as earlier suggested and the primary amino group is protonated last, then the 1 nitrogen in the substituted ring will be protonated in-between them. However, there is no evidence outside of the analogy of basicity enhancement for placing the first two protonations in this order for 3-amino-1,5-naphthyridine. In the 2- and 4-amino isomers this order should be reversed for the first two protonations.

Amino-1,6-naphthyridines. The values obtained for the first, second, and third dissociation constants for 1,6-naphthyridine and its amino isomers are given in Table II. The most basic site for protonation of 1,6-naphthyridine was shown by NMR spectroscopy to be N-6.[16] Its first pK_a' value, determined by potentiometric titration, was 3.78 ± 0.03.[17] The second dissociation constant, which was determined polarographically in aqueous perchloric acid, was found to be −0.30.[18] However, no range of values or temperature of solution was given. The second pK_a' value (−0.13 ± 0.06) was determined here with all proper specifications.

Table I
Dissociation Constants of Amino-1,5-naphthyridines

Compd[f]	First pK_a'[a]	Spread	Second pK_a'	Spread	Temp, °C	Third pK_a'	Spread	Temp, °C	Analytical wavelength, nm
1,5-NTD	3.05[b]	±0.02	−0.90[d]	±0.11	24.9 ± 1.0				313
2-A-1,5-NTD	5.73	±0.05	1.12[d]	±0.11	23.2 ± 1.0				352
3-A-1,5-NTD	4.90	±0.06	−0.60[e]	±0.15	24.0 ± 1.0	−6.86[e]	±0.03	25.0 ± 1.0	248[c]
4-A-1,5-NTD	7.70	±0.06	−1.54[e]	±0.05	23.2 ± 1.0				255

[a] All determined at 20.0 ± 0.1°. [b] 2.91 ± 0.03 at 20° potentiometrically (ref 8), 3.2 by partition coefficients (ref 9). [c] 248 used for both second and third pK_a' measurements, a peak is formed at 248 for the second pK_a' and disappears after the third protonation. [d] Concentration 4×10^{-5} *M*. [e] Concentration 2×10^{-5} *M*. [f] NTD = naphthyridine, X-A = position of substitution of amino group.

Table II
Dissociation Constants of Amino-1,6-naphthyridines

Compd	First pK_a'[a]	Spread	Second pK_a'	Spread	Temp, °C	λ, nm	Third pK_a'	Spread	Temp, °C	λ, nm
1,6-NTD[i]	3.78[b]	±0.03	−0.13[c,e]	±0.06	23.5	228				
2-A-1,6-NTD	6.38	±0.05	2.29[d]	±0.07	22.0	238				
3-A-1,6-NTD	4.89	±0.04	0.50[e]	±0.07	23.2	236	−5.18[h]	±0.08	24.5	423
4-A-1,6-NTD	7.53	±0.06	2.12[e]	±0.04	24.1	256				
5-A-1,6-NTD	6.45	±0.05	1.26[g]	±0.06	23.0	350				
8-A-1,6-NTD	5.23	±0.05	−1.07[f]	±0.06	22.0	272[j]	−7.31	±0.06	21.5	272[j]

[a] All determined at 20.0 ± 0.1°. [b] Reference 17. [c] Reference 18, −0.30 (no range given) determined polarographically in 1 *M* $HClO_4$. [d] Amine concentration 2.0×10^{-5} *M*. [e] Amine concentration 4.0×10^{-5} *M*. [f] Amine concentration 6.0×10^{-4} *M*. [g] Amine concentration 1.0×10^{-4} *M*. [h] Amine concentration 1.4×10^{-4} *M*. [i] See footnote *f*, Table I. [j] 272 nm was used for both second and third pK_a' measurements; a peak is formed at 272 nm for the second pK_a' and disappears after the third protonation.

Using the same criteria as in the amino-1,5-naphthyridines, the sites of protonation of the amino-1,6-naphthyridines can be put forward. In the case of 2-amino-1,6-naphthyridine, the first pK_a' value shows a basicity enhancement (Δ 2.60) compared to the parent compound—similar to a comparison of pK_a' values between 2-aminoquinoline and quinoline[11] (Δ 2.40). It appears that protonation then occurs at N-1. With 4-amino-1,6-naphthyridine, the basicity is enhanced by 3.75 p*K* units. This parallels, by a similar amount of enhancement, that found in 4-aminoquinoline (Δ 4.23) and 4-aminopyridine (Δ 4.72). Therefore, it is suggested that protonation takes place in the substituted ring. The first pK_a' value of the 5-amino isomer exhibits an enhanced basicity over that of 1,6-naphthyridine (Δ 2.67). This correlates with that seen with 1-aminoisoquinoline (Δ 2.22), indicating that proton addition is taking place at N-6. It can be strongly suggested that the first protonation occurs at the ring which directly tautomerizes with the substituted amino group.

The enhanced basicity of 3-amino-1,6-naphthyridine (Δ 1.11) correlates well with that of 7-aminoisoquinoline (Δ 0.80) but not 3-aminoquinoline (Δ 0.01). Therefore, the site of the proton addition probably occurs at N-6 rather than N-1. The pK_a' value of the 8-amino isomer shows basicity enhancement (Δ 1.45) similar to 3-aminoisoquinoline (Δ 0.88) but not 8-aminoquinoline (Δ −0.95). This implies that protonation also occurs at N-6.

Only the 3-amino- and 8-amino-1,6-naphthyridines could be protonated a third time. The ultraviolet spectra of these isolated trications in strongly acidic media resemble that of the 1,6-naphthyridinium ion. It was previously shown that the ultraviolet spectra of the isolated dications of the aminoquinolines and aminoisoquinolines strongly resemble the quinolinium and isoquinolinium ions, respectively.[3,4] This suggests that the final site of protonation is the primary amine group of these two isomers with the second proton being added at the second ring nitrogen atom—N-1.

A superficial comparison of the second pK_a' values in the 1,5- and 1,6-naphthyridines series shows that, in the latter case, a slightly high basicity of analogous amines is observed. This may be attributed to the position of substitution of the ring nitrogen atoms. Since there is a greater distance between these basic centers in the amino-1,6-naphthyridines, there will be less electrostatic interactions upon diprotonation.

Ultraviolet Spectra. The absorption spectra of the neutral molecules and the cationic species are in Table III.

Experimental Section

Potentiometric Determination of the Dissociation Constants. Potenti ometric dissociation constants were measured by established methods.[5]

Spectrophotometric Determination of the Dissociation Constants. The procedure used for the spectrophotometric determination of the second and third dissociation constants was the same as described previously[3,4] except that a Perkin-Elmer 350 ultraviolet–visible recording spectrophotometer was used for some values in the 1,6-naphthyridine series.

Synthesis and Purification of the Appropriate Amines. The melting points were taken on a Fisher-Johns melting point block. The NMR spectra were obtained with a Varian T-60 or a Varian HA-60 spectrometer. All NMR spectra were obtained in the solvent indicated and recorded in units of δ (parts per million). 4-Aminopyridine,[19] 1,5-naphthyridine[17] 2- and 4-amino-1,5-naphthyridine,[20] 3-amino-1,5-naphthyridine,[21,22] 1,6-naphthyridine,[23] and 2-amino-1,6-naphthyridine[22] were prepared and purified as before.

3-Amino-1,6-naphthyridine. 3-Bromo-1,6-naphthyridine[22] (565 mg, 2.70 mmol) and 160 mg of copper(II) sulfate were added to 90 ml of ammonium hydroxide (*d* 0.9). After heating at 160° for 40 hr, the reaction mixture was cooled and made strongly basic with potassium hydroxide pellets. The basic solution was continuously extracted with ether, whereupon the ether was evaporated and the residue (142 mg) sublimed at 150° (0.1 mm), yield 111 mg. The crude product was chromatographed on alumina (Brockman Grade III) with 5% anhydrous methanol–dichloromethane. The product fractions were combined and sublimed at 180°, yield 96 mg (25.8%), mp 223–224°.

Anal. Calcd for $C_8H_7N_3$: C, 66.21; H, 4.83; N, 28.97. Found: C, 66.06; H, 4.83; N, 29.01.

NMR (CF_3CO_2D) (external MeSi) 9.68 (s, 5-H), 9.25 (d, 7-H), 8.57 (s, 2-H, 4-H), 8.32 (d, 8-H), $J_{7,8}$ = 2.6 Hz.

Table III
Ultraviolet Spectra of Amino-1,X-naphthyridines (X = 5, 6)

Compd	Solvent	pH or H_0	Species[a]	Registry no.	λ_{max}, nm	Log ϵ_{max}
1,5-NTD	0.01 *N* NaOH	~12	N	254-79-5	248, 257, 266, 296, 302, 308	3.66, 3.65, 3.56, 3.73, 3.79, 3.76
	H_2O	5.0	N		249, 297, 303, 310	3.65, 3.75, 3.81, 3.79
	$HCl-H_2O$[6]	0.1	M	55570-43-9	268, 305, 313	3.54, 3.99, 4.04
	$H_2SO_4-H_2O$	1.0	M		265, 304, 312	3.57, 3.95, 3.98
	$H_2SO_4-H_2O$	−8.03	D	55570-44-0	262, 272, 301, 305, 313	3.58, 3.56, 4.06, 4.01, 4.26
2-A-1,5-NTD	0.01 *N* NaOH	~12	N	17965-80-9	277, 248, 258, 334	4.50, 3.73, 3.70, 3.92
	$H_2SO_4-H_2O$	3.0	M	55570-45-1	222, 328, 344	4.50, 4.16, 4.05
	$H_2SO_4-H_2O$	−10.0	D	55570-46-2	223, 336, 351	4.50, 4.25, 4.12
3-A-1,5-NTD	0.01 *N* NaOH	~12	N	14756-77-5	234, 260, 347	4.44, 3.66, 3.79
	$H_2SO_4-H_2O$	2.0	M	55570-47-3	241, 272, 392	4.42, 3.83, 4.01
	$H_2SO_4-H_2O$	−3.0	D	55570-48-4	248, 398	4.54, 3.81
	$H_2SO_4-H_2O$	−10.0	T	55570-49-5	261, 271, 306, 315	3.63, 3.60, 4.09, 4.25
4-A-1,5-NTD	0.01 *N* NaOH	~12	N	27392-68-3	243, 324	4.35, 3.76
	$H_2SO_4-H_2O$	3.0	M	55570-50-8	242, 294, 327	4.35, 3.68, 4.07
	$H_2SO_4-H_2O$	−6.0	D	55570-51-9	255, 288, 301, 355	4.41, 3.56, 3.65, 3.88
1,6-NTD	$NaOH-H_2O$	~12	N	253-72-5	314, 303, 254, 222	3.76, 3.81, 3.85, 4.65
		6.00[b]	N		314, 303, 248, 222	3.45, 3.50, 3.50, 4.34
	$H_2SO_4-H_2O$	1.50	M	19665-18-0	325, (316), (268), (258), 250	3.86, (3.90), (2.60), (3.75), 3.81
	$HCl-H_2O$	1.00[b]	M		309, 316, 267, 248	3.65, 3.23, 3.40, 3.50
	$H_2SO_4-H_2O$	−3.00	D	55570-52-0	(318), 311, (254), 228	(3.99), 3.04, (3.76), 4.60
2-A-1,6-NTD	KH_2PO_4–Borax	8.60	N	17965-81-0	316, (283), (272), 263, 237	3.79, (3.84), (3.83), 3.76, 4.93
	Na_2HPO_4–citric acid	4.60	M	55570-53-1	312, 298, 236	4.06, 4.14, 4.83
	$H_2SO_4-H_2O$	1.00	D	55570-54-2	(316), 305, 296, 268, (248), 238	(3.80), 4.02, 3.98, 3.75, (4.08), 4.63
3-A-1,6-NTD	$NaOH-H_2O$	~12	N	53454-30-1	343, (261), (241)	3.79, (4.08), (3.11)
	$H_2SO_4-H_2O$	2.80	M	55570-55-3	390, 284, 252, 236	3.46, 3.97, 4.28, 4.36
	$H_2SO_4-H_2O$	−3.20	D	55570-56-4	423, 305, 272, 243	3.54, 3.86, 3.99, 4.28
	$H_2SO_4-H_2O$	−9.95	T	55570-57-5	314	3.80
4-A-1,6-NTD	$NaOH-H_2O$	~12	N	28593-08-0	331, 242	4.01, 4.19
	Na_2HPO_4–citric acid	4.00	M	55570-58-6	333, 321, 243	4.14, 4.23, 4.18
	$H_2SO_4-H_2O$	−2.00	D	55570-59-7	348, 297, 256, 248	4.06, 3.68, 4.08, 4.11
5-A-1,6-NTD	$NaOH-H_2O$	~12	N	55570-60-0	350, 303, 243	3.65, 3.64, 4.26
	$H_2SO_4-H_2O$	3.00	M	55570-61-1	325, 287, (243), (234)	3.82, 3.81, (3.86), (4.03)
	$H_2SO_4-H_2O$	−3.00	D	55570-62-2	350, 295, (240), 245	3.84, 3.80, (3.97), 4.00
8-A-1,6-NTD	$NaOH-H_2O$	~12	N	55570-63-3	330, 248	3.48, 4.28
	$H_2SO_4-H_2O$	2.00	M	55570-64-4	356, 258	3.70, 4.11
	$H_2SO_4-H_2O$	−5.00	D	55570-65-5	327, 271, 241	3.40, 4.23, 4.10
	$H_2SO_4-H_2O$	−10.01	T	55570-66-6	(311), 304, (252)	(3.22), 3.30, (2.92)

[a] N = neutral molecule, M = monocation, D = dication, T = trication, NTD = naphthyridine, X-A = position of substitution of amino group. [b] At this pH the spectrum of the pure monocation is not completely isolated. The solvent the spectrum was taken in is not mentioned and it is assumed that $HCl-H_2O$ is the solvent as in some of Albert's other work. Reference 16.

4-Amino-1,6-naphthyridine. This isomer was used as previously prepared:[24] NMR (CF_3CO_2D) (external Me_4Si) 9.73 (s, 5-H), 8.49 (d, 7-H), 8.06 (d, 2-H), 7.97 (d, 8-H), 6.38 (d, 3-H), $J_{2,3}$ = 7.0, $J_{7,8}$ = 7.0 Hz.

5-Amino-1,6-naphthyridine. An admixture of 0.88 g (5.34 mmol) of 5-chloro-1,6-naphthyridine,[25] 1.0 g of acetamide, and 1.76 g of phenol was heated in an oil bath at 140°. Gaseous ammonia was passed into the melt for 1 hr. The temperature quickly rose to 190°, then dropped slowly to 160° and maintained there. After cooling to room temperature, the residue was mixed with 10 ml of

25% aqueous sodium hydroxide. The precipitated acetamide was removed by filtration and the filtrate was extracted with ether (4 × 25 ml). The dried (KOH pellets) ether extract was evaporated to dryness and the residue was vacuum sublimed at 165° (0.1 mm). A yellow solid was isolated (0.124 g) which had a melting point of 190–199°. This was dissolved in 5.0 ml of water and made strongly basic with sodium hydroxide pellets until precipitation was complete. The yellow precipitate was removed by vacuum filtration, washed with small amounts of ice-cold water, dried, and vacuum sublimed, yield 0.102 g, mp 204–206°. The alkaline solution from the ether extraction was made more basic with sodium hydroxide pellets until precipitation was complete. The precipitate was removed by filtration, washed with ice-cold water, dried, and vacuum sublimed at 165° (0.1 mm), yield 0.197 g, mp 204–206°, total yield 0.299 g (38.7%). Anal. Calcd for $C_8H_7N_3$: C, 66.21; H, 4.83. Found: C, 66.19; H, 4.86. NMR (CF_3CO_2D) (external Me_4Si): 9.55 (d, 2-H), 9.18 (d, 7-H), 8.25 (m, 3-H), 8.22 (d, 4-H), 7.42 (d, 8-H), $J_{2,3}$ = 8.0, $J_{3,4}$ = 8.0, $J_{7,8}$ = 6.4 Hz.

8-Amino-1,6-naphthyridine. Crude 8-bromo-1,6-naphthyridine[22] (8.25 g) was combined with 150 ml of ammonium hydroxide (*d* 0.9) and 1.0 g of anhydrous copper(II) sulfate. The reaction mixture was heated in a reaction bomb for 39 hr at 180°. The contents of the bomb were cooled, made strongly basic with potassium hydroxide pellets, and continuously extracted with ether for 48 hr. The ether was dried over anhydrous calcium chloride and evaporated away on a steam bath. Yield of crude material was 2.27 g. The crude product was chromatographed on a silica gel column with methanol–benzene (20:80). From the column, 1.34 g of purified amine was isolated which was recrystallized from absolute ethanol, yield 0.95 g, mp 135–137°. Anal. Calcd for $C_8H_7N_3$: C, 66.21; H, 4.83; N, 28.97. Found: C, 66.50; H, 5.04; N, 28.70. NMR (CF_3CO_2D) (external Me_4Si): 9.50 (d, 2-H), 9.17 (d, 4-H), 8.98 (s, 5-H), 8.35 (s, 7-H), 8.18 (m, 3-H), $J_{2,3}$ = 5.2, $J_{3,4}$ = 8.8 Hz.

Registry No.—3-Bromo-1,6-naphthyridine, 17965-73-0; ammonium hydroxide, 1336-21-6; 5-chloro-1,6-naphthyridine, 23616-32-2; 8-bromo-1,6-naphthyridine, 17965-74-1.

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(1) To whom inquiries should be addressed.
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Synthesis of Pyrimidine and Purine Nucleosides from L-Lyxopyranose and L-Arabinopyranose

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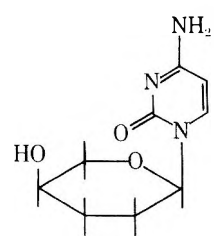
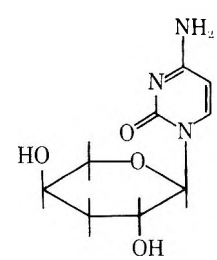
The syntheses of the following α-L-pentopyranosyl nucleosides are reported: 1-α-L-arabinopyranosyluracil (**5**), 1-α-L-lyxopyranosyluracil (**6**), 1-α-L-arabinopyranosylcytosine (**7**), 1-α-L-lyxopyranosylcytosine (**8**), 9-α-L-arabinopyranosyladenine (**13**), and 9-α-L-lyxopyranosyladenine (**16**). The uracil nucleoside **6** was converted to 2,2′-anhydro-1-α-L-xylopyranosyluracil (**9**), which was ring opened to give 1-α-L-xylopyranosyluracil (**10**). Deamination of **16** gave 9-α-L-lyxopyranosylhypoxanthine (**17**). Phosphorylation of the isopropylidene derivative of **16** followed by deblocking gave 9-(4-*O*-phosphoryl-α-L-lyxopyranosyl)adenine (**19**), which was deaminated to give 9-(4-*O*-phosphoryl-α-L-lyxopyranosyl)hypoxanthine (**20**).

Until recently, all known naturally occurring nucleosides have been of the D configuration.[1] Two cytosine nucleoside antibiotics, pentopyranine A and C, which are of the α-L configuration, have recently been isolated[2] from the fermentation broth of *Streptomyces griseochromogenes*. The syntheses of these nucleosides have been described by Fox and coworkers.[3] Several synthetic nucleosides derived from L sugars have previously been reported.[4] Baker and coworkers prepared a number of α-L-rhamnopyranosyl purines and pyrimidines.[5] In the present work α-L-lyxopyranosyl nucleosides (**2**) are viewed as being similar to natural ribonucleosides (**1**) in the configurations of the three hydroxyl groups of the carbohydrate moiety relative to the aglycon. Similarly, α-L-arabinopyranosyl nucleosides (**4**) may be considered as analogous to β-D-xylofuranosyl nucleosides (**3**) (Chart I). The structural relationship of these α-L-pentopyranosyl nucleosides to the nucleoside antibiotics pentopyranine A and C is also evident.



Pentopyranine A



Pentopyranine C

This report describes the synthesis of certain pyrimidine and purine α-L-pentopyranosyl nucleosides derived from

Chart I

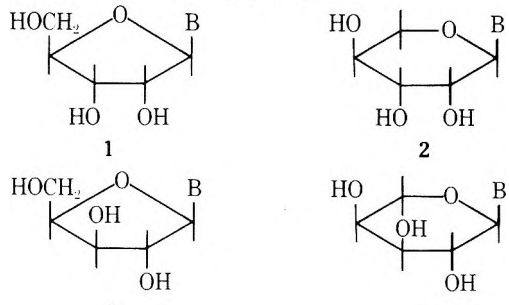
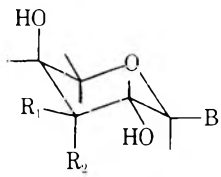


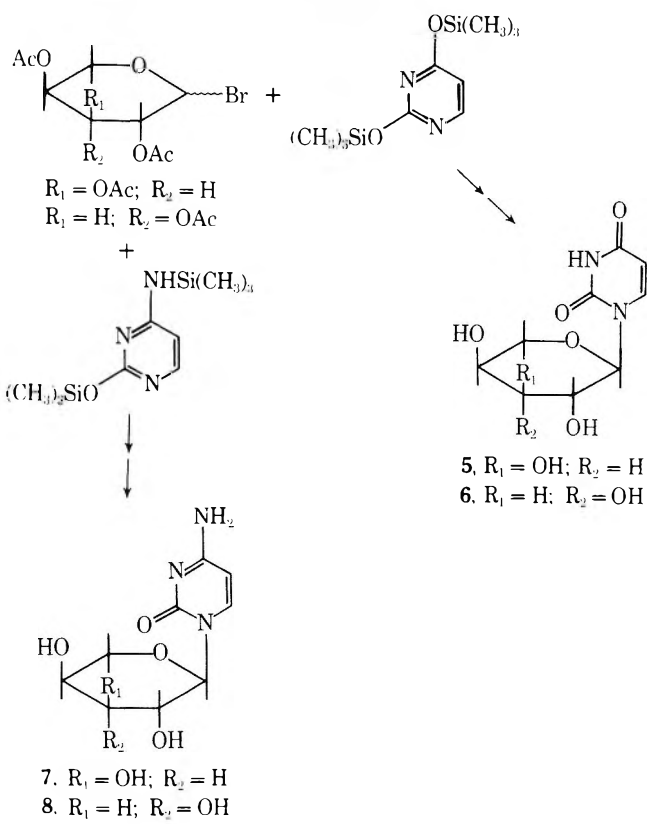
Chart II



5, R_1 = OH; R_2 = H
6, R_1 = H; R_2 = OH

L-lyxose and L-arabinose. The syntheses of the pyrimidine nucleosides were approached by glycosylation of the trimethylsilyl derivatives of uracil and cytosine with the appropriate blocked pyranosyl halides (Scheme I).

Scheme I



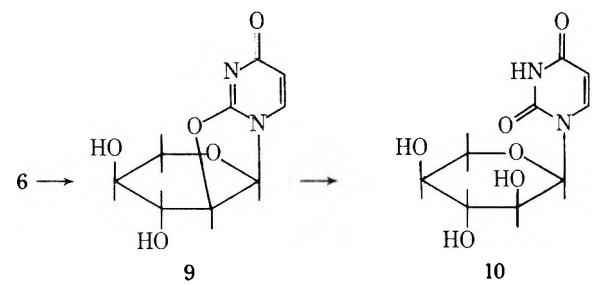
7, R_1 = OH; R_2 = H
8, R_1 = H; R_2 = OH

Treatment of the bis(trimethylsilyl) derivative of uracil with 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosyl bromide in acetonitrile at room temperature afforded, after deacylation of the blocked intermediate, 1-α-L-arabinopyranosyluracil (**5**). The same procedure with 2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl bromide provided the crystalline blocked nucleoside which was deacetylated to give 1-α-L-lyxopyranosyluracil (**6**). The ultraviolet spectra of both **5** and **6** are consistent with N-1 glycosylation of uracil. The coupling constants for the anomeric protons of **5** ($J_{1',2'}$ = 8.5 Hz) and **6** ($J_{1',2'}$ = 9.0 Hz) establish the α configuration for these nucleosides, since these values are consistent only with the trans-diaxial configuration for $H_{1'}$–$H_{2'}$ of the α anomer in the L series with the C1 conformation[6] (Chart II).

The syntheses of the cytosine L nucleosides were similar to those of the uracil nucleosides **5** and **6.** The treatment of the bis(trimethylsilyl) derivative of cytosine with the blocked arabinopyranosyl bromide afforded 1-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)cytosine,[7] which was isolated as the crystalline hemihydrobromide salt in 82% yield. This blocked nucleoside was treated with sodium bicarbonate and then deacetylated to provide 1-α-L-arabinopyranosylcytosine (**7**). The same glycosylation procedure using 2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl bromide again gave the blocked nucleoside as a crystalline hemihydrobromide salt. Deblocking of this intermediate gave 1-α-L-lyxopyranosylcytosine (**8**). The ultraviolet and NMR spectra of **7** and **8** are consistent with glycosylation at N-1 of cytosine and the α-anomeric configuration for these nucleosides.

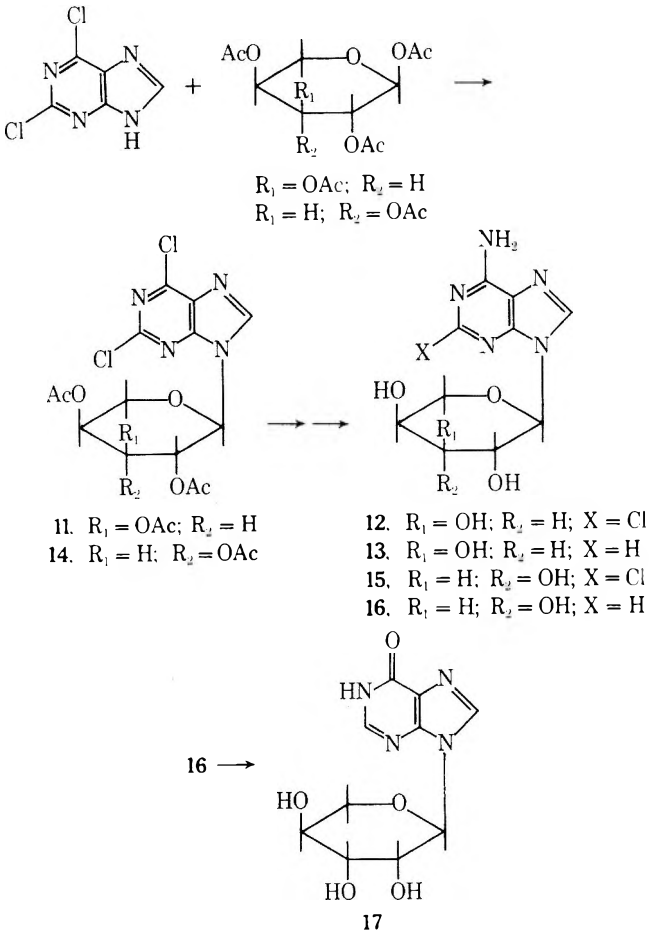
Cyclonucleoside formation of pyrimidine nucleosides is well known.[8] Certain 2,2′-anhydropyranosylpyrimidines have been obtained from the corresponding mesyl derivatives.[9] Treatment of nucleosides containing cis hydroxyl groups which are trans to the aglycon with diphenyl carbonate leads to 2,2′-anhydropyrimidine nucleosides.[10] This procedure with 1-(2-deoxy-β-D-ribopyranosyl)thymine has been reported to give the 2,3′-anhydronucleoside via the 3′,4′-cyclic carbonate.[11] Treatment of 1-α-L-lyxopyranosyluracil (**6**) with diphenyl carbonate and sodium bicarbonate in dimethylformamide afforded an anhydronucleoside **9** which exhibited an ultraviolet spectrum characteristic of a uracil cyclonucleoside. The structure of **9** was established as the 2,2′-anhydronucleoside and not the 2,3′-anhydro derivative as follows (Scheme II). Treatment of **9** with aqueous sodium hydroxide gave the uracil nucleoside **10.** Comparison of **10** with 1-α-L-arabinopyranosyluracil (**5**), which would result from opening of a 2,3′-anhydronucleoside, showed that these products are different. All properties of **10** are consistent with the 1-α-L-xylopyranosyluracil structure and the cyclonucleoside **9** is thus 2,2′-anhydro-1-α-L-xylopyranosyluracil.

Scheme II

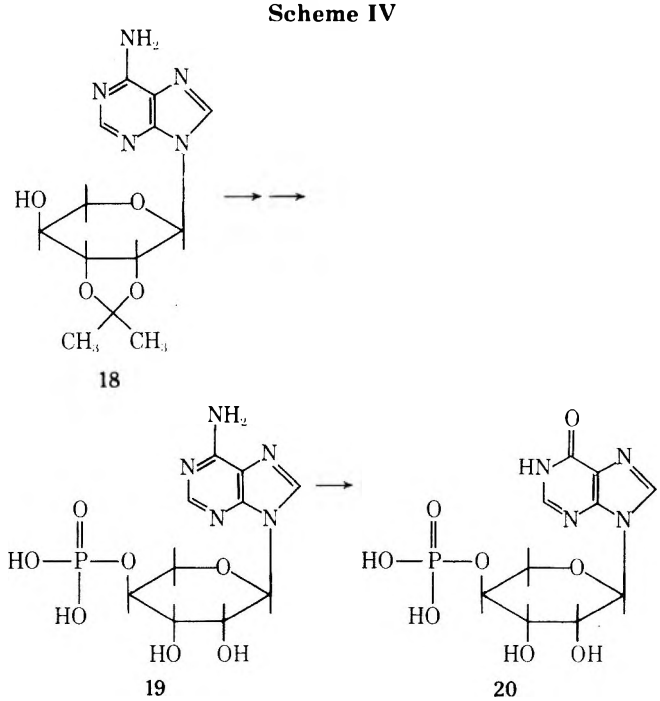


As an approach to the synthesis of purine nucleosides of L-arabinopyranose and L-lyxopyranose, the acid-catalyzed fusion procedure[12] with 2,6-dichloropurine and the tetra-*O*-acetyl sugars was employed (Scheme III). Fusion of 2,6-dichloropurine with 1,2,3,4-tetra-*O*-acetyl-α-L-arabinopyranose in the presence of an acid catalyst afforded crystalline 2,6-dichloro-9-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)purine (**11**). Treatment of **11** with methanolic ammonia gave 6-amino-2-chloro-9-α-L-arabinopyranosylpurine (**12**), which was dehalogenated to provide 9-α-L-arabinopyranosyladenine (**13**). Starting with 1,2,3,4-tetra-*O*-acetyl-α-L-lyxopyranose, the same sequence of reactions gave the blocked 2,6-dichloropurine nucleoside (**14**), the 6-amino-2-

Scheme III



Scheme IV



chloro derivative (**15**), and finally 9-α-L-lyxopyranosyladenine (**16**). A second route to **16** by glycosylation of N^6-benzoyladenine was investigated. Treatment of N^6-benzoyladenine with 2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl bromide in the presence of mercuric cyanide[13] gave N^6-benzoyl-9-(2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl)adenine. Removal of blocking groups gave 9-α-L-lyxopyranosyladenine (**16**) identical with the product obtained via the acid-catalyzed fusion procedure. A second nucleoside derivative from the glycosylation of N^6-benzoyladenine appears to be the debenzoylated derivative, since deblocking of this product also gave **16**. Deamination of the adenine nucleoside **16** with nitrous acid gave 9-α-L-lyxopyranosylhypoxanthine (**17**). The ultraviolet and NMR spectra ($J_{1',2'}$ = 8.0–10.0 Hz) of these purine nucleosides establish these products as 9-α-L-pyranosylpurines.

The synthesis of nucleotide analogs of certain of the pyranosyl nucleosides obtained in this work was of interest. The procedure of Yoshikawa et al.[14] was used to phosphorylate the 4′-hydroxyl group of 9-(2,3-*O*-isopropylidene-α-L-lyxopyranosyl)adenine (**18**). Thus, treatment of **18** with phosphoryl chloride in triethyl phosphate followed by removal of the isopropylidene group and purification of the product by DEAE chromotography gave 9-(4-*O*-phosphoryl-α-L-lyxopyranosyl)adenine (**19**) (Scheme IV). An additional nucleotide analog was obtained by deamination of **19** with nitrous acid, which gave 9-(4-*O*-phosphoryl-α-L-lyxopyranosyl)hypoxanthine (**20**).

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were obtained on a Hitachi Perkin-Elmer R20A spectrometer using DSS or Me_4Si as internal standards. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Thin layer chromatography was performed on silica gel F254 (Woelm) and components were visualized with a uv lamp (254 mμ) or by spraying the plates with 10% sulfuric acid in methanol and heating at ca. 110°. Activated charcoal for chromatography was Type UU (Barneby-Cheney, Columbus, Ohio). Trimethylsilyl derivatives were prepared using the general procedure of Wittenburg.[15] The heterocyclic bases were heated under reflux in an excess of hexamethyldisilazane with a catalytic amount of ammonium sulfate under anhydrous conditions for an average of 24 hr. The excess of hexamethyldisilazane was removed by distillation under vacuum and the residue (oil or crystalline solid) was used directly without further purification.

Tetra-*O*-acetyl-α-L-lyxopyranose[16] and tetra-*O*-acetyl-α-L-arabinopyranose[17] were prepared by stirring a mixture of the sugar and acetic anhydride in the presence of a catalytic amount of 4-dimethylaminopyridine[18] at room temperature until the sugar was completely dissolved. The solution was evaporated to dryness under reduced pressure and the tetra-*O*-acetyl derivatives[19] were crystallized from ethanol. Tri-*O*-acetyl-β-L-arabinopyranosyl bromide[20] and tri-*O*-acetyl-α-L-lyxopyranosyl bromide[21] were prepared by bubbling hydrogen bromide into an ice-cold solution of the tetra-*O*-acetyl derivative in dry dichloromethane for 40–45 min. The solution was kept at 0° for 1 hr and at room temperature for 15 min. The solvent was removed under diminished pressure. In both cases the bromo acetyl sugar crystallized. 2,3,4-Tri-*O*-acetyl-α-L-lyxopyranosyl bromide is reported in the literature[21] as a syrup. In our hands the product crystallized (mp 110–112°).

1-α-L-Arabinopyranosyluracil (5). A solution of tri-*O*-acetyl-β-L-arabinopyranosyl bromide[20] (3.87 g, 11.1 mmol) and the bis(trimethylsilyl) derivative of uracil [prepared from 1.35 g (12.0 mmol) of uracil] in dry acetonitrile (100 ml) was kept at room temperature for 6 days. The solution was evaporated to dryness and the residue was chromatographed on a column of silica gel (250 g) packed in chloroform. Elution with 20:1 chloroform–acetone provided the tri-*O*-acetyl derivative of **5** (3.4 g, 83%) as a chromatographically pure foam. This product (2.7 g, 0.73 mmol) was treated with methanol (100 ml) containing sodium methoxide (from 100 mg of sodium) at room temperature overnight. The solution was neutralized with Dowex 50 (H^+) and filtered and the solvent was removed. The product was crystallized from ethanol containing a few drops of water to give **5** (0.90 g, 50%): mp 254–255°; $[\alpha]^{25}D$ +86.4° (c 1, water); uv λ_{max} (pH 1) 257 nm (ϵ 10,850); λ_{max} (pH 11) 257 nm (ϵ 8200); NMR (DMSO-d_6–D_2O) δ 7.67 (d, 1, $J_{6,5}$ = 8.0 Hz, H-6), 5.73 (d, 1, $J_{5,6}$ = 8.0 Hz, H-5), 5.28 (d, 1, $J_{1'2'}$ = 8.5 Hz, H-1′).

Anal. Calcd for $C_9H_{12}N_2O_6$: C, 44.26; H, 4.95; N, 11.47. Found: C, 44.47; H, 5.02; N, 11.45.

1-α-L-Lyxopyranosyluracil (6). A solution of the bis(trimethylsilyl) derivative of uracil [from 2.46 g (22.0 mmol) of uracil] and tri-*O*-acetyl-α-L-lyxopyranosyl bromide[21] [from 6.36 g (20.0 mmol)

of the tetraacetate] in dry acetonitrile (150 ml) was kept at room temperature for 7 days. The solvent was removed and the residue was coevaporated successively with toluene and ethanol. The residue was dissolved in chloroform and the solution was washed with aqueous sodium bicarbonate and with water and dried over sodium sulfate. The solution was evaporated to dryness and the product was crystallized from ethyl acetate–cyclohexane to give 5.4 g (73%) of the tri-*O*-acetyl derivative of **6**: mp 208–209°; $[\alpha]^{25}D$ +73.8° (*c* 1, chloroform); uv λ_{max} (pH 1) 257 nm (ϵ 10,670); λ_{max} (pH 11) 256 nm (ϵ 7730); NMR ($CDCl_3$) δ 9.58 (br s, 1, NH), 7.37 (d, 1, $J_{6,5}$ = 8.0 Hz, H-6), 6.05 (d, 1, $J_{1',2'}$ = 9.0 Hz, H-1'), 5.80 (d, 1, $J_{5,6}$ = 8.0 Hz, H-5), 5.49 (t, 1, $J_{3,2} = J_{3,4}$ = 3.5 Hz, H-3'), 5.25 (q, 1, $J_{1'2'}$ = 9.0, $J_{2'3'}$ = 3.5 Hz, H-2'), 2.22 and 2.0 (2 s, 3 each, CH_3).

Anal. Calcd for $C_{15}H_{18}N_2O_9$: C, 48.65; H, 4.90; N, 7.57. Found: C, 48.73; H, 4.95; N, 7.49.

The blocked nucleoside (1.11 g, 3.0 mmol) was treated with methanol (75 ml) containing sodium methoxide (from 200 mg of sodium) at room temperature for 2 hr. The solution was neutralized with Dowex 50 (H^+), filtered, and evaporated to dryness. The product was crystallized from aqueous ethanol to give 0.63 g (86%) of **6**: mp 256–257°; $[\alpha]^{25}D$ +10° (*c* 1, water); uv λ_{max} (pH 1) 258 nm (ϵ 10,660); λ_{max} (pH 11) 258 nm (ϵ 8060); NMR (DMSO-d_6–D_2O) δ 7.72 (d, 1, $J_{6,5}$ = 8.0 Hz, H-6), 5.74 (d, 1, $J_{5,6}$ = 8.0 Hz, H-5), 5.68 (d, 1, $J_{1',2'}$ = 9.0 Hz, H-1').

Anal. Calcd for $C_9H_{12}N_2O_6$: C, 44.26; H, 4.95; N, 11.47. Found: C, 44.32; H, 4.91; N, 11.46.

1-α-L-Arabinopyranosylcytosine (7). A solution of the bis(trimethylsilyl) derivative of cytosine [from 2.44 g (22.0 mmol) of cytosine] and 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosyl bromide (6.78 g, 20.0 mmol) in dry acetonitrile (100 ml) was kept at room temperature for 3 days. The solvent was removed and the residue was coevaporated successively with toluene and ethanol. Ethanol was added to the residue and the resulting product was collected by filtration and dried over phosphorus pentoxide to give 6.7 g (82%) of the tri-*O*-acetyl derivative of **7** as the hemihydrobromide salt. Recrystallization from ethanol gave pure material: mp 246–248°; $[\alpha]^{25}D$ +60° (*c* 1, ethanol); uv λ_{max} (pH 1) 273 nm (ϵ 12,900); λ_{max} (pH 11) 265 nm (ϵ 8670); NMR (DMSO-d_6–D_2O) δ 7.82 (d, 1, $J_{6,5}$ = 8.0 Hz, H-6), 6.13 (d, 1, $J_{5,6}$ = 8.0 Hz, H-5), 5.95 (d, 1, $J_{1',2'}$ = 8.0 Hz, H-1').

Anal. Calcd for $C_{15}H_{19}N_3O_8 \cdot 0.5HBr$: C, 43.96; H, 4.79; N, 10.25; Br, 9.74. Found: C, 44.01; H, 4.77; N, 10.22; Br, 9.65.

The above blocked nucleoside (6.0 g, 14.6 mmol) was suspended in chloroform and the mixture was shaken with aqueous sodium bicarbonate. The chloroform solution was washed with water, dried over sodium sulfate, and evaporated to dryness to give 4.35 g (80%) of 1-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)cytosine as a homogenous foam. This product was treated with methanol saturated at 0° with ammonia and the solution was kept at 25° for 20 hr. The solvent was removed and the residue was coevaporated several times with methanol. The product was crystallized from ethanol to give 2.2 g (76%) of **7**: mp 266–267°; $[\alpha]^{25}D$ +99.9° (*c* 1, water ; uv λ_{max} (pH 1) 275 nm (ϵ 12,420); λ_{max} (pH 11) 267 nm (ϵ 8600); NMR (DMSO-d_6–D_2O) δ 7.63 (d, 1, $J_{6,5}$ = 8.0 Hz, H-6), 5.84 (d, 1, $J_{5,6}$ = 8.0 Hz, H-5), 5.41 (d, 1, $J_{1',2'}$ = 8.0 Hz, H-1').

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.51; H, 5.56; N, 17.32.

1-α-L-Lyxopyranosylcytosine (8). A solution of the bis(trimethylsilyl) derivative of cytosine [prepared from 2.44 g (22.0 mmol) of cytosine] and 2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl bromide [from 6.36 g (20.0 mmol) of the tetra -*O*-acetyl derivative] in dry acetonitrile (100 ml) was kept at room temperature for 3 days. The solvent was removed and the residue was coevaporated with toluene. Addition of ethanol to the residue gave a solid product (7.0 g, 85%). Recrystallization from ethanol provided the pure tri-*O*-acetyl derivative of **8** as the hemihydrobromide salt, mp 263–264°.

Anal. Calcd for $C_{15}H_{19}N_3O_8 \cdot 0.5HBr$: C, 43.96; H, 4.79; N, 10.25; Br, 9.74. Found: C, 44.09; H, 4.59; N, 10.12; Br, 10.00.

Chloroform was added to the above blocked nucleoside (7.0 g, 17.0 mmol) and the mixture was shaken with aqueous sodium bicarbonate. The chloroform solution was washed with water, dried over sodium sulfate, and evaporated to dryness to give 4.5 g (71%) of the tri-*O*-acetyl derivative of **8** as an amorphous solid. This product (4.0 g) was treated with methanolic ammonia (100 ml) at room temperature for 24 hr. The solvent was removed and the residue was dissolved in methanol. Silica gel (20 g) was added to the solution and the mixture was evaporated to dryness. The silica gel mixture was applied to a column of silica gel (80 g) packed in chloroform. Elution with chloroform (150 ml), ethyl acetate (500 ml), 9:1 ethyl acetate–methanol (1 l.), and 7:3 ethyl acetate–methanol (2 l.) provided, after crystallization from ethyl acetate–methanol, 2.0 g (75%) of **8**: mp 246–247° dec; $[\alpha]^{25}D$ +21.4° (*c* 1, water); uv λ_{max} (pH 1) 275 nm (ϵ 11,950); λ_{max} (pH 11) 235 nm (ϵ 7550), 266 (8150); NMR (DMSO-d_6–D_2O) δ 7.67 (d, 1, $J_{6,5}$ = 8.0 Hz, H-6), 5.88 (d, 1, $J_{5,6}$ = 8.0 Hz, H-5), 5.78 (d, 1, $J_{1',2'}$ = 9.0 Hz, H-1').

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.37; H, 5.48; N, 17.11.

2,2'-Anhydro-1-α-L-xylopyranosyluracil (9). A mixture of 1-α-L-lyxopyranosyluracil (**6**, 1.0 g, 4.0 mmol), diphenyl carbonate (1.14 g, 5.3 mmol), and sodium bicarbonate (20 mg) in dimethylformamide (2.0 ml) was heated in an oil bath at 150° for 20 min. The mixture was poured into ether (120 ml) and the gummy solid was dried over phosphorus pentoxide. Then the solid was dissolved in methanol and silica gel (5 g) was added. The mixture was evaporated to dryness, slurried in a small volume of chloroform, and applied to a column of silica gel (40 g) packed in chloroform. Elution with 9:1 chloroform–methanol (500 ml) and 7:3 chloroform–methanol (500 ml) gave a chromatographically pure solid that was crystallized from ethanol to yield 0.54 g (60%) of **9**: mp 214–216°; $[\alpha]^{25}D$ −126.5° (*c* 1, water); uv λ_{max} (pH 1) 249 nm (ϵ 8500), 224 (8500); λ_{max} (pH 11) 249 nm (ϵ 8500), 229 (6800); NMR (DMSO-d_6–D_2O) δ 7.85 (d, 1, $J_{6,5}$ = 7.5 Hz, H-6), 5.98 (d, 1, $J_{5,6}$ = 7.5 Hz, H-5), 6.00 (d, 1, $J_{1',2'}$ = 6.0 Hz, H-1').

Anal. Calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.39. Found: C, 47.90; H, 4.27; N, 12.39.

1-α-L-Xylopyranosyluracil (10). Compound **9** (0.23 g, 1.0 mmol) was treated with 0.2 *N* aqueous sodium hydroxide (10 ml) at room temperature for 3 hr. The reaction mixture was neutralized with Dowex 50 (H^+), filtered, and evaporated to dryness. The residue was coevaporated several times with ethanol and the product was crystallized from ethanol to give 0.15 g (62%) of **10**: mp 205–207°; $[\alpha]^{25}D$ +107.4° (*c* 1, water); uv λ_{max} (pH 1) 262 nm (ϵ 11,430); λ_{max} (pH 11) 262 nm (ϵ 8770); NMR (DMSO-d_6–D_2O) δ 7.81 (d, 1, $J_{6,5}$ = 8.0 Hz, H-6), 5.76 (d, 1, $J_{1',2'}$ = 5.0 Hz, H-1'), 5.64 (d, 1, $J_{5,6}$ = 8.0 Hz, H-5).

Anal. Calcd for $C_9H_{12}N_2O_6$: C, 44.26; H, 4.95; N, 11.47. Found: C, 44.05; H, 5.13; N, 11.28.

2,6-Dichloro-9-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)-purine (11). 2,6-Dichloropurine (4.7 g, 25.0 mmol) and 1,2,3,4-tetra-*O*-acetyl-α-L-arabinopyranose (7.95 g, 25.0 mmol) were heated in an oil bath at 160°. When the mixture melted, bis(*p*-nitrophenyl) phosphate (100 mg) was added and the heating was continued for 10 min under vacuum. The residue was dissolved in chloroform and the solution was washed with aqueous sodium bicarbonate and with water, dried over sodium sulfate, and evaporated to dryness. The product was crystallized from ethanol to give 3.7 g of **11**, mp 151–153°. The filtrate was concentrated to dryness and the residue (7 g) was dissolved in a small amount of chloroform and applied to a silica gel column (150 g) packed in chloroform. Elution with chloroform provided 2.5 g more of nucleoside that was recrystallized from ethanol. Total yield of recrystallized product **11** was 5.6 g (50%): $[\alpha]^{25}D$ +52.3° (*c* 1, chloroform); uv λ_{max} (ethanol) 272 nm (ϵ 10,300); NMR (DMSO-d_6) λ 8.98 (s, 1, H-8), 6.17 (d, 1, $J_{1',2'}$ = 8.0 Hz, H-1').

Anal. Calcd for $C_{16}H_{16}Cl_2N_4O_7$: C, 42.99; H, 3.58; N, 12.53; Cl, 15.88. Found: C, 43.11; H, 3.62; N, 12.46; Cl, 15.80.

6-Amino-2-chloro-9-α-L-arabinopyranosylpurine (12). A mixture of compound **11** (3.0 g, 6.7 mmol) and methanol saturated with ammonia at −20° (100 ml) was kept in a bomb at room temperature for 2 days. The solution was concentrated to almost dryness and the residue was coevaporated several times with ethanol. The ethanolic solution was concentrated to a small volume and kept at −5° overnight. The solid product was collected by filtration and recrystallized from water to give 1.6 g (80%) of **12**: mp >300°; $[\alpha]^{25}D$ +62.2° (*c* 1, dimethylformamide); uv λ_{max} (pH 1) 263 nm (ϵ 15,780); λ_{max} (pH 11) 263 nm (ϵ 15,780); NMR (DMSO-d_6–D_2O) δ 8.35 (s, 1, H-8), 5.32 (d, 1, $J_{1',2'}$ = 9.0 Hz, H-1').

Anal. Calcd for $C_{10}H_{12}ClN_5O_4$: C, 39.81; H, 4.00; N, 23.21; Cl, 11.75. Found: C, 39.60; H, 4.14; N, 23.08; Cl, 11.64.

9-α-L-Arabinopyranosyladenine (13). A mixture of compound **12** (0.90 g, 3.0 mmol), 10% palladium on charcoal (0.68 g), and sodium acetate (0.30 g) in water (600 ml) was shaken in a Parr hydrogenator at 52 psi for 24 hr at room temperature. The catalyst was removed by filtration and the solvent was evaporated to a small volume. The solution was percolated through a column of activated charcoal. The column was washed with water until salt free and the product was eluted with ethanol–water–concentrated ammonium hydroxide (10:10:1). The product was crystallized from ethanol to give 0.65 g (81%) of **13**, mp 269–270° dec. Another crystalline

form of **13** with mp 235–236° dec was obtained when the product was crystallized from aqueous ethanol: $[\alpha]^{25}D$ +35.3° (c 1, water); uv λ_{max} (pH 1) 255 nm (ϵ 14,500); λ_{max} (pH 11) 258 nm (ϵ 14,800); NMR (DMSO-d_6–D_2O) δ 8.22 and 8.34 (2 s, 2, H-2 and H-8), 5.40 (d, 1, $J_{1',2'}$ = 9.0 Hz, H-1').

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot H_2O$: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.20; H, 5.41; N, 24.46.

2,6-Dichloro-9-(2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl)purine (14). 2,6-Dichloropurine (4.70 g, 25.0 mmol) and tetra-*O*-acetyl-α-L-lyxopyranose (7.95 g, 25.0 mmol) were fused in the presence of bis(*p*-nitrophenyl) phosphate (100 mg) in an oil bath at 160° for 15 min under reduced pressure. The residue was dissolved in chloroform and the solution was washed with aqueous sodium bicarbonate and with water. The organic solution was dried over sodium sulfate, filtered, and evaporated to dryness. The residue was chromatographed on silica gel using chloroform as eluent. The appropriate fractions were collected and evaporated to dryness to give 5.6 g (50%) of chromatographically pure **14**. Recrystallization from ethanol gave an analytical sample: mp 177–179°; $[\alpha]^{25}D$ +72.4° (c 1, chloroform); uv λ_{max} (pH 1) 272 nm (ϵ 10,900); λ_{max} (pH 11) 272 nm (ϵ 13,370); NMR ($CDCl_3$) δ 8.30 (s, 1, H-8), 6.07 (d, 1, $J_{1',2'}$ = 9.0 Hz, H-1').

Anal. Calcd for $C_{16}H_{16}Cl_2N_4O_7$: C, 42.99; H, 3.58; N, 12.53; Cl, 15.88. Found: C, 43.03; H, 3.48; N, 12.49; Cl, 16.00.

6-Amino-2-chloro-9-α-L-lyxopyranosylpurine (15). Compound **14** (3.0 g, 6.7 mmol) was treated at room temperature for 4 days with methanol saturated with ammonia at −20°. The solution was concentrated to almost dryness and the residue was coevaporated several times with ethanol. The ethanolic solution was concentrated to a small volume and kept at −5° overnight. The product was collected by filtration to give 1.9 g (94%) of **14**. Recrystallization from water provided 1.6 g of analytical product: mp >300°; $[\alpha]^{25}D$ +26.4° (c 1, dimethylformamide); uv λ_{max} (pH 1) 263 nm (ϵ 15,500); λ_{max} (pH 11) 263 nm (ϵ 15,800); NMR (DMSO-d_6–D_2O) δ 8.37 (s, 1, H-8), 5.64 (d, 1, $J_{1',2'}$ = 9.0 Hz, H-1').

Anal. Calcd for $C_{10}H_{12}ClN_5O_4$: C, 39.81; H, 4.00; N, 23.21; Cl, 11.75. Found: C, 39.84; H, 4.13; N, 23.15; Cl, 11.92.

9-α-L-Lyxopyranosyladenine (16). Method 1. A mixture of **15** (0.80 g, 2.65 mmol), 10% palladium on charcoal (0.60 g), and sodium acetate (0.30 g) in water (600 ml) was shaken on a Parr hydrogenator at 53 psi for 24 hr. The catalyst was removed by filtration and the solution was evaporated to dryness. The residue was dissolved in a small volume of water and percolated through a column of activated charcoal. The column was washed with water until the eluate was salt free and the product was eluted with ethanol–water–concentrated ammonium hydroxide (10:10:1). Concentration of the appropriate fractions provided the product which was crystallized from ethanol to give 0.43 g (61%) of **16**: mp 179–181°, resolidification and final mp 249–250°; $[\alpha]^{25}D$ −19.3° (c 1, water); uv λ_{max} (pH 1) 256 nm (ϵ 14,900); λ_{max} (pH 11) 258 nm (ϵ 15,200); NMR (DMSO-d_6–D_2O) δ 8.40 and 8.26 (2 s, 2, H-2 and H-8), 5.77 (d, 1, $J_{1',2'}$ = 9.5 Hz, H-1').

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot H_2O$: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.30; H, 5.14; N, 24.50.

Method 2. A mixture of 2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl bromide [from 9.54 g (30.0 mmol) of tetra-*O*-acetyl derivative], mercuric cyanide (9.0 g), and anhydrous calcium sulfate (15.0 g) in dry nitromethane (100 ml) was added to a solution of N^6-benzoyladenine (7.17 g, 30.0 mmol) in dry nitromethane (250 ml). The mixture was refluxed for 3 hr excluding moisture and stirred at room temperature overnight. The reaction mixture was filtered hot and the filtrate was evaporated to dryness. The residue was treated with chloroform, the mixture was filtered, and the solution was washed with 30% aqueous potassium iodide and with water. The organic layer was dried over sodium sulfate and evaporated to a syrup. The residue was dissolved in chloroform containing a small amount of methanol and applied to a silica gel column (600 g), packed in chloroform. Elution with 25:1 chloroform–methanol provided as the faster moving product 5.3 g (35%) of N^6-benzoyl-9-(2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl)adenine: mp 206–207° (from ethanol); $[\alpha]^{25}D$ +43.6° (c 1, chloroform); uv λ_{max} (ethanol) 277 nm (ϵ 21,560).

Anal. Calcd for $C_{23}H_{23}N_5O_8$: C, 55.53; H, 4.66; N, 14.08. Found: C, 55.48; H, 4.79; N, 13.85.

Subsequent fractions from the column gave 4.0 g of the above blocked nucleoside mixed with another compound which was not characterized. Treatment of this mixture with sodium methoxide as described below gave only the deblocked nucleoside **16**, which indicates that the contaminant is 9-(2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl)adenine.

The above blocked (N^6-benzoyl) nucleoside (4.97 g, 10.0 mmol) was refluxed with methanol (200 ml) containing sodium methoxide (from 200 mg of sodium) for 45 min. The solution was neutralized with Dowex 50 (H^+), filtered, and evaporated to dryness. The product was crystallized from ethanol to give 2.3 g (86%) of 9-α-L-lyxopyranosyladenine (**16**), identical with the product obtained by method 1.

9-α-L-Lyxopyranosylhypoxanthine (17). To an ice-cooled suspension of **16** (1.0 g, 3.74 mmol) in water (10 ml) and glacial acetic acid (1.5 ml) was added sodium nitrite (1.3 g, 20.0 mmol). The mixture was stirred at room temperature for 48 hr. The solution was evaporated to dryness and coevaporated with acetic acid (5 ml). The residue was dissolved in water and applied to a column containing 35 ml of Dowex 50 (H^+). The column was eluted with water and the fractions containing uv-absorbing material were evaporated. The product was crystallized from aqueous ethanol to give 0.70 g (70%) of **17**: mp 232–233°; $[\alpha]^{25}D$ −16.4° (c 1, water); uv λ_{max} (pH 1) 248 nm (ϵ 12,830); λ_{max} (pH 11) 252 nm (ϵ 14,070); NMR (DMSO-d_6–D_2O) δ 8.34 and 8.15 (2, s, 2, H-2 and H-8), 5.74 (d, 1, $J_{1',2'}$ = 10.0 Hz, H-1').

Anal. Calcd for $C_{10}H_{12}N_4O_5$: C, 44.77; H, 4.51; N, 20.88. Found: C, 44.42; H, 4.68; N, 20.67.

9-(2,3-*O*-Isopropylidene-α-L-lyxopyranosyl)adenine (18). A mixture of **16** (3.0 g, 11.2 mmol), 2,2-dimethoxypropane (75 ml), acetone (75 ml), and 70% perchloric acid (1.5 ml) was stirred at room temperature for 3 hr. The solution was neutralized with 2 *N* aqueous potassium hydroxide and filtered. The filtrate was evaporated to dryness and the product was purified by column chromatography on silica gel (125 g) with 40:1 chloroform–methanol as eluent. Evaporation of fractions containing the product gave 3.2 g (88%) of **18** as amorphous material: $[\alpha]^{25}D$ −61.6° (c 1, chloroform); NMR (DMSO-d_6–D_2O) δ 8.52 and 8.29 (2 s, 2, H-2 and H-8), 5.60 (d, 1, $J_{1',2'}$ = 8.0 Hz, H-1'), 1.55 and 1.36 (2, s, 3 each, CH_3).

Anal. Calcd for $C_{13}H_{17}N_5O_4 \cdot H_2O$: C, 48.00; H, 5.89; N, 21.53. Found: C, 47.99; H, 5.91; N, 21.64.

9-(4-*O*-Phosphoryl-α-L-lyxopyranosyl)adenine (19). A solution of phosphoryl chloride (4.6 g, 30.0 mmol) and triethyl phosphate (35 ml) was cooled to 0° and 18[22] (2.62 g, 8.05 mmol) was added with stirring. The mixture was stirred at 0–5° for 18 hr and for 6 hr at room temperature. After cooling the mixture to 0°, ice water was added and the pH was adjusted to 3 with 2 *N* sodium hydroxide. The solution was extracted with chloroform to remove triethyl phosphate and the aqueous phase was desalted on a column of charcoal (80 ml). The column was washed with water until salt-free and the product was eluted with ethanol–water–concentrated ammonium hydroxide (1:1:1). Fractions containing the product were evaporated to dryness to give 2.5 g of crude material. TLC (silica gel, 7:3 acetonitrile–0.1 *N* aqueous ammonium chloride) indicated that this product was partially deisopropylidenated. Treatment of the product with 90% trifluoroacetic acid (30 ml) for 5 min at room temperature followed by evaporation of this mixture and several coevaporations of the residue with ethanol provided the crude deblocked phosphate mixed with the nucleoside **16**. This material was dissolved in water and the pH of the solution was adjusted to 8.5 with 1 *N* ammonium hydroxide. The solution was applied to a column of DEAE cellulose (HCO_3^-, 700 ml) and elution was with a gradient of water–0.3 *M* triethylamine bicarbonate (1000 ml each) followed by 0.3–0.4 *M* triethylamine bicarbonate (500 ml each). Fractions containing the nucleotide were evaporated to dryness and the residue was coevaporated several times with water. The product was dissolved in water and passed through a Dowex 50 (H^+) column (50 ml) using water to elute the nucleotide. The fractions containing the product were combined and evaporated to a small volume. Addition of ethanol gave crystalline **19** (1.58 g, 56%): mp 246–247° dec; uv λ_{max} (pH 1) 255 nm (ϵ 14,900); λ_{max} (pH 11) 258 nm (ϵ 15,200).

Anal. Calcd for $C_{10}H_{14}N_5O_7P$: C, 34.59; H, 4.06; N, 20.17. Found: C, 34.36; H, 4.08; N, 19.99.

9-(4-*O*-Phosphoryl-α-L-lyxopyranosyl)hypoxanthine (20). A suspension of **19** (0.35 g, 1.0 mmol) in acetic acid (10 ml) was cooled to 15° and a solution of sodium nitrite (0.10 g, 1.5 mmol) in water (0.5 ml) was added. The mixture was stirred in a stoppered flask for 48 hr at room temperature. The resulting solution was evaporated to dryness and the residue was dissolved in water. The solution was passed through a Dowex 50 (H^+) column (5 ml); the product was eluted with water. Fractions containing nucleotide were evaporated to dryness. The residue was dissolved in water and lyophilized to give **20** (0.22 g, 63%) as an amorphous product: uv λ_{max} (pH 1) 248 nm (ϵ 11,800); λ_{max} (pH 11) 252 nm (ϵ 12,700).

Anal. Calcd for $C_{10}H_{13}N_4O_8P\cdot0.5H_2O$: C, 33.62; H, 3.95; N, 15.69. Found: C, 33.57; H, 3.86; N, 15.64.

Registry No.—**5,** 55555-55-0; **5** triacetate, 55530-09-1; **6,** 55555-56-1; **6** triacetate, 55530-10-4; **7,** 55530-11-5; **7** triacetate, 55530-12-6; **7** triacetate ½ HBr, 55530-13-7; **8,** 55530-14-8; **8** triacetate, 55530-15-9; **8** triacetate ½ HBr, 55530-16-0; **9,** 55530-17-1; **10,** 55555-57-2; **11,** 55530-18-2; **12,** 55530-19-3; **13,** 17434-53-6; **14,** 55530-20-6; **15,** 55530-21-7; **16,** 55555-58-3; **17,** 55530-22-8; **18,** 55530-23-9; **19,** 55530-24-0; **20,** 55530-25-1; tri-*O*-acetyl-β-L-arabinopyranosyl bromide, 14227-90-8; bis(trimethylsilyl)uracil, 10457-14-4; tri-*O*-acetyl-α-L-lyxopyranosyl bromide, 55555-59-4; bis(trimethylsilyl)cytosine, 18037-10-0; 1,2,3,4-tetra-*O*-acetyl-α-L-arabinopyranose, 17080-99-8; tetra-*O*-acetyl-α-L-lyxopyranose, 2595-11-1; N^6-benzoyladenine, 4005-49-6; N^6-benzoyl-9-(2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl)adenine, 55530-26-2; 2,2-dimethoxypropane, 77-76-9; phosphoryl chloride, 10025-87-3; 2,6-dichloropurine, 1839-23-2.

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Synthesis of 5-Vinyluridine and 5-Vinyl-2′-deoxyuridine as New Pyrimidine Nucleoside Analogs

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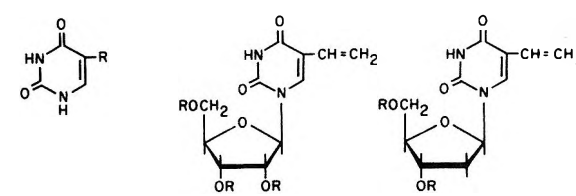
5-Formyluracil condensed smoothly with carbethoxymethylenetriphenylphosphorane to give *trans*- and *cis*-3-(5-uracilyl)acrylic acid ethyl ester (**3**). The analogous reaction, using methylenetriphenylphosphorane leading to 5-vinyluracil (**1**), failed. Alternatively, 5-chloromethyluracil was converted to the phosphonium salt **4** by reaction with triphenylphosphine. **4** readily condensed with paraformaldehyde in the presence of base to afford **1** in good yield. Condensation of the trimethylsilyl derivative of **1** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of stannic chloride gave, after deblocking, 5-vinyluridine (**7**). Similarly, condensation of the trimethylsilyl derivative **5** with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride, followed by transesterification with sodium methoxide, gave 5-vinyl-2′-deoxyuridine (**10**) and its α anomer **11**. The anomeric configuration was determined by NMR spectroscopy.

In view of the antiviral activity of 5-ethyl-2′-deoxyuridine,[1,2] which has been reported to be comparable to that of 5-iodo-2′-deoxyuridine[1,3] vs. Herpes Simplex and Vaccinia viruses, and that of other 5-alkylpyrimidine nucleosides,[4,5] it appeared worthwhile to synthesize 5-vinyluridine (**7**) and 5-vinyl-2′-deoxyuridine (**10**), whose 5 substituent has a van der Waals radius in-between that of the methyl and ethyl groups.

Although the necessary intermediate **1** had previously been prepared by dehydration[6] of 5-(1-hydroxyethyl)uracil, decarboxylation[7] of 3-(5-uracilyl)propenoic acid, and also by the base-catalyzed condensation[8] of 2-dimethoxymethyl-3-methoxybutyrate with urea, the yields were very low. Since a larger amount of **1** was needed for the synthesis of nucleosides, we sought to develop an improved procedure for the preparation of **1**.

Initially, we attempted the synthesis of **1** by condensation of methylenetriphenylphosphorane with 5-formyluracil (**2**), which was obtained by the oxidation of 5-hydroxymethyluracil.[9] However, this procedure failed to furnish **1** under a variety of experimental conditions. The failure of **2** to undergo Wittig reaction with methylenetriphenylphosphorane parallels the observation made by other workers,[10,11] when only trace amounts of 6-vinylpyrimidines were obtained by condensation of this relatively unstable ylide with 6-formylpyrimidines. Satisfactory results were



1: R = CH=CH$_2$ **6**: R = COC$_6$H$_5$ **8**: R = p-CH$_3$C$_6$H$_4$CO
3: R = CH=CH-COOEt **7**: R = H **10**: R = H

obtained, however, when an ylide stabilized by conjugation was used in the Wittig reaction of **2**. Thus, condensation of 2 with carbethoxymethylenetriphenylphosphorane in DMF, at room temperature, proceeded smoothly to yield 70% of the (4:3) *trans*- and *cis*-3-(5-uracilyl)acrylic acid ester (**3**). The identity of each component in the mixture was determined by the different coupling constants of the vinyl protons.

Alternatively, the procedure similar to that described by Klein and Fox,[11] for the synthesis of 6-vinyluracil, was chosen for the preparation of **1**. 5-Chloromethyluracil, which was readily prepared from 5-hydroxymethyluracil by treatment with concentrated HCl,[12] afforded, upon reaction with triphenylphosphine in DMF, under nitrogen, 5-uracilylmethyltriphenylphosphonium chloride (**4**). The phosphonium salt **4** reacted with paraformaldehyde in DMF in the presence of excess sodium ethoxide to give 5-vinyluracil (**1**) in good yield. While this work was in progress, an interesting synthetic procedure for the preparation of **1** appeared in the literature.[13]

For the preparation of nucleosides, **1** was converted to its trimethylsilyl derivative (**5**) by reaction with hexamethyldisilazane in the presence of a catalytic amount of ammonium sulfate.[14] Condensation of the crude **5** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in 1,2-dichloroethane, at room temperature, in the presence of stannic chloride[15] gave 2′,3′,5′-tri-*O*-benzoyl-5-vinyluridine (**6**). The blocked nucleoside (**6**) was purified by silica gel chromatography. Removal of the protecting benzoyl groups from **6**, by treatment with sodium methoxide in methanol, afforded 5-vinyluridine (**7**). It is generally recognized that condensation of the protected ribofuranosyl 1-*O*-acetate with trimethylsilylpyrimidines by the procedure of Niedballa and Vorbrüggen[15] leads almost exclusively to the corresponding β-nucleosides. The NMR spectrum of **7** showed the coupling constant $J_{1',2'} = 3$ Hz, a value somewhat indicative of the β configuration.[16] The β configuration of **7** was further substantiated by the difference in the chemical shifts ($\Delta\delta$) of the methyl signals of the isopropylidine derivative of **7**, which is 0.20, as reported by Imbach and his coworkers[17,18] ($\Delta\delta < 0.15$ for the α anomer and >0.15 for the β anomer).

Treatment of 2,4-bis(trimethylsilyloxy)-5-vinylpyrimidine (**5**) with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride[19] in dry benzene at 0–5° for 2 hr, and then at room temperature for 8–10 hr under nitrogen, in the presence of stannic chloride furnished a 40% yield of the blocked nucleosides **8** and **9**, with an anomeric ratio of $\beta/\alpha = 3:1$. A large portion of the β anomer (**8**) was separated from the mixture by fractional crystallization and the remaining mixture, containing α and β anomers, was resolved by chromatography on a dry silica gel column using benzene–ethyl acetate (7:3) as the eluent.

Transesterification of **8** by sodium methoxide in methanol furnished the desired 5-vinyl-2′-deoxyuridine (**10**). Assignment of the β configuration to **10** was made on the basis of the NMR spectrum, wherein the anomeric proton appeared as the characteristic triplet.[20,21] Similarly, deblocking of the protected nucleoside **9** by sodium methoxide in methanol afforded 1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-5-vinyluracil (**11**). In the NMR spectrum of **11**, the anomeric proton appeared as a pair of doublets,[20,21] supporting the α configuration of the nucleoside.

The site of glycosidation of the nucleosides (**7**, **10**, and **11**) was assigned at N-1 on the basis of the uv spectra. While the uv spectra of N-1 substituted uracil derivatives show little change when compared at pH 7 or pH 12, the N-3 substituted uracil derivatives at pH 12 undergo a strong bathochromic shift of the maxima and an increase in the extinction coefficient.[14,22] The uv spectra of the compounds **7**, **10**, and **11** remained unchanged at pH 7 or 12, supporting the above conclusion.

Experimental Section

General Procedure. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Uv spectra were measured on a Cary Model 14 spectrophotometer, and NMR spectra on Varian A-60 and XL-100 spectrometers using Me_4Si as internal standard. The mass spectra were recorded on a CEC 21-491 double-focusing mass spectrometer using an ionization voltage of 70 eV. Thin layer chromatography was performed on silica gel N-HR/uv_{254} precoated plastic sheets (Brinkman); the spots were detected by uv absorbance or by spraying with 10% (v/v) sulfuric acid–ethanol and heating. Column chromatography was done on silica gel (60–200 mesh), J. T. Baker No. 3405. 5-Hydroxymethyluracil was purchased from Raylo Chemicals Limited, Edmonton, Alberta. Microanalyses were performed by Robertson Laboratory, Florham Park, N.J.

***trans*- and *cis*-3-(5-Uracilyl)acrylic Acid Ethyl Ester (3).** Anhydrous 5-formyluracil[8] (1.20 g, 0.0086 mol) was suspended in 50 ml of dry DMF and to this was added 4.50 g (0.0129 mol) of carbethoxymethylenetriphenylphosphorane. The reaction mixture was stirred at room temperature for 20 hr, at which time TLC, using benzene–ethyl acetate (3:7), showed essentially the disappearance of 5-formyluracil. The DMF was evaporated and the product was crystallized from absolute ethanol, yielding 1.26 g (70%) of the analytically pure **3** as colorless crystals: mp 215–216°; λ_{max} (MeOH) 299 nm (ε 14,651), 261 (10,255); λ_{min} (MeOH) 275 (9441), 227 (ε 2767).

The NMR spectrum of the crystalline **3** showed it to be a mixture of the cis and trans isomers in the ratio of 3:4. Some of the trans isomer was separated from the mixture by fractional crystallization from ethanol: mp 258–259°; NMR (DMSO-d_6) δ 1.25 (t, 3, OCH_2CH_3), 4.17 (q, 2, OCH_2CH_3), 6.86 and 7.45 (two AB doublets, 2, J_{trans} = 16.5 Hz, CH=CH), 8.08 (s, 1, H-6), 11.45 (br, 2, 2NH's).

No attempt was made to isolate the cis isomer from the mixture. However, the NMR signals corresponding to the cis isomer of the mixed spectrum can be described as follows: NMR (DMSO-d_6) δ 1.23 (t, 3, OCH_2CH_3), 4.17 (q, 2, OCH_2CH_3), 5.88 and 6.90 (two AB doublets, 2, J_{cis} = 12.5 Hz, CH=CH), 8.75 (s, 1, H-6), 11.40 (br, 2, 2NH's).

Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.76; N, 13.33. Found: C, 51.18; H, 4.75; N, 13.05.

5-Uracilylmethyltriphenylphosphonium Chloride (4). To a suspension of 5-chloromethyluracil[11] (8.50 g, 0.0527 mol) in 100 ml of dry DMF was added 20.00 g (0.0763 mol) of triphenylphosphine. The mixture was stirred at 100° under nitrogen for 16 hr. A clear solution thus obtained was then evaporated to dryness. The residue was triturated with anhydrous ether to remove the unreacted triphenylphosphine. The product was obtained as a colorless, crystalline solid, yield 21.50 g (96%). Recrystallization from absolute ethanol gave the analytical sample: mp 287–288°; λ_{max} (MeOH) 274 nm (ε 10,717), 267 (11,644), λ_{min} (MeOH) 247 (6595).

Anal. Calcd for $C_{23}H_{20}N_2O_2PCl \cdot 1.5H_2O$: C, 61.40; H, 5.11; N, 6.22; Cl, 7.89. Found: C, 61.73; H, 5.31; N, 6.09; Cl, 8.13.

5-Vinyluracil (1). A mixture of the phosphonium chloride **4** (6.50 g, 0.0154 mol, dried over P_2O_5 at 110° for 10 hr) and paraformaldehyde (2.7 g, 0.0900 mol, dried over P_2O_5 at 50° for 12 hr) was suspended in 300 ml of dry DMF. To the stirred suspension was added dropwise under nitrogen a solution of sodium ethoxide (prepared from 1.60 g of sodium metal in 100 ml of absolute ethanol). The addition of the sodium ethoxide led to the dissolution of most of the solid, although a clear solution could not be obtained. After a few minutes, the reaction mixture became turbid as a precipitate formed. After all the sodium ethoxide was added (20 min), the thick suspension was stirred at room temperature under nitrogen for 18 hr. The reaction mixture was then warmed to 50–60° for 20 min, cooled to room temperature, and evaporated to dryness. The solid material was taken up in 400 ml of MeOH, neutralized with Dowex 50 (H^+) resin, and filtered. The clear solution was evaporated to dryness and the residue was triturated with ether to remove triphenylphosphine oxide. The crude material thus obtained was 1.90 g (89%). After two recrystallizations from water, 1.69 g of **1** was obtained (80% yield). The analytical sample was prepared by pouring the material in a small amount of water on a dry silica gel column, eluting with ethyl acetate, and finally crystallization from

water: mp 250–285° (lit.[6] mp 248° dec, lit.[7] mp 230–270°); λ_{max} (MeOH) 288 nm (ϵ 8452), 238 (13714), λ_{min} (MeOH) 259 (ϵ 4398); mass spectrum *m/e* 138 (M^+), 139 ($M^+ + 1$); NMR (DMSO-d_6) δ 5.06 (2 d, 1, J_{AC} = 11, J_{BC} = 3 Hz, H-C), 5.94 (2 d, 1, J_{AB} = 18, J_{BC} = 3 Hz, H-B), 6.40 (2 d, 1, J_{AB} = 18, J_{AC} = 11 Hz, H-A), 7.58 (s, 1, H-6), 11.12 (s, 2, 2 NH).

Anal. Calcd for $C_6H_6N_2O_2$: C, 52.20; H, 4.39; N, 20.30. Found: C, 52.14; H, 4.53; N, 20.11.

2,4-Bis(trimethylsilyloxy)-5-vinylpyrimidine (5). A mixture of well-dried **4** (1.65 g, 0.0120 mol), hexamethyldisilazane (35 ml), and 30 ml of dry benzene was heated under reflux in the presence of anhydrous ammonium sulfate (0.03 g). After 6–7 hr, a clear solution resulted. The solvents were evaporated in vacuo and the oily product was coevaporated with dry toluene. The crude trimethylsilyl derivative (**5**) thus obtained was utilized directly for condensation with protected sugars.

2′,3′,5′-Tri-*O*-benzoyl-5-vinyluridine (6). To a solution of **5** [prepared from 0.67 g (0.0049 mol) of **1**] and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (3.00 g, 0.0059 mol) in 50 ml of dry 1,2-dichloroethane was added slowly a solution of 0.2 ml of stannic chloride[12] in 15–20 ml of 1,2-dichloroethane. The reaction mixture was stirred at room temperature for 16 hr under anhydrous conditions. TLC of the mixture using benzene–ethyl acetate (7:1) showed the presence of essentially one major spot (R_f 0.69) in addition to some unreacted sugar. The solution was extracted with saturated aqueous sodium bicarbonate and three times with water, and dried over anhydrous sodium sulfate. The solvent was removed by evaporation and the crude **6** was purified on a dry silica gel column, eluting with benzene–ethyl acetate (7:1). After evaporation, **6** was obtained as a colorless foam. Crystallization from absolute ethanol gave 1.65 g (58%) of the analytically pure **6**, mp 141–142°.

Anal. Calcd for $C_{32}H_{26}N_2O_9$: C, 65.98; H, 4.47; N, 4.81. Found: C, 65.96; H, 4.64; N, 4.76.

5-Vinyluridine (7). A solution of **6** (0.89 g, 0.0015 mol) and sodium methoxide (0.15 g, 0.0028 mol) in 100 ml of methanol was stirred at room temperature for 45 min. It was then neutralized with Dowex 50 (H^+) resin and filtered, and the resin was washed with methanol. The combined filtrate was evaporated and the residue was crystallized from ethanol, giving 0.37 g (89%) of **7**: mp 160–165° sintered, 255–260° dec; λ_{max} (MeOH) 291 nm (ϵ 9450), 237 (11,285), λ_{min} (MeOH) 259 (3983); NMR (DMSO-d_6) δ 5.12 (2 d, 1, J_{AC} = 11, J_{BC} = 3 Hz, H-C), 5.78 (d, 1, $J_{1',2'}$ = 3 Hz, H-1′), 5.88 (2 d, 1, J_{AB} = 18, J_{BC} = 3 Hz, H-B), 6.38 (2 d, 1, J_{AB} = 18, J_{AC} = 11 Hz, H-A), 8.20 (s, 1, H-6), 11.40 (s, 1, NH).

Anal. Calcd for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.19; N, 10.37. Found: C, 48.79; H, 5.34; N, 10.17.

1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-5-vinyluracil (8) and 1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl)-5-vinyluracil (9). A solution of the trimethylsilyl derivative **5** [prepared from 1.65 g (0.0120 mol) of **1**] and 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride[17] [obtained from 6.50 g (0.0169 mol) of methyl-2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranoside[17]] in 150 ml of dry benzene was kept in ice under a nitrogen atmosphere. To this cooled solution was added slowly 0.4 ml of stannic chloride in 100 ml of dry benzene over a period of 20 min. About 100 ml of anhydrous 1,2-dichloroethane was also added to the reaction mixture. The mixture was stirred for 2–3 hr at 0–5° and then at room temperature for 8–10 hr. The solution was extracted with saturated aqueous sodium bicarbonate and twice with water, and dried over anhydrous sodium sulfate. TLC of the mixture using benzene–ethyl acetate (7:3) showed essentially two major products with R_f values 0.45 and 0.53, together with some minor products. The mixture was evaporated to dryness, giving a colorless foam, which was dissolved in 300 ml of acetone and then evaporated to approximately 10 ml when crystallization started. Methanol (10–15 ml) was added and the crystals were filtered. TLC of this crystalline material, in the above solvent system, showed it to be the β anomer **8** (0.90 g, R_f 0.53). The mother liquor containing the α and β anomers was chromatographed on a dry silica gel column, eluting with benzene–ethyl acetate (7:3). The first fraction containing the β anomer was evaporated, furnishing the crystalline material, which was recrystallized from methanol to yield 0.86 g of **8**. Thus the pure β anomer **8** was obtained in a total yield of 1.76 g (30%), mp 172–173°.

Anal. Calcd for $C_{27}H_{26}N_2O_7$: C, 66.12; H, 5.31; N, 5.71. Found: C, 66.11; H, 5.49; N, 5.65.

Evaporation of the second fraction gave the crystalline α anomer **9**, which was recrystallized from ethanol, 0.53 g (9%), mp 136–137°.

Anal. Calcd for $C_{27}H_{26}N_2O_7$: C, 66.12; H, 5.31; N, 5.71. Found: C, 65.91; H, 5.53; N, 5.54.

5-Vinyl-2′-deoxyuridine (10). To a suspension of compound **8** (0.40 g, 0.0008 mol) in 100 ml of dry methanol was added a freshly prepared solution of sodium methoxide (0.15 g of sodium in 50 ml of methanol). The mixture was stirred at room temperature for 2 hr, neutralized with Dowex 50 (H^+) resin, and filtered, and the resin was washed with methanol. The combined filtrates were evaporated to dryness. The residue was triturated with ether to remove the methyl *p*-toluate. This procedure yielded 0.16 g (76%) of the deblocked nucleoside **10**. Recrystallization from absolute ethanol gave the analytical sample: mp 230–235° with effervescence, 260–265° dec; λ_{max} (MeOH) 292 nm (ϵ 9190), 238 (12,253), λ_{min} (MeOH) 260 (4021); NMR (DMSO-d_6) δ 5.14 (2 d, 1, J_{AC} = 11, J_{BC} = 3 Hz, H-C), 5.90 (2 d, 1, J_{AB} = 18, J_{BC} = 3 Hz, H-B), 6.18 (t, 1, $J_{1',2'}$ = 6.5 Hz, H-1′), 6.42 (2 d, 1, J_{AB} = 18, J_{AC} = 11 Hz, H-A), 8.14 (s, 1, H-6), 11.40 (br, 1, NH).

Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5.51; N, 11.02. Found: C, 51.69; H, 5.74; N, 10.72.

1-(2-Deoxy-α-D-*erythro*-pentofuranosyl)-5-vinyluracil (11). A suspension of 0.24 g (0.0005 mol) of **9** in 50 ml of dry methanol was treated with sodium methoxide (0.08 g of sodium in 50 ml of methanol). After 2 hr of stirring at room temperature, the solution was neutralized with Dowex 50 (H^+) resin, filtered, and evaporated. Trituration of the residue with ether gave 0.10 g (80%) of **11**. An analytical sample was prepared by recrystallization from ethanol: mp 235–240° with effervescence, 260–265° dec; λ_{max} (MeOH) 292 nm (ϵ 9024), 239 (11,698), λ_{min} (MeOH) 260 (ϵ 4177); NMR (DMSO-d_6) δ 5.12 (2 d, 1, H-C), 5.88 (2 d, 1, H-B), 6.14 (d of d, 1, $J_{1',2'}$ = 2.5 and 7.0 Hz, H-1′), 6.42 (2 d, 1, H-A), 8.06 (s, 1, H-6), 11.38 (br, 1, NH).

Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5.51; N, 11.02. Found: C, 51.69; H, 5.78; N, 10.72.

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Registry No.—**1**, 37107-81-6; *cis*-**3**, 55520-59-7; *trans*-**3**, 55520-60-0; **4**, 55520-61-1; **5**, 55520-62-2; **6**, 55520-63-3; **7**, 55520-64-4; **8**, 55520-65-5; **9**, 55520-66-6; **10**, 55520-67-7; **11**, 55520-68-8; 5-formyluracil, 1195-08-0; 5-chloromethyluracil, 3590-48-5; triphenylphosphine, 603-35-0; hexamethyldisilazane, 999-97-3; 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, 6974-32-9; 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl-5-vinyluracil, 3601-89-6.

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Pentacyclodecane Chemistry. XII. Proton Nuclear Magnetic Resonance Spectral Correlations of 6- and 5-Substituted Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]- and -[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane (1,3- and 1,4-Bishomocubyl) Derivatives[1]

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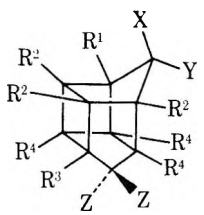
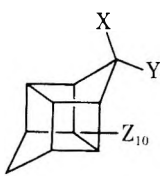
The proton magnetic resonance spectra of 30 derivatives (secondary and tertiary alcohols, formates, acetates, tosylates, chlorides, and hydrocarbons) of 1,3- (**1**) and 1,4-bishomocubane (**33**) have been measured. For a given isomeric pair of 1,3-bishomocubyl derivatives, the signals produced by an anti proton or by protons on an anti substituent always appear at fields higher than those produced by the corresponding syn protons. The corresponding signals due to the 1,4-bishomocubyl derivatives appear at intermediate fields. The chemical shift differences $\Delta\delta$ ($\delta_{syn} - \delta_{anti}$) for a given pair of 1,3-bishomocubyl isomers increase slightly and then decrease with an increase in the number (n) of intervening atoms between the proton in question and the methylene bridge carbon atom (n, $\Delta\delta$: 0, 0.23–0.29; 1, 0.29–0.32; 2, 0.11–0.14; 3, 0.10–0.11; 4, 0.03–0.09 ppm). The stereochemistries of the Diels–Alder dimerization of 1,2,3,4,5-pentachlorocyclopentadiene (**45**) and the reaction of *endo-anti*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ol (**51**) with thionyl chloride were determined with the aid of these correlations.

Some aspects of the NMR spectra of 1,3- and 1,4-bishomocubyl[2] derivatives have been discussed briefly.[3] The shielded α protons of certain ketones (**24**,[3e] **26**,[3e] **40**,[3a] and others[3e]), ketals (**29**,[3e] **39**,[3a] and others[3e]), a ketone hydrate,[3e] and the brominated hydrocarbon **25**[3e] have been pointed out, but there appears to be no simple explanation to account for this shielding.[3e] The effects of various substituents on the chemical shifts of protons on other tertiary carbon atoms of some 1,3-bishomocubyl derivatives also have been discussed.[3e] The effects of a bromine atom on the chemical shifts of various protons on the ethylene ketal of the ketone **24** have been calculated and compared with the experimental values.[3f] The low absolute magnitude of the geminal coupling constant of the 1,3 hydrocarbon **1** was suggested to be due to the small C–CH_2–C angle.[3b]



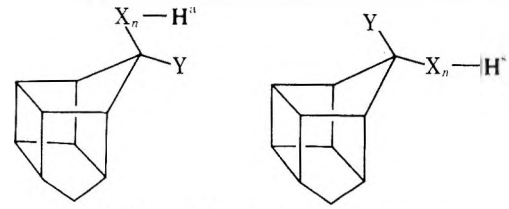
1
2, Y = OH
3, X = OH
4, Y = OCHO
5, X = OCHO
6, Y = OAc
7, X = OAc
8, Y = OTs
9, X = OTs
10, X = Cl
11, X = Me; Y = OH
12 X = OH; Y = Me
13, X = Me, Y = OCHO
14, X = OCHO; Y = Me
15, X = Me; Y = OAc
16, X = OAc; Y = Me
17, X = Me; Y = OTs
18, X = OTs; Y = Me
19, X = Me; Y = OPNB
20, X = Ph; Y = OH
21, X = Ph; Y = OPNB
22, X = Y = OMe
23, X, Y = CH_2
24, X, Y = O
25, $R^1 = R^3$ = Br
26, R^1 = Br; X, Y = O
27, $R^1 = R^2$ = Cl; X, Y = O
28, $R^1 = R^2$ = Ph; X, Y = O
29, $R^1 = R^3$ = Br; X = Y = Z = OMe
30, $R^1 = R^2 = R^3 = R^4$ = Cl
31, $R^1 = R^2 = R^3 = R^4$ = Cl; X = Y = Z = OMe
32, $R^1 = R^2 = R^3 = R^4$ = Cl; X = Y = OMe; Z = Br



33
34, Y = OH
35, Y = OCHO
36, Y = OAc
37, Y = OTs
38, X = Y = OMe
39, X, Y = OCH_2CH_2O
40, X, Y = O
41, Z = Cl
42, X = Y = OMe; Z = Cl
43, X, Y = OCH_2CH_2O; Z = Cl

(unspecified substituents are H)

Table I
NMR Chemical Shift Differences between Syn and Anti Protons of 1,3-Bishomocubyl Derivatives as a Function of Distance from the Methylene Group



X = C, O, or S; Y = H or functional group

n	$\Delta\delta$ ($\delta_H{}^s - \delta_H{}^a$), ppm
0	0.23–0.29
1	0.29–0.32
2	0.11–0.14
3	0.10–0.11
4	0.03–0.09
5	0.00–0.04
7	0.01–0.03

Results and Discussion

We have determined the NMR spectra of a large number of 1,3- and 1,4-bishomocubyl derivatives (**1–21, 23, 24, 33–37, 40, 41**) over the past several years.[2,4] In particular we have accumulated data on a number of syn- and anti-substituted isomer pairs of 1,3-bishomocubane **1**. Spectra typical of the series, those of the syn and anti alcohols **2** and **3**, are shown in Figures 1 and 2. The data for protons on the methylene bridges or protons on functional groups attached to the methylene bridges are given in Tables III–XI which will appear in the microfilm edition of this journal. (See paragraph at end of paper regarding supplementary material.) Some data reported by other workers[5] also have been included.

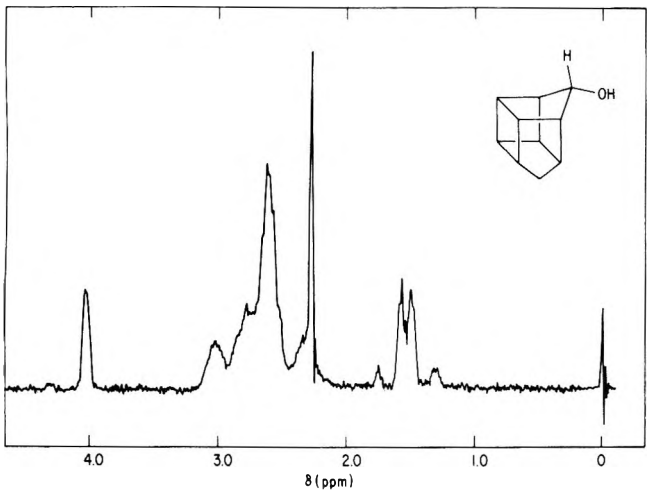


Figure 1. NMR spectrum of *syn*-pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]-decan-6-ol (**2**) in deuteriochloroform (60 MHz).

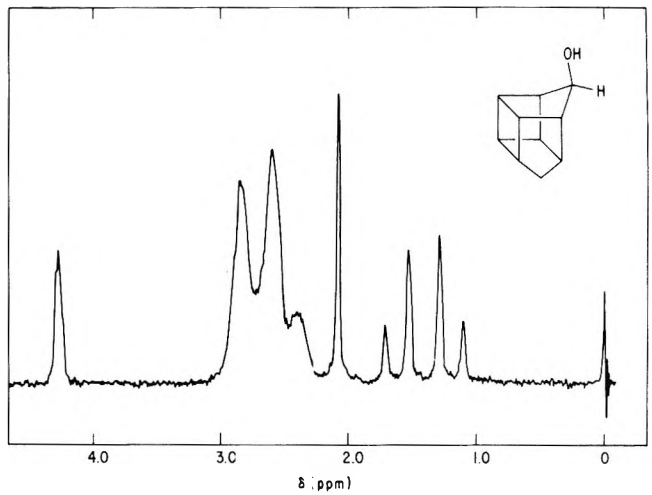
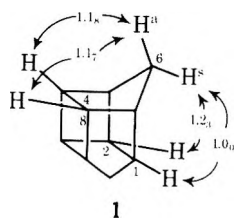


Figure 2. NMR spectrum of *anti*-pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]-decan-6-ol (**3**) in deuteriochloroform (60 MHz).

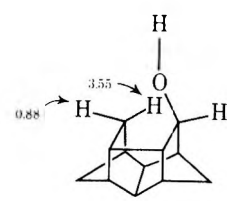
In all isomers examined, the anti protons (H^a) always appeared at higher field than the syn protons (H^s). The magnitude of the chemical shift difference $\Delta\delta$ ($\delta_{H^s} - \delta_{H^a}$) is dependent on the distance of the proton from the methylene carbon atom. In general the shift difference decreases with increasing distance. An exception is the case where the proton is separated by one atom from the methylene carbon atom. A summary of these data is given in Table I.

Steric compression by the proton on C-1 may explain the downfield shift of the syn protons compared with the anti protons. Crude measurements made with ball and spring models of the hydrocarbon **1** indicated that the syn proton–C-1 proton distance is the shortest of the four proton–proton distances (relative) shown in the figure.



1

A number of examples of this type of steric deshielding have been reported;[6] an outstanding example is the half-cage alcohol **44**[6a] (chemicals shifts shown).



44

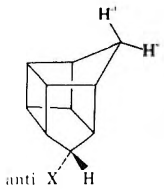
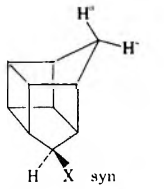
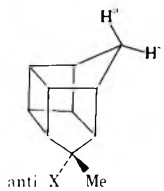
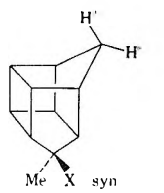
It is also possible that the syn proton deshielding of **1** and its derivatives is due to some anisotropic factor caused by the twisted rings. The rather sharp decrease in the chemical shift differences for protons on syn and anti substituents as the number of interposed atoms increases (Table I) (except n = 1) is a natural consequence of the greater distance between the C-1 proton and the proton in question. Models of the C-6 methyl derivatives (n = 1) indicate that in some conformations the methyl protons are considerably closer to the four protons on the tertiary carbon atoms C-1, -2, -4, and -8 than are the syn and anti protons which are bonded directly to the methylene bridge carbon atoms.

The protons on the methylene group which bear a functional group or on functional groups attached to the methylene carbon atom of the 1,4-bishomocubyl derivatives always had chemical shifts intermediate between those of the corresponding protons of the syn and anti 1,3-bishomocubyl derivatives where the differences in shifts were outside of the experimental error (±~0.02 ppm). In general the shift of the 1,4 derivative was closer to that of the anti 1,3 derivative than to that of the syn 1,3 derivative.

The chemical shifts of the methylene groups (-CH^{a}H^s-) were assigned on the basis that the anti proton always occurred at the higher field as was observed for the protons on the methylene bridge which bears a functional group. Interestingly, the chemical shift difference between the methylene protons was always greater for the anti isomers (Table II). The data in Table II are for both CCl_4 and $CDCl_3$ solutions; very little difference in chemical shifts was noted for the two solvents. For the secondary derivatives (first two entries in Table II) it will be noted that the syn methylene proton (H^s) signals occur over a relatively narrow chemical shift range while the anti methylene proton (H^a) signals occur over a wider range. Thus the change in chemical shift differences ($\Delta\delta$) is due almost entirely to an upfield shift of the anti methylene proton signal of the anti-X isomer compared with the anti methylene proton signal of the syn-X isomer. The reason for this phenomenon is not readily apparent; it may be due to some conformational change which occurs on substituting the syn-X group for an anti-X group. The same general trend is also observed in the methyl derivatives (last two entries in Table II), but the effect is not so pronounced. Chemical shift differences larger than those shown in Table II are observed when the tertiary ring carbon atoms are unsymmetrically substituted, e.g., **27** and **28**. The geminal coupling constants, $J_{H^aH^s}$, are all in the range 10.5–11.9 Hz, except for the highly chlorinated derivatives **27** and **30**. The chemical shifts of the secondary methylene protons of the 1,4-bishomocubyl derivatives are all in the range of 1.33–1.45 ppm, except for those derivatives with chlorine atoms on the tertiary ring carbon atoms.

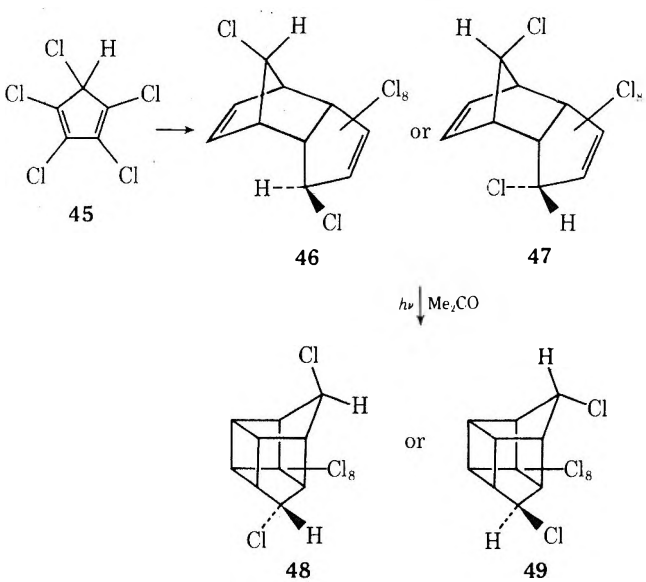
The chemical shifts of the protons on the methylene group which bears the functional group and the chemical shifts of the protons on the functional groups show a regular dependence on the solvent. The solvent shift ($\delta_{CDCl_3} - \delta_{CCl_4}$) for the former protons ranges from 0.06 to 0.12 ppm; most of the values are near 0.10 ppm. For protons on atoms

Table II
NMR Chemical Shift Differences of Methylene Protons of Syn and Anti 1,3-Bishomocubyl Derivatives

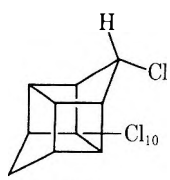
Compd type	Chemical shift ranges, ppm		Chemical shift difference range, $\Delta\delta$ ($\delta_{H^s} - \delta_{H^a}$)	X
	H^a	H^s		
 anti X H	1.21–1.45	1.58–1.67	0.36–0.39	H, OH, OCHO, OAc, OTs, Cl
 H X syn			0.18–0.20	OH, OCHO, OAc, OTs
 anti X Me	1.27–1.39	1.58–1.66	0.31–0.33	OH, OCHO, OAc, OTs
 Me X syn			0.22–0.27	OH, OCHO, OAc, OTs, OPNB

$\alpha - \epsilon$ to the ring methylene group, the solvent shift is ~0.03–0.11 ppm.

The above correlations are useful for the structure elucidation of bishomocubyl derivatives. For example, Williamson and coworkers[7] have shown that pentachlorocyclopentadiene **45** dimerized thermally to give a dimer which had



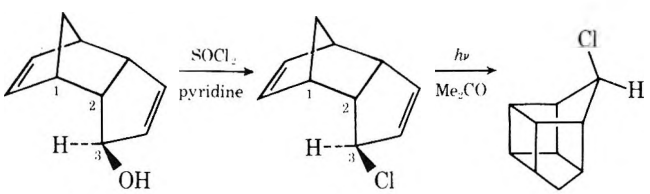
either structure **46** or **47**. Irradiation of the dimer in acetone solution gave a 1,3-bishomocubyl derivative[8] with either structure **48** or **49**. The NMR spectrum of the caged compound **48** or **49** exhibited a sharp singlet at 4.56 ppm (solvent not reported). Ungefug and Scherer[5j] also reported the same product, δ 4.61 ppm ($CDCl_3$), which they prepared in the same manner as Williamson and coworkers. The anti,anti isomer **48** reasonably can be assigned as the correct structure based on a comparison of the chemical shifts of the protons on **48** and the 1,4-bishomocubyl derivative **50**[4b] (δ 4.28 ppm in CCl_4, 4.31 in $CDCl_3$). The syn proton signal of **48** is expected to appear downfield from that of the 1,4-bishomocubyl **50** proton. The anti proton chemical shift for the syn,syn derivative **49** is expected to be slightly upfield from 4.3 ppm. For two reasons the undecachloro derivative **50** is a satisfactory model for comparison with the decachloro compounds **48** and **49** even though the second methylene groups of **48** and **49** bear only one chlorine atom while the second methylene group of **50** bears two chlorine atoms. First, the chemical shifts of the 1,4-bishomocubyl derivatives' methylene protons are not very sensitive to substituents on the other methylene group. Second, the chemical shift of the methylene protons of the



50

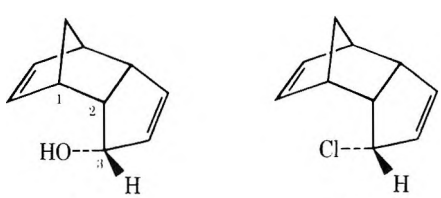
decachloro 1,4-bishomocubyl derivative **41** (2.57 ppm) is intermediate between those of the syn and anti protons of the octachloro 1,4-bishomocubyl derivative **30** (2.84, 2.54 ppm) (the second methylene group of **30** is replaced with a dichloromethylene group in **41**). The same comparison can be made for the methoxy protons of compounds **31** (3.60, 3.47 ppm), **32** (3.66, 3.51 ppm), and **42** (3.55 ppm). The chemical shift difference between compounds **48** and **50** is 0.30 ppm; that between the syn proton of **30** and the protons of **41** is 0.27 ppm. Thus the Diels–Alder dimer of the diene **45** has structure **46**, the one predicted on the basis of the less severe nonbonded interactions in the Diels–Alder transition state.[7] Mackenzie and Young[9] also concluded that **46** was the correct structure of the diene **45** dimer on the basis of other NMR data.

Another example of the utility of these NMR correlations involves the stereochemistry of the reaction of the endo-anti dienol **51** with thionyl chloride and pyridine to



51 **52** **10**

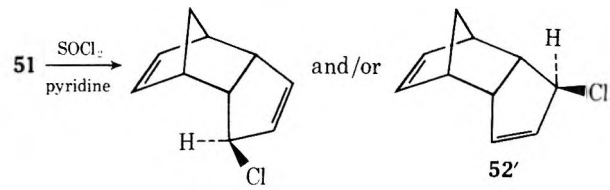
give an allylic chloride, presumably the anti isomer **52**.[1a] Irradiation of the chloride **52** in acetone gave a monochloro-1,3-bishomocubane,[8] presumably the anti isomer **10**.[1a] The chemical shift difference of the methylene protons of the caged chloride **10** is 0.38 ppm, consistent only with the chlorine atom being at the anti position (Table II). The NMR spectrum of the diene **52** also was consistent with the anti chlorine stereochemistry. In particular the signal for the proton on the carbon atom which bears the chlorine atom appeared as a narrow multiplet (~11 Hz base width). The signal for the proton on the carbon atom which bears the hydroxyl group of the anti dienol **51** also was a narrow multiplet (~11 Hz base width).[10] In contrast the corresponding proton of the syn dienol **53** was a doublet, J_{23} =



53 **54**

8.5 Hz, with further smaller splitting evident (~16 Hz base width).[10] The NMR spectrum of the syn chloride **54** is expected to show a similar pattern for the proton on the carbon atom which bears the chlorine atom. The larger coupling, J_{23}, in the syn hydroxy isomer **53** probably is due to the H-2–H-3 dihedral angle being nearly 0° as determined from molecular models.[11] The H-2–H-3 dihedral angle in the anti isomers **51** and **52** is about 120°, and therefore J_{23} is expected to be small.[11]

Thus the reaction of the anti alcohol **51** with thionyl chloride in pyridine either occurs with retention (SNi) **52** and/or retention with allylic rearrangement (SNi′ or SN2′) **52′**. The reaction of alcohols with thionyl chloride in pyridine usually results in inversion of configuration[12] while allylic alcohols react with thionyl chloride in ether to give rearranged chlorides in which the chlorine atom attacks the allylic system on the same side from which the oxygen



52 **52′**

atom leaves.[13] In pyridine where chloride ion is present, the stereochemical result would likely be the same, since SN2′ reactions occur with the nucleophile entering on the same side as that from which the leaving group departs.[14]

Experimental Section

The proton NMR spectra were obtained by Mr. F. L. Beman and coworkers with a Varian A-60 analytical spectrometer operating at 60 MHz or by Dr. J. P. Heeschen and coworkers with a Varian HA-100 high-resolution spectrometer operating at 100 MHz. The NMR solution concentrations were 10–20%. All proton chemical shifts (δ) are relative to internal tetramethylsilane (positive when downfield from the reference) and are accurate to ~±0.02 ppm; coupling constants are accurate to ~0.2 Hz. Chemical shifts (in hertz) of protons which produced AB quartet patterns were calculated from the expression δ = midpoint ± $\nu_{AB}/2$, where $\nu_{AB} = [\nu_1 - \nu_4)(\nu_2 - \nu_3)]^{1/2}$ and ν_1, ν_2, ν_3, and ν_4 are the resonance frequencies of the four lines of the AB quartet.[15]

References for the syntheses and characterizations of the compounds are given in the tables in the microfilm edition of this journal.

Registry No.—**1**, 6707-86-4; **2**, 13351-15-0; **3**, 15776-05-3; **4**, 39522-31-1; **5**, 39522-32-2; **6**, 55399-44-5; **7**, 55399-45-6; **8**, 16872-36-9; **9**, 16966-85-1; **10**, 51965-71-0; **11**, 51965-68-5; **12**, 52021-57-5; **13**, 51965-72-1; **14**, 52021-58-6; **15**, 52916-90-2; **16**, 52949-82-3; **17**, 33823-77-7; **18**, 33823-78-8; **19**, 51965-75-4; **20**, 51965-73-2; **21**, 51965-74-3; **23**, 33744-62-6; **24**, 15584-52-8; **33**, 6707-88-6; **34**, 13351-14-9; **35**, 39522-33-3; **36**, 55319-54-5; **37**, 55319-55-6; **40**, 15745-99-0; **41**, 15443-23-9.

Supplementary Material Available. NMR chemical shifts of protons on the methylene bridges or protons on functional groups attached to the methylene bridges of compounds **1**–**43** (Tables III–XI) 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 $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2380.

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New Diastereomers of Podophyllotoxin. Related Hydroxy Acids

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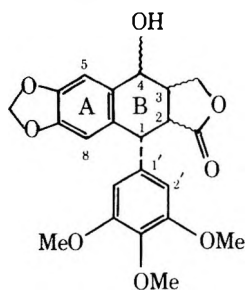
Two new diastereomers of podophyllotoxin, L-epiisopicropodophyllin (**8**) and L-epiisopodophyllotoxin (**6**), and two new related hydroxy acids, L-4-deoxyisopicropodophyllic acid (**13**) and L-epiisopodophyllic acid (**17**), are described. An unusual cleavage of a lactone under hydrogenolysis conditions was encountered. Compounds **6** and **8** were found to have cytotoxic activity against cells derived from human carcinoma of the nasopharynx in cell culture.

Of the eight possible diastereomers in the L series[1] represented by podophyllotoxin, four members (**1–4**) are known,[2] and two (**5** and **6**) are present as unresolved components in their racemic forms.[3] In this paper we report one of the two remaining diastereomers, **8**, in addition to **6** in optically active form,[3] and two new derived hydroxy acids, **13** and **17** (Chart I).

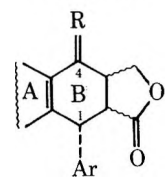
Chart I



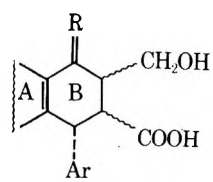
1	podophyllotoxin	(2α, 3β, 4α)	
2	epipodophyllotoxin	(2α, 3β, 4β)	
3	picropodophyllin	(2β, 3β, 4α)	
4	epipicropodophyllin	(2β, 3β, 4β)	
5	isopodophyllotoxin	(2β, 3α, 4β)	**5a** DL
6	epiisopodophyllotoxin	(2β, 3α, 4α)	**6a** DL
7	isopicropodophyllin	(2α, 3α, 4β)	
8	epiisopicropodophyllin	(2α, 3α, 4α)	

Isopicropodophyllone (**9**) (Chart II) is a recently reported[4] naturally occurring keto lignan from *Podophyllum pleianthum*, which had been prepared by isomerization[5] of podophyllotoxone[6] (**10**). On reduction with $NaBH_4$, **9** yielded two lactone alcohols; the minor product[7] (12%) is podophyllotoxin (**1**), and the major (66%) is an isomeric alcohol, **8**. On the basis of previous work[3,6] in which reduction of the ketones **10**, **11**, and **12** (DL form) with $ZnBH_4$[7] each yielded an alcohol with unchanged configuration at the three asymmetric centers **1**, **2**, and **3**, the major alcohol **8** would be expected to have the 1α,2α,3α configuration of the parent ketone, with orientation of the hydroxy group at C-4 uncertain.

Chart II[a]



9	isopicropodophyllone	(2α, 3α, R = O)
10	podophyllotoxone	(2α, 3β, R = O)
11	picropodophyllone	(2β, 3β, R = O)
12	DL-isopodophyllotoxone	(2β, 3α, R = O)
14	4-deoxyisopicropodophyllin	(2α, 3α, R = H, H)
16	4-deoxyisopodophyllotoxin	(2β, 3α, R = H, H)



13	4-deoxyisopicropodophyllic acid	(2α, 3α, R = H, H)
15	4-deoxyisopodophyllic acid	(2β, 3α, R = H, H)
17	epiisopodophyllic acid	(2β, 3α, R = H, αOH)

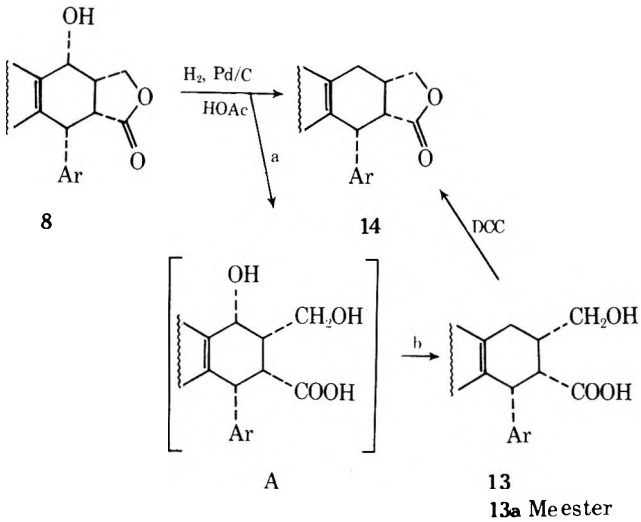
[a] In this and subsequent charts partial formulas are used, and Ar at C-1 indicates the 3,4,5-trimethoxyphenyl group.

Confirmation that **8** had retained the all-cis (α) configuration at centers 1, 2, and 3, and determination of configuration of the C-4 hydroxyl group, were accomplished by correlation with known compounds. Hydrogenolysis (Pd/C) yielded the expected known deoxylactone **14** as a minor product (24%), the major product being the hydroxy acid **13**, which could be lactonized to **14**. Product **13** was unexpected; hydrogenolyses under identical conditions have been reported[2,8,9] for podophyllotoxin (**1**) and its other known diastereoisomers **2**, **3**, and **5**, and in each instance

the corresponding deoxylactone was obtained in good yield; no cleavage to hydroxy acid was found. Additionally all four deoxylactones were found to be stable to similar treatment with palladium catalyst in acetic acid.[10] We have carried out hydrogenations of **1**, **3**, **6**, and **14** and encountered no cleavage products.

Since deoxylactone **14** is unchanged under conditions that cause cleavage of **8** to **13**, it follows that opening of the lactone ring (step a) takes place before the C-4 hydroxyl is replaced (step b), and dihydroxy acid A would be an intermediate in the overall reaction (Scheme I). However, attempts to show the presence of A by following the course of reaction by TLC have been unsuccessful even in decelerated reaction conditions of lowered proportions of catalyst and decreased hydrogen pressure. Apparently the cleavage step a is much slower than the hydrogenolysis step b, so that A does not accumulate. In support of this we have found that under hydrogenolysis conditions which produce **13** from **8** slowly, the hydrogenation of dihydroxy acid **17** to the corresponding monohydroxy acid **15** proceeds rapidly, the reaction being complete within minutes. The conversion of **8** to **13** and the known[11] deoxylacetone **14** confirms its 1α,2α,3α configuration.

Scheme I



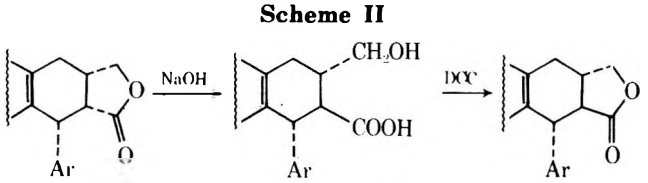
8 14 A 13

13a Me ester

Neither the monohydroxy acid **13** (1α,2α,3α) nor the dihydroxy acid **17** (1α,2β,3α,4α, see below) has been reported previously. Both acids are lactonized readily when heated, or treated with acid or dicyclohexylcarbodiimide (DCC). At 70 eV the mass spectrum of **13** shows a very minor (2%) molecular ion, and that of **17**, 4%; their spectra are essentially those of the corresponding lactones. However, at 70 eV mass spectra of their methyl esters (13α and 17α) do show normal molecular ions.

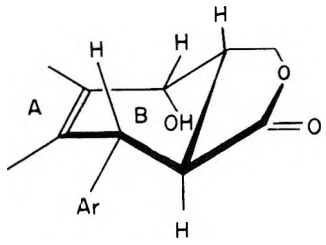
Previous work[10] showing that cleavage of **14** under even mild conditions was accompanied by epimerization at C-2 to yield the all-trans (1α,2β,3α) hydroxy acid **15**, which could be relactonized to deoxylactone **16** (Scheme II), suggested a route for conversion of **8** to an optically active, 1α,2β,3α diastereoisomer, either **5** or **6**.

Scheme II



14 15 16

15a Me ester

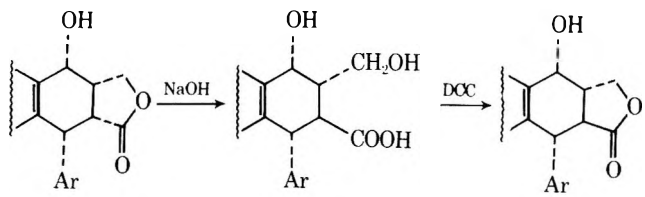


COMPOUND 6

Figure 1. Conformational formula (partial) of L-epiisopodophyllotoxin (**6**).

When actually tried, the reaction proceeded as desired, with formation of dihydroxy acid **17**, which consequently led to a hydroxylactone, **5** or **6** (Scheme III). Since in an exploratory experiment NaOH was found not to cause epimerization of hydroxy acid **13** at C-2, it is likely that **8** is first epimerized before the lactone ring is opened. Both **5** and **6** are known in their DL forms, **5a** and **6a**; the acetates of **6** and **6a**[11] were found to be identical in uv, ir, NMR, and mass spectral comparisons, but differed as expected with respect to optical rotation (**6** has [α]D −37.5°).

Scheme III



8 17 6

17a Me ester

The identity of **6** and **6a** establishes simultaneously the 4α-OH configuration of **8**, as in both reaction steps involved in converting **8** to **6** retention of configuration at C-4 (as well as at C-3) should be expected. Thus **8** is L-(+)-epiisopicropodophyllin,[12] and **6** is L-(−)-epiisopodophyllotoxin.

The stereochemistry of podophyllotoxin and several related compounds has been elucidated in publications appearing over a number of years.[2,13,14] Recently an X-ray crystallographic study[15] of bromopodophyllotoxin confirmed the original absolute configurational assignment[16] of podophyllotoxin in refutation of doubts[17] cast on the correctness of the Schrecker and Hartwell assignment. The X-ray work also supports the conformational conclusions arrived at previously.

The main features of the conformations of podophyllotoxin (**1**) and picropodophyllin (**3**) can be applied in deducing the conformations of the two new toxins **6** and **8**.

Epiisopodophyllotoxin (**6**) is analogous to **1** in having a trans-fused lactone ring which imposes on the cyclohexene ring B a rigid half-chair conformation. Unlike the two half-chair forms of cyclohexene which normally invert readily,[18] the two forms are distinct, each being held rigidly by the lactone fusions; **1** has the 2α,3β half chair while the isopodo **6** has the 2β,3α. Accordingly, in **1** the 1α aromatic substituent and the 4α hydroxyl are quasi-axial and quasi-equatorial, respectively, but in **6** the two groups are conformationally reversed (Figure 1).

Picropodophyllin (**3**) and epiisopicropodophyllin (**8**) also constitute an analogous pair. Both have cis-fused lactone

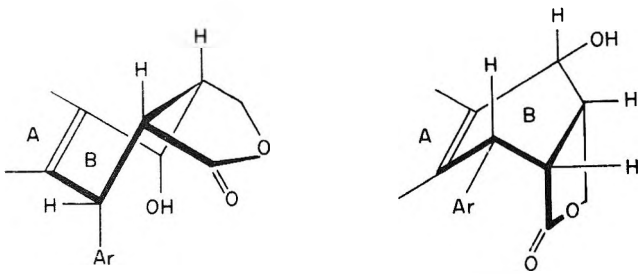


Figure 2. Conformational formulas (partial) of the half-boat forms of L-epiisopicropodophyllin (8).

rings which fix ring B in flexible half-boat forms, each of which can flip between two conformers.[14,19] The two isomers 3 and 8 differ in the cis fusion of the lactone ring, one being α and the other β configurated. Figure 2 illustrates the two conformers A and B of the $2\alpha,3\alpha$ isomer. It is seen that in conformer B the substituents at 1 and 4 are both equatorial, and in A they are both axial. In a previous NMR study,[14] **3**, its acetate, and the corresponding ketone were shown to exist in the two conformations. The equilibrium proportions of the two conformers were deduced to be different in the three compounds, and the differences were attributed mainly to the increase in steric interaction between the substituent at C-4 and the remainder of the molecule in changing from oxygen (attached to trigonal carbon), to hydroxy, and to acetoxyl.

Cleavage of the lactone ring in the hydrogenolysis of **8** is intriguing; we are not aware of a similar opening of a lactone under hydrogenolysis conditions. Since under identical conditions only **8** among the several diastereomers undergoes the cleavage reaction, and since the deoxylactone **14**, with the same configurations as compound **8** at positions 1, 2, and 3, is not cleaved, it is clear that the special geometry of **8**, particularly that of the hydroxy group at C-4, is the key to the course of reaction. It may be more than coincidence that among the diastereomers, **8** has a conformation which brings the 4-OH closest[20] to the oxido oxygen of the lactone. The reaction appears to be complex and an explanation of the cleavage simply on the basis of a hydrogen bonding interaction is obviously inadequate. The roles of catalyst and hydrogen need to be considered,[21] as preliminary studies of the hydrogenolytic cleavage show that no reaction takes place without the presence of all three components: acetic acid as solvent, Pd/C as catalyst, and a hydrogen atmosphere.

The hydroxy group in D,L-epiisopodophyllotoxin (**6a**) was originally assigned the β configuration on the assumption that $ZnBH_4$ reduction of the ketone **12** would yield an equatorial alcohol,[2] as was true of the trans lactone **10**, but on the basis of NMR studies the assignment was reversed.[13]

The $ZnBH_4$ reductions of isomeric ketones **10** and **11** (mentioned above) have also been reported[3] to give 4α alcohols; thus all four diastereomeric ketones yield alcohols of α configuration despite the difference in conformations of the structures. For ketone **9**, which has two flexible conformers analogous to A and B of alcohol **8**, it can be seen from a model that regardless of which conformer reacts in the reduction, the β side of the molecule is much more open for attack of the hydride reagent. For ketone **12** the situation is much less obvious; possibly the additional distortion of ring B caused by the lactone trans fused through the $2\beta,3\alpha$ equatorial bonds moves the quasi-equatorial aromatic group at C-1 more toward the underside of the average plane of the A, B, C rings.[18]

Cytotoxic Activity. The two alcohols showed significant inhibitory activity against cells derived from human carcinoma of the nasopharynx carried in cell culture, in assays conducted under the auspices of the Drug Development Branch, National Cancer Institute. Compounds **6** and **8** had ED_{50} values (in μg/ml) of 6×10^{-3} and 9×10^{-1}, respectively.

Experimental Section[22]

Epiisopicropodophyllin (8). To a solution of ketone **9** (1 g) in MeOH–dioxane (4:1 v/v) was added $NaBH_4$ (800 mg) at 0°. After the mixture had stood for 1 hr at 0°, it was poured on ice, treated with acetic acid dropwise until no more gas was evolved, diluted with water, and extracted with $CHCl_3$ (3 × 50 ml). Removal of solvent after drying gave a residue (920 mg) which was crystallized from $CHCl_3$–MeOH to give 580 mg of **8**: mp 262–263°; $[\alpha]D$ +15° (c 1.03, pyridine); uv max (EtOH) 293 nm (ϵ 3.51) and 250 (3.12); ir (KBr) 2.90 (OH) and 5.68 μm (lactone C=O); NMR (DMSO) τ 6.37 (s, 9 H, OMe), 3.90 (s, 2 H, $-OCH_2O-$), 3.64 (s, 2 H, C-2′,6′), 3.47 (s, H, C-8), 2.86 (s, H, C-5), and 5.34 (perturbed d, H, C-1), other signals are merged with methoxy and DMSO-d_5 resonances; mass spectrum (70 eV) *m/e* 414 (M^+, 100), 396 (2), 181 (52), 173 (58), 169 (23), and 153 (67).

Anal. Calcd for $C_{22}H_{22}O_8 \cdot \frac{1}{2}H_2O$: C, 62.41; H, 5.43. Found: C, 62.40; H, 5.48.

The mother liquor by preparative TLC (EtOAc–hexane 3:1) yielded 80 mg more of **8** (total yield 66%) and 120 mg (12%) of needles (from $CHCl_3$–MeOH) which was identified as podophyllotoxin by direct comparison with an authentic sample (TLC, ir, mixture melting point, and $[\alpha]D$); its acetate was also shown to be identical with podophyllotoxin acetate.

Acetate of 8 was prepared with acetic anhydride in pyridine at 25° and crystallized from CCl_4 as fine needles (92%): mp 97–98°; $[\alpha]D$ −29.5° (c 0.91, $CHCl_3$); ir ($CHCl_3$) 5.65 (lactone C=O) and 5.78 μm (ester C=O); NMR ($CDCl_3$) τ 7.88 (s, 3 H, –OCOMe), 7.07 (m, 2 H, C-2, 3), 6.17 (s, 6 H, OMe), 6.10 (s, 3 H, OMe), 5.69 (perturbed d, 2 H, $-CH_2O-$), 5.52 (perturbed d, H, C-1), 3.98 (s, 2 H, $-OCH_2O-$), 3.58 (s, 2 H, C-2′,6′), 3.40 (s, H, C-8), and 3.15 (s, H, C-5); mass spectrum (70 eV) *m/e* 456 (M^+, 28), 396 (2), 185 (26), 168 (8), and 153 (8).

Epiisopodophyllotoxin (6). To a $CHCl_3$ solution of **17** (150 mg) was added 100 mg of DCC, and the solution was left at 25° for 1 hr. After removal of solvent and rinsing with warm MeOH (to remove excess DCC) the residue (98 mg) was crystallized ($CHCl_3$–MeOH) to give **6** as colorless needles: mp 248–250°; $[\alpha]D$ −37.5° (c 0.53, pyridine); uv max (EtOH) 291 nm (ϵ 3.58) and 245 (3.20); ir (KBr) 2.85 (OH) and 5.64 μm (lactone C=O); NMR (DMSO) τ 6.32 (s, 3 H, OMe), 6.37 (s, 6 H, OMe), 4.07 (s, 2 H, $-OCH_2O-$), 3.80 (s, H, C-8), 3.47 (s, 2 H, C-2′,6′), 3.15 (s, H, C-5), other signals are merged with methoxy and DMSO-d_5 resonances; mass spectrum (70 eV) *m/e* 414 (M^+, 100), 399 (7), 396 (3), 185 (23), 181 (25), 168 (33), and 153 (42).

Acetate of 6 was prepared as for the acetate of **8**. The product crystallized as fine needles (MeOH): mp 238–240°; $[\alpha]D$ +24.0° (*c* 0.54, $CHCl_3$); ir ($CHCl_3$) 5.62 (lactone C=O) and 5.80 μm (ester C=O); NMR ($CDCl_3$) τ 7.79 (s, 3 H, OCOMe) 6.06 (s, 6 H, OMe), 6.04 (s, 3 H, OMe), 3.90 (s, 2 H, $-OCH_2O-$), 3.40 (s, H, C-8), 3.35 (s, 2 H, C-2′,6′), 2.95 (s, H, C-5); mass spectrum (70 eV) *m/e* 456 (M^+, 35), 441 (2), 396 (5), 185 (22), 181 (18), 168 (100), and 153 (50).

Anal. Calcd for $C_{24}H_{24}O_9 \cdot CH_3OH$: C, 61.47; H, 5.73. Found: C, 61.35; H, 5.54.

The acetates of **6** and **6a**[11] were found to be identical by direct comparison of their ir, NMR, and mass spectra and by TLC.

Hydrolysis of 8. A suspension of **8** (100 mg), 10% palladium on charcoal (100 mg), and 20 ml of acetic acid was shaken at 25° in a Parr apparatus under hydrogen pressure (40 psi) for 8 hr. Filtration of the catalyst and evaporation of solvent yielded a solid residue (78 mg) which by preparative TLC (ether) gave two compounds: one (R_f 0.78), obtained as colorless needles (24 mg, 24%) from $CHCl_3$–MeOH, was identified as 4-deoxyisopicropodophyllin (**14**) by direct comparison with an authentic sample[11] (mixture melting point, ir, mass spectrum), mp 202–203°, $[\alpha]D$ −131.6° (c 0.38, $CHCl_3$) (lit.[2] mp 202–203°, $[\alpha]D$ −113° in pyridine). The second compound (R_f 0.42), 38 mg (38%), was obtained in amorphous form, mp 95–97°, and characterized as 4-deoxyisopicropodophyllic acid (**13**): ir ($CHCl_3$) 2.95 (OH) and 5.85 μm (carboxy C=O); NMR ($CDCl_3$) τ 6.25 (s, 6 H, OMe), 6.15 (s, 3 H, OMe), 4.12 (s, 2 H, $-OCH_2O-$), 3.54 (s, H, C-8), 3.50 (s, 2 H, C-2′,6′) 3.44 (s, H, C-5);

mass spectrum (30 eV) *m/e* 416 (M^+, 10), 398 (100), 181 (60), 168 (30), and 153 (26). [At 70 eV, M^+ (416) had relative intensity of 2%.]

Methyl Ester 13a. An ethereal solution of **13** (18 mg) was treated with diazomethane and processed to yield after preparative TLC a homogeneous powder: mp 99–101°; $[\alpha]D$ +46.4° (c 0.73, $CHCl_3$); ir ($CHCl_3$) 2.95 (OH) and 5.80 μm (ester C=O); NMR ($CDCl_3$) τ 6.59 (s, 3 H, CO_2Me), 6.21 (s, 6 H, OMe), 6.14 (s, 3 H, -OMe), 4.12 (s, 2 H, $-OCH_2O-$), 3.57 (s, 2 H, C-2′,6′), and 3.42–3.27 (m, 2 H, C-5,8); mass spectrum *m/e* 430 (M^+, 33), 398 (37), 371 (6), 197 (100), 185 (78), 181 (78), 169 (55), and 153 (47).

4-Deoxyisopicropodophyllin (14). To a solution of **13** (10 mg) in 2 ml of $CHCl_3$ was added DCC (6 mg). After 30 min the reaction product was purified by preparative TLC (EtOAc–hexane, 1:1) to obtain crystalline material, mp 201–202°, identified as **14** by direct comparison with an authentic sample.

Epiisopodophyllic Acid (17). Hydroxylactone **8** (300 mg) was stirred in NaOH solution (4 g in 100 ml of 50% aqueous ethanol) at 25° for 8 hr. The solution after dilution with water was extracted with $CHCl_3$ (2 × 20 ml) to remove neutral material (30 mg). The aqueous portion was neutralized with 2 *N* HCl and extracted with $CHCl_3$ (4 × 20 ml). The organic layer was washed with water, dried, and evaporated to yield 240 mg (80%) of residue which crystallized from $CHCl_3$–MeOH as needles of **17**: mp 126–128°; ir ($CHCl_3$) 2.90 (OH) and 5.88 μm (carboxy C=O); mass spectrum (70 eV) *m/e* 432 (M^+, 4).

The neutral nonsaponified material was found to be a mixture of compounds **8** and **6** by TLC.

Methyl Ester 17a. By treatment with diazomethane, **17** (15 mg) after processing afforded colorless crystals: mp 166–168°; $[\alpha]D$ −257.5° (*c* 0.40, $CHCl_3$); ir ($CHCl_3$) 2.90 (OH) and 5.80 μm (ester C=O); NMR ($CDCl_3$) τ 6.50 (s, 3 H, $-CO_2Me$), 6.27 (s, 3 H, OMe), 6.20 (s, 3 H, OMe), 4.15 (s, 2 H, $-OCH_2O-$), 3.73 (s, H, C-8), 3.64 (s, 2 H, C-2′,6′), and 3.24 (s, H, C-5); mass spectrum (70 eV) *m/e* 446 (M^+, 14), 414 (70), 399 (16), 168 (100), and 153 (38).

Hydrogenolysis Experiments. 1. Attempted Hydrogenolysis or Cleavage of 8 and 14. A. A mixture of **8** (20 mg), 20 mg of 10% Pd/C, and 10 ml of HOAc was shaken at reduced pressure (no H_2) for 15 hr; **8** was recovered unchanged.

B. A suspension of **8** (20 mg) in 10 ml of HOAc was shaken under 40 psi pressure of hydrogen for 18 hr; **8** was recovered unchanged.

C. A suspension of **14** (15 mg), 10 mg of 10% Pd/C, and 10 ml of HOAc was shaken at 40 psi hydrogen pressure for 18 hr; **14** was unchanged.

2. Comparison of Rates of Hydrogenolysis of 8 and 17. In parallel experiments with **8** and **17**, employing 20 mg of compound, 25 mg of 10% Pd/C, and 15 ml of HOAc, shaken at 5 psi of hydrogen pressure, in which the reactions were monitored at intervals by TLC, compound **17** was found to be completely consumed in 5 min, being converted to a compound of R_f 0.41. By preparative TLC the product was isolated and crystallized, mp 206–208°, and characterized as 4-deoxyisopodophyllic acid (**15**) by conversion to the methyl ester 15a and the deoxylactone **16**.

Methyl ester 15a was prepared by treatment of **15** with diazomethane. The ester was obtained as needles ($CHCl_3$–MeOH): mp 198–200°; $[\alpha]D$ −20.8° (c 0.58, $CHCl_3$); ir ($CHCl_3$) 2.95 (OH) and 5.80 μm (ester C=O) (lit.[2] mp 200–201°, $[\alpha]D$ −23.0°).

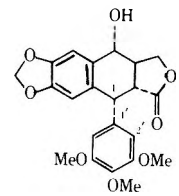
4-Deoxyisopodophyllotoxin (16) was prepared by cyclization of **15** with DCC and obtained as needles, mp 250–252°, $[\alpha]D$ +75.6° (c 0.68, pyridine). Identity was established by comparison with an authentic sample (TLC, ir, mixture melting point, and $[\alpha]D$). Compound **8** (R_f 0.39) showed little change at 5 min and underwent reaction slowly to products with R_f 0.78 (minor) and 0.42 (major). The former corresponds to that of **14** and the latter to **13**. A considerable proportion of **8** remained even after 3 hr. In a separate experiment at 38 psi hydrogen pressure reaction was complete (TLC) after 14 hr.

Acknowledgments. This work was supported in part by USPHS Grant CA-11507. We wish to thank Dr. A. von Wartburg and Sandoz, Ltd., and Dr. W. J. Gensler for lignan samples. Mass spectral determinations were performed by the Mass Spectrometry Laboratory, University of Tennessee.

Registry No.—**6**, 55568-79-1; **6** acetate, 55515-05-4; **8**, 55568-80-4; **8** acetate, 55515-06-5; **9**, 55515-07-6; **13**, 55515-08-7; **13a**, 55515-09-8; **14**, 55568-81-5; **15**, 55515-10-1; **15a**, 55515-11-2; **16**, 17187-81-4; **17**, 518-48-9; **17a**, 55515-12-3; diazomethane, 157-22-2.

References and Notes

(1) The absolute configuration at C-1 of most of the known compounds related to podophyllotoxin (**1**), whether natural or synthetic, is the same as that of the latter. We subscribe to a suggestion of Schreier (ref 13a,



1

footnote 31) to assign to these compounds the L absolute configuration. (An alternative convention based on the absolute configuration of C-1 by the *RS* system [Cahn, Ingold, and Prelog, *Angew. Chem., Int. Ed. Engl.*, **5**, 385 (1966)] would not be feasible; for where C-1 in podophyllotoxin is *R*, in 2′-bromopodophyllotoxin[15] it is *S*). The only known close relatives of **1** of the D series are (+)-picrosikkimotoxin and (−)-epipicrosikkimotoxin, both compounds obtained through reactions on an intermediate of the D series which had been derived by resolution of DL-α-apopicrosikkimotoxic acid.[13a]

(2) J. L. Hartwell and A. W. Schrecker, *Prog. Chem. Org. Nat. Prod.*, **15**, 83 (1958).
(3) W. J. Gensler and F. Johnson, *J. Am. Chem. Soc.*, **85**, 3670 (1963).
(4) F. C. Chang, C. Chiang, and V. N. Aiyar, *Phytochemistry*, in press.
(5) A. von Wartburg, private communication.
(6) W. J. Gensler, F. Johnson, and A. D. Sloan, *J. Am. Chem. Soc.*, **82**, 6074 (1960).
(7) $ZnBH_4$ was used in the previous reductions when it was found that $NaBH_4$ on **10** and **11** in ethanol gave rise to an acid of uncertain structure.[6] Sodium borohydride in methanol used in the present reduction was unexceptional, the minor product **1** appears to result from the changes **9** → **10** → **1**; supporting evidence for this will be presented in a future paper on the diastereomeric ketones.
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(20) An interaction of the two groups, such as by hydrogen bonding, might promote a nucleophilic attack (of solvent) at the carbonyl carbon, resulting in hydrolysis of the lactone. Approximate OH···O (4-OH···oxido oxygen of lactone) bond distances obtained by measurement of Dreiding conformational models of the eight diastereomers, **1–8**, show that conformer A of alcohol **8** has the shortest such distance by 0.4 Å.
(21) The palladium on charcoal used in our reactions is a commercial product (Engelhard), and the possibility that Pd of several oxidation states may be present is not precluded.
(22) Melting points were determined on an electrical hot stage and are uncorrected. Infrared spectra were obtained using a Perkin Infracord 137. Optical rotation measurements were obtained with a Carl Zeiss photoelectric precision polarimeter. Ultraviolet spectra were measured on a Beckman Acta T. M. III spectrometer. Mass spectra were obtained on a Finnegan 1015 GC-MS spectrometer. Nuclear magnetic resonance spectra were done on a Varian A-60A spectrometer, with tetramethylsilane as internal reference; chemical shifts are given on the τ scale.

Structure and Stereochemistry of Isomeric Penam and Cepham Derivatives[1]

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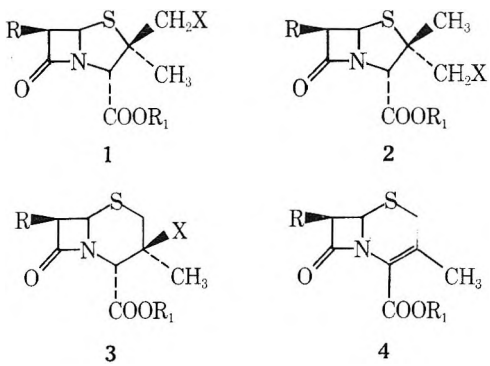
The ^1H and ^{13}C NMR spectra of a number of isomeric penam and cepham derivatives are reported. On the basis of these data assignments of structure and stereochemistry of penams and cephams have been made. In addition an independent study by X-ray diffraction has also confirmed the structure and stereochemistry of the title compounds.

The synthesis and chemical transformations of the title compounds are described in the preceding communication.[2] Working with these isomers, we, as well as others,[3] have encountered difficulties in distinguishing the structures and stereochemistry of isomeric penams and cephams. A more extended study of the nuclear magnetic resonance (NMR) spectra of these compounds has led to the development of additional methods that are useful in making structural and configurational distinctions in these systems.

The major difference between the penams (1 and 2), the cephams (3), and cephems (4) is in the size of the heterocyclic ring attached to the four-membered azetidinone. The β-lactam is easily characterized by the carbonyl stretching frequency between 1778 and 1806 cm^{-1} in the infrared spectrum. The cephem system (4) is also easily recognized through the carbonyl bands of the ir spectrum, as well as through proton chemical shifts and absence of the 4-H singlet in the ^1H NMR spectrum. The ir and ^1H NMR spectra of compound types 1, 2, and 3, however, are very similar. In the ^1H NMR spectra, for example, one observes for all three structural types (1) a methyl singlet; (2) an AB system due to the methylene group; (3) a one-proton singlet of the 3-H or 4-H; and (4) the pattern of resonances characteristic of the two methine proton resonances of the azetidinone ring. Attempts to distinguish between penam and cepham structures by arguments based upon proton chemical shifts and long-range proton–proton coupling are seldom successful. To overcome these difficulties, we have undertaken a study of the ^{13}C NMR spectra of these compounds.



1 2

3 4

The ^{13}C NMR spectroscopy has been shown to be useful in the elucidation of the structural problems of a different type of penicillins and cephalosporins.[4,5] The first step in interpreting the ^{13}C NMR spectra of these compounds is to identify those resonances due to the substituents R and R_1. This is generally easily effected through comparisons of these spectra to those of simple model compounds. Of the remaining resonances of the nucleus of the penam or cepham system (cf. Tables III and IV), three can be identified on the basis of their chemical shifts as being due to the carbonyl carbons. These resonances show a surprising degree of variation throughout these series, and at present we have no reliable means of assigning them specifically. Because of the long T_1 values characteristic of carbonyl carbons,[6] these resonances show misleading peak intensities and are occasionally difficult to detect, especially when only limited amounts of material are available. In compounds with structure 4 two resonances in the range typical of olefinic carbons make the recognition of this structural type straightforward.

In the upfield region of compounds of structures 1–3 one observes six carbon resonances. Through the use of off-resonance decoupling[6] one can easily assign these resonances to nonprotonated, methine, methylene, and methyl carbons. The methyl carbon resonances occur in the same range of chemical shifts (20–30 ppm) in structures 1–4, and provide no reliable guide in distinguishing between these structural types. In cepham structures of type 3 the nonprotonated carbon is directly substituted by X. Because of the widely varying α effects[6] of the X substituents, this leads to wider variation in the shifts of the C-3 resonances of 3 than observed for the C-2 resonances of 1 and 2. Despite this fact the chemical shift of the nonprotonated carbons is not a reliable guide in differentiating penam and cepham systems.

In fact, these two structural types are most easily distinguished through the chemical shift of the methylene carbons. In penam systems (1 and 2) the methylene carbon is directly substituted by X and is, therefore, deshielded to a degree which is largely dependent upon the electronegativity of this substituent.[7] In cepham systems, however, the only electronegative substituent on the methylene carbon is sulfur, which is known[7] to have an unusually small α effect. As a result, the methylene resonances of structural type 3 come into resonance in the chemical shift range 35 ± 4 ppm, while those of 1 or 2 are found below 42 ppm.

In the proton NMR spectra of these compounds, it is generally possible to assign the resonances of the methine protons specifically (cf. Tables I and II). Used in conjunction with selective proton decoupling,[6] these assignments can be used to identify specifically the three methine carbon resonances. Tables III and IV show that the carbon substituted by R has a relatively constant shift in all structural types (1–4). The other two methine carbons resonate at lower field in the penams than their analogs in the cephams. This parallels results from carbohydrate chemistry,[8] where a general deshielding of carbons in five-membered furanose systems relative to the six-membered pyranoses has been noted. It would appear, then, that the chemical shifts of the methine carbons of the thiazolidine

Table I
^{1}H NMR Data of Penam Derivatives

Compd No.[a]	R[b]	X	2α-CH_3	2β-CH_3	2α-CH_2X	2β-CH_2X	3-H	5-H	6-H
1a	Ft	Cl		1.93	3.77, 3.91 (11.5)		4.78	5.61 (4.5)	5.70 (4.5)
1b	Ft	Br		1.97	3.7, 3.9 (11.5)		4.8	5.6	5.6
1a	Ft	OAc		1.83	4.15, 4.29 (12)		4.71	5.57 (4.5)	5.64 (4.5)
1a	Ft	NO_3		1.88	4.69		4.79	5.60 (4.5)	5.71 (4.5)
2a	Ft	Cl	1.58			3.59, 4.51 (11.8)	5.14	5.74	5.74
2a	Ft	OAc	1.46			4.30, 4.68 (12)	5.0	5.63	5.63
2a	Ft	NO_3	1.53			4.72, 5.16 (11.5)	4.94	5.77	5.74
2b	Ft	Cl	1.57			3.68, 4.52 (12)	5.14	5.73	5.73
2b	Ft	Br	1.60			3.68, 4.50 (11.5)	5.30	5.80	5.80
2b	V	Cl	1.52			3.50	5.08	5.72	5.72
2c	Ft	Cl	1.51			3.62, 4.43 (12)	5.12	5.70	5.70
2c	Ft	NO_3	1.43			4.69, 5.16 (11.5)	4.95	5.77	5.77

[a] In structure numbers, a represents compounds in which R_1 = CH_3, while **b** and **c** indicate that R_1 is *p*-nitrobenzyl and *p*-methoxybenzyl, respectively. [b] Abbreviations used are Ft = phthalimido and V = phenoxyacetamido.

Table II
^{1}H NMR Data of Cepham Derivatives

Compd No.[a]	R[b]	X	3α-CH_3	CH_2S	4-H	6-H	7-H
3a	Ft	Cl	1.75	3.06, 3.44 (14.5)	4.95	5.40 (4.5)	5.61 (4.5)
3a	Ft	OH	1.35	2.54, 3.51 (14)	4.58	5.46 (4.5)	5.60 (4.5)
3a	Ft	OAc	1.60	3.32, 3.63 (14.5)	4.95	5.40 (4.5)	5.57 (4.5)
3a	Ft	NO_3	1.73	3.42	5.10	5.42 (4.5)	5.60 (4.5)
3b	Ft	OH	1.28	3.33	4.51	5.36 (4.5)	5.79 (4.5)
3b	V	Cl	1.67	2.75, 3.66 (14)	4.83	5.4 (4.5)	5.67, 5.83
3b	V	Br	1.85	2.75, 3.55 (14)	4.94	5.36 (4.5)	5.66, 5.79
3c	Ft	Cl	1.62	2.98, 3.41 (14)	4.93	5.37 (4.5)	5.58 (4.5)
3c	Ft	OH	1.28	2.48, 3.5 (14)	4.58	5.45 (4.5)	5.60 (4.5)
3c	Ft	OAc	1.61	2.98, 3.42 (14)	4.92	5.39 (4.5)	5.60 (4.5)
3c	Ft	NO_3	1.58	3.39	5.11	5.43 (4.5)	5.60 (4.5)
4a	Ft		2.33	2.85, 3.74 (15)		5.11 (4.5)	5.73 (4.5)
4b	Ft		2.35	3.00, 3.76 (15)		5.13 (4.5)	5.75 (4.5)
4b	V		2.17	3.20, 3.57 (18)		5.02 (4.5)	5.78, 5.92
4c	Ft		2.30	3.02, 3.70 (16)		5.12 (4.5)	5.75 (4.5)

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I.

Table III
^{13}C Chemical Shifts[a] in Penam Systems

	R[b]	R_1[b]	X	2	CH_3(2)	CH_2X(2)	3	5	6	7	$COOR_1$(4)	R(CO)	Σ[c]
1	Ft	CH_3	H	65.8	27.9	31.0	70.8	66.9	58.5	168.3	166.4	166.4	196.0
1	V	CH_3	H	64.0	26.2	31.3	69.7	67.2	57.6	167.3	167.1	172.3	194.5
1	Ft	CH_3	Cl	70.7	23.0	52.9	65.3	67.6	59.7	167.7	166.5	166.4	192.6
1	V	pNB	Cl	69.1	22.1	52.6	65.0	67.0	59.6	167.9	166.5	171.3	191.6
1	Ft	CH_3	NO_3	67.0	22.4	77.1	65.4	67.4	59.6	167.2	166.5	166.7	192.4
2	Ft	CH_3	Cl	70.5	27.5	51.4	68.9	67.2	58.8	167.8	166.4	167.8	194.9
2	Ft	CH_3	NO_3	66.9	25.6	75.6	68.8	67.3	58.4	167.9	166.4	168.1	194.5

[a] In parts per million downfield from internal Me_4Si. All spectra were run in deuteriochloroform solution. [b] Representative spectra of R and R_1 groups follow: Ft: C(1, 2), 131.3; C(3, 6), 123.8; C(4, 5), 134.5, OCH_3: 52.5. pNB: CH_2, 68.1; Ar(1), 141.4; Ar(2, 6), 128.9; Ar(3, 5), 123.7; Ar(4), 147.9; V: CH_2, 66.0; Ar(1), 156.5; Ar(2, 6), 114.7; Ar(3, 5), 129.6; Ar(4), 122.3. pMB: CH_2, 67.5; Ar(1), 142.0; Ar(2, 6), 130.5; Ar(3, 5), 114.0; Ar(4), 159.8; OCH_3, 55.3. [c] The values in this column represent the sums of the C(3), C(5), and C(6) chemical shifts.

and thiazine rings can be used to distinguish between penam and cepham systems.

In some cases specific assignment of the methine resonances is difficult or ambiguous. In such instances the sums of the methine chemical shifts are useful. The last columns of Tables III and IV present these sums for penam and cepham systems. When the substituents R, R_1, and X are equivalent, this sum is about 20 ppm further toward lower field in the penam than in the cepham system. When chemical shifts are measured relative to internal tetramethylsilane, this sum rarely exceeds 175 ppm for compounds of structure **3**.

After having initially distinguished penams **1** and **2** from the cepham **3** by ^{13}C NMR spectroscopy, we noted a generality in the ^{1}H NMR spectra of these compounds which can be used more conveniently for this purpose. Thus, the gem-

Table IV
^{13}C Chemical Shifts[a] in Cepham and Cephem Systems

	R[b]	R_1[b]	X	C(2)	C(3)	C(3')	C(4)	C(6)	C(7)	C(8)	$COOR_1$(4)	R(CO)	Σ[d]
3	Ft	CH_3	OH	35.3	64.4	24.7	60.8	53.4	58.6	167.3	168.5	161.6	172.8
3	Ft	pMB	OH	35.2	64.4	24.6	60.8	53.2	58.5	167.2	167.6	161.5	172.5
3	Ft	CH_3	ONO_2	31.2	80.7	21.2	55.7	54.2	58.7	167.1	166.4	161.8	168.6
3	Ft	pMB	Cl	37.5	61.7	28.7	61.3	54.0	58.8	167.0	c	161.6	174.1
4	Ft	CH_3		31.5	123.6	20.0	145.5	59.2	59.2	166.5	162.1	160.9	
4	V	pNB		30.3	121.9	20.1	142.5	56.9	58.3	168.7	164.1	161.4	

[a] In parts per million from internal Me_4Si. [b] See footnote *b*, Table III, for representative spectra of the R and R_1 fragments. [c] Not observed. [d] The values in this column represent the sums of the C(4), C(6), and C(7) chemical shifts for structural type 3.

inal coupling constants observed for the methylene protons in **1** and **2** are consistently in the range of 11.5–12.0 Hz; this coupling in compounds **3** is larger, ranging from 14.0 to 14.5 Hz. In cases wherein this coupling constant can be measured, this criterion should be most useful in distinguishing penams from cephams.

Inspection of Tables III and IV shows that the chemical shifts of carbons throughout these molecules are dependent to varying extents upon the identity of X. In some cases these differences can be explained in terms of the β and γ effects of the substituents.[7] In structure **1**, for example, the chemical shift of carbon 3 shows increasing shielding as X progresses through the sequence H, Br, and Cl. Such a result is consistent with the γ effects of these substituents.[7] Other carbon chemical shift changes are more difficult to explain. Thus the resonance of carbon 6 of **2** appears about 1 ppm toward higher field from that of carbon 6 in **1**, even though the C(5) resonances of the two structures are virtually identical. When both isomers (**1** and **2**) are available, this difference in the C(6) chemical shift may in fact be used to distinguish configurations in these penam systems.

A much more convenient way of distinguishing between structures **1** and **2**, however, depends upon the chemical shift of the methyl protons in these systems. The data in Table I show that the chemical shifts of the protons of 2β-methyl groups are at uniformly lower field than those of the epimeric 2α analogs. Also useful in differentiating between **1** and **2** is the observation that the chemical shifts of the azetidinone protons at positions 5 and 6 are consistently more similar in **2**. In fact these resonances generally occur as two-proton singlets at 60 MHz. More rigorous assignment of configuration in these penam systems can be obtained from measurement of the nuclear Overhauser enhancements.[9]

Through judicious use of ^{13}C and ^{1}H NMR data, therefore, it is easily possible to distinguish between structures **1**–**4**. Continuing studies are directed toward efforts to use these data to elucidate conformations in these systems.

The structure and stereochemistry of **1** (R = Ft; R_1 = CH_3; X = Cl) were also confirmed by X-ray diffraction methods. Crystals appearing as colorless needles were grown from a mixture of methylene chloride and diethyl ether. The space group is $P2_1$, with two molecules in the unit cell having the dimensions a = 11.246 ± 0.002 Å, b = 7.003 ± 0.002 Å, c = 12.773 ± 0.002 Å, and β = 99.58 ± 0.01°. The intensities of 2019 independent nonzero reflections were measured on a Syntex $P2_1$ automated diffractometer using monochromated copper radiation.

The positions of the sulfur and chlorine atoms were located from a $E^2 - 1$ map. An E map calculated using the phases of the sulfur and chlorine atoms showed the positions of the remaining nonhydrogen atoms. Refinement by the least-squares method, using anisotropic temperature factors, brought the R factor down to 0.115. A difference electron density map calculated at this point revealed an unresolved column of electron density, probably due to a disordering of solvent molecules. Attempts to account for the solvent in further least-squares refinements were unsuccessful. Final refinement was done without including the disordered solvent and converged at a R factor of 0.113. The conformation of the molecule is shown in Figure 1.

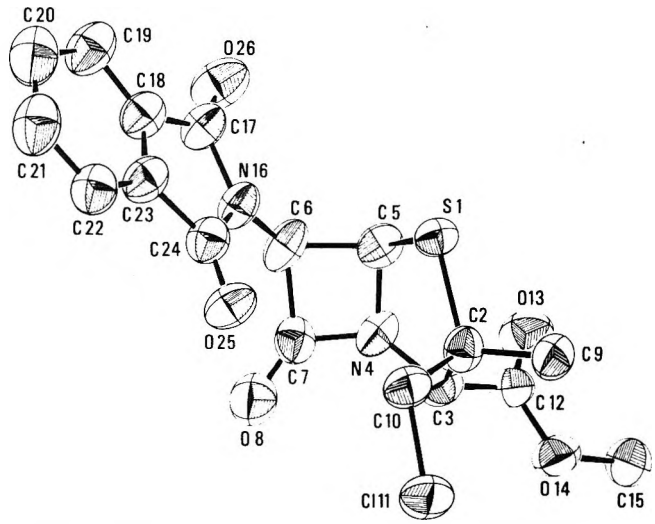


Figure 1. Skeletal conformation of methyl 6β-phthalimido-2β-chloromethyl-2α-methylpenam-3α-carboxylate (**1**) in the crystalline state. Thermal ellipsoids are drawn to include 50% probability.

Experimental Section

The preparation of the compounds studied has been previously described.[2] Carbon-13 NMR spectra were measured in deuteriochloroform solution using concentrations ranging from 0.2 to 0.5 *M*. Initial spectra were recorded at 15.1 or 25.2 MHz at Indiana University, Bloomington, Ind. Subsequent spectra were measured on a Jeol PS-100 Fourier transform spectrometer operating at 25.15 MHz. NMR spectra were recorded using Varian T-60 and HA-100 spectrometers in $CDCl_3$ with Me_4Si as internal reference.

Registry No.—**1a** (R = Et; X = Cl), 51415-59-9; **1a** (R = Et; X = OAc), 39269-09-5; **1a** (R = Et; X = NO_3), 51815-60-2; **1a** (R = Et; X = H), 19788-65-9; **1a** (R = V; X = H), 2315-05-1; **1b** (R = Ft; X = Br), 55450-53-8; **1b** (R = V; X = Cl), 51415-43-1; **2a** (R = Ft; X = Cl), 39067-79-3; **2a** (R = Ft; X = OAc), 55450-54-9; **2a** (R = Ft; X = NO_3), 55450-55-0; **2b** (R = Ft; X = Cl), 51815-65-7; **2b** (R = Ft; X = Br), 55520-58-6; **2b** (R = V; X = Cl), 55450-56-1; **2c** (R = Ft; X = Cl), 52353-29-4; **2c** (R = Ft; X = NO_3), 51815-58-8; **3a** (R = Ft; X = Cl), 40146-21-2; **3a** (R = Ft; X = OH), 51815-69-1; **3a** (R = Ft; X = OAc), 55450-57-2; **3a** (R = Ft; X = NO_3), 55450-58-3; **3b** (R = Ft; X = OH), 55450-59-4; **3b** (R = V; X = Cl), 51546-66-8; **3b** (R = V; X = Br), 55450-60-7; **3c** (R = Ft; X = Cl), 51815-67-9; **3c** (R = Ft; X = OH), 55450-61-8; **3c** (R = Ft; X = OAc), 55450-62-9; **3c** (R = Ft; X = NO_3), 55450-63-0; **4a** (R = Ft), 38584-05-3; **4b** (R = Ft), 51415-20-4; **4b** (R = V), 28974-31-4; **4c** (R = Ft), 51815-59-9.

Supplementary Material Available. Tables of fractional coordinates and anisotropic thermal parameters 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 $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2388.

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Conformations of the Radical Anions from Dialkyl Maleates and Fumarates

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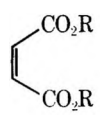
Both dialkyl maleates and fumarates give the same mixture of monoanion radicals, as several workers have noted. It is proposed that all the conformations observed are trans at the original carbon–carbon double bond, and that syn and anti alkyl conformations are observed with primary alkyl groups. This proposal requires that surprisingly slow carbonyl carbon–alkoxyl oxygen rotation occurs in the radical anions.

Electrolytic reduction of dialkyl maleate (1) and fumarate (2) esters in DMSO produces the same mixture of radical anion ESR spectra, indicating that cis–trans isomerization occurs rapidly in the radical anions.[1] Our attribution of the two isomers of $(1,2)\cdot^-$ which we observed to the trans



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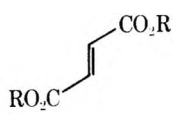
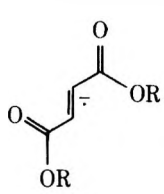


2

and cis radical anions was incorrect, as the simple fact that we saw substantial amounts of both isomers should have told us; the cis isomer is far more sterically hindered than the trans one, and both of the reported isomers must be trans.[2] The ESR spectra[3] and electrochemistry[4] of these and similar compounds were studied in DMF by Il'yasov and coworkers, and Bard and coworkers have greatly extended such studies.[5] Kemp and coworkers[6] have studied the ESR spectra of these radical anions in liquid ammonia using solvated electrons for generation, and were able to discern no less than four dimethyl maleate–fumarate radical anions. They point out that the two major components A and B (see Table I), which correspond to the species we reported in DMSO, are accompanied by minor components C and D, which have significantly larger g factors. Diethyl fumarate–maleate behaved in a similar manner except that only one minor component was discerned. They attributed the major components A and B to conformations of the fumarate radical anion **3** and **4**, and the minor components C



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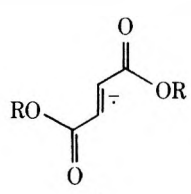

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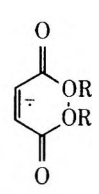

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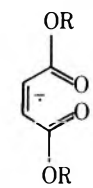

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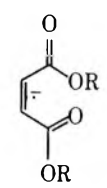

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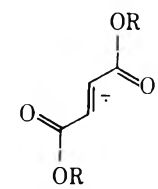


8

and D to the maleate anions **5** and **6**, stating that **7** was not observed because it would have inequivalent vinyl splittings, whereas A–D were observed to have equivalent ones. They also said additional components cannot be ruled out of these complex spectra, which show many overlapping lines. The remaining symmetrical trans form **8** is also a possibility for A or B.

In the earlier work, we also reported that a second type of species was generated at higher potential and longer electrolysis times, and attributed it to the anion radical of monoalkyl maleate–fumarate anion.[1] Il'yasov and coworkers[3] stated disbelief in this assignment, and wish to attribute the species to oligomers of some sort, for which they give a couple of structures.

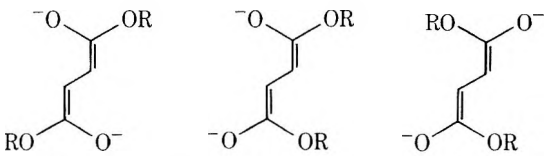
In hopes of discovering more about the isomers of the maleate–fumarate radical anion conformations, we have done additional ESR work on these systems.

Results and Discussion

The radical anions from dimethyl and diethyl fumarate–maleate give complex spectra which are not very long lived in DMSO, and we had significantly less resolution then Kemp and coworkers.[6] The minor conformations they report in ammonia are quite probably also present in DMSO. Since alkyl can be on either of the two types of oxygen present, which we will refer to as "inner" and "outer", there are three dialkyl fumarate conformations (the oi and io conformers being identical when the alkyl groups are the same). If all were of equal energy, one would observe a 1:2:1 mixture of oo, oi, and ii conformations, and the oi confor-

Table I
ESR Data for Some Dialkyl Maleate–Fumarate Anion Radicals

Starting compd	Species	Relative	a(Hv)	a(alkyl)	g shift
1 or 2 (R = R′ = Me)[6]	A	Major	6.83 (2 H)	1.39 (4 H)	
	B	Major	6.62 (2 H)	1.39 (4 H)	+0.0001
	C	Minor	6.73 (2 H)	1.35 (4 H)	+0.0003
	D	Minor	6.73 (2 H)	1.35 (4 H)	+0.0006
9	I	~0.5	6.53 (2 H)		
	II	~0.3	6.30, 6.54		+0.00008
	III	~0.2	6.42		+0.00005
10	I	~0.6	7.01, 6.44	1.17	
	II	~0.2	6.76, 6.51	1.18	+0.00009
	III	~0.2	6.98, 6.25	0.82	+0.00038

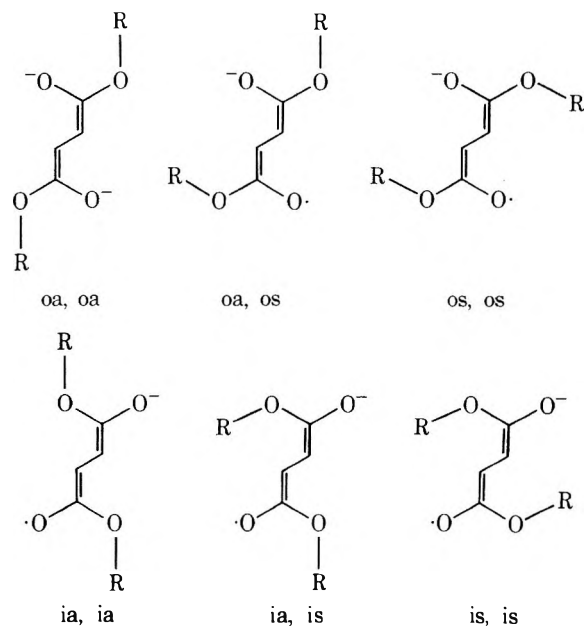


oo (4) oi (3) ii (8)

mation would have nonequivalent hydrogen splittings. To simplify the spectra and increase the anion radical lifetime,[5b] we have investigated two additional cases, di-*tert*-butyl maleate **9** (**1**, R = R′ = *t*-Bu) and *tert*-butylmethyl maleate **10** (**1**, R = *t*-Bu; R′ = Me); the *tert*-butyl groups, as expected, showed no splitting. The ESR data for these compounds appears in Table I. From both **9** and **10**, we were definitely able to distinguish three isomers, but small unattributed lines were present, and it is certainly possible that even isomers present in substantial amount would be so completely masked by lines from the attributed species that we might have missed them. The "amount" column is only estimated by peak height, and is not at all reliable.

The three observed isomers from **9** correspond well with the expectation for oo, oi, and ii. There is a slight preference for either oo or ii, but all three are actually present in substantial amount, and there is very little preference between "inner" and "outer" alkyl group in fumarate anion radical. All three have very similar *g* factors, making it likely that all three are actually present in dimethyl and diethyl fumarate as well, but not discernible because of the complexity of the spectra. No large *g* factor forms were observed, and the simplicity of the spectra require that we would have seen such species had they been there in substantial amount. For the radical anions from **10**, we were only able to discern two of the four possible (and presumably present) "low *g* factor" conformations. Presumably the other two are lurking somewhere under the major peaks, but it is not obvious where. We also saw one other conformation (**10**, III) which has the larger *g* factor that Kemp and coworkers observed for minor conformations from dimethyl and diethyl maleate–fumarate, and attributed to maleate forms.

If conformation III from **10** is attributed to a maleate form, however, one is hard pressed to explain why a similar conformation was not observed from **9**, since the *tert*-butyl groups of maleate conformations **6** and **7** could be tucked away from other parts of the molecule as efficiently as they could in the fumarate forms. Furthermore, attribution of C and D of Table I, and hence **10**, III, to the maleate form is inconsistent with the experimental results of Bard and coworkers,[5c] who found that reduction and reoxidation of the maleate gave complete isomerization to the fumarate. We suggest that even the high *g* factor radical anions are fumarate forms, and that the reason that more than three isomers are observable is that in addition to isomerism between "inner" and "outer" oxygens, syn–anti isomerism at the *O*-alkyl groups is being observed. There would then be in principle ten different isomers (six of the 16 possible isomers generated by each end having i or o alkyl group in s or a position are identical with six others), as is shown for the oo and ii isomers below (there are also now four oi isomers,



oa, oa oa, os os, os

ia, ia ia, is is, is

not shown). These isomers would not have equivalent steric interactions. There is little or no steric difference between oa, oa, oa, ia, and ia, ia conformations, but all syn conformations are sterically destabilized, and it is clear that is conformations are considerably destabilized compared to os conformations. It is also worth noting that all fumarate conformations are less destabilized sterically than any maleate conformations (of which there are also ten, considering s,a isomerization, although all is maleate conformations are absurdly hindered).

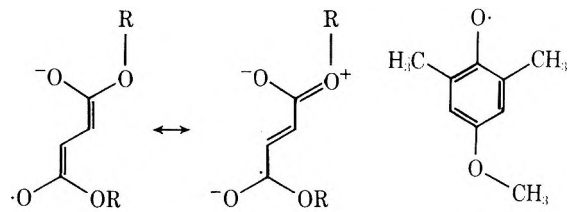
If the high *g* factor conformation(s) observed are attributed to conformations having "outer" syn alkoxyl groups (such as oa, os), this would take care of both of the objections raised above to the maleate assignment, since the bulky *tert*-butyl group would be unlikely to present syn in detectable amount, and of course all fumarate radical anions will oxidize to neutral fumarate.

The problem with this assignment is, of course, whether one would really expect carbonyl carbon–oxygen rotation to be slow on the ESR time scale at room temperature, so that syn conformations would give distinct spectra. Although we find such slow rotation as we are forced to pos-

Table II
ESR Data for Monoalkyl Fumarate Dianion Radicals (15, 16)

Alkyl group	Species	a(Hv)	a(alkyl)	g factor shift	Registry no.
tert-Butyl	I	9.80, 2.77			
	II	9.78, 2.60		0.00011	55569-43-2
Isopropyl	I	9.84, 3.11	0.47 (1 H)		
	II	9.80, 2.93	0.33 (1 H)	0.00009	55569-44-3
Ethyl[1]	I	10.24, 2.78	0.91 (2 H)		
	II	10.13, 2.69	0.69 (2 H)	0.00012	55569-45-4
Methyl[1]	I	10.11, 2.81	1.02 (3 H)		
	II	10.03, 2.75	0.77 (3 H)	0.00012	55569-46-5

tulate surprising, stabilization of the oxadienyl fragment by a conjugated alkoxyl oxygen, as shown in resonance structures **11** ↔ **12**, could lead to such behavior. The best model

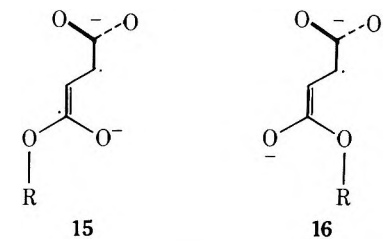


11 **12** **13**

we have thought of for such an interaction is the 4-alkoxyphenoxy radical **13**, for which an activation energy for aryl-O rotation of 7.8 ± 1 kcal/mol was measured by ESR.[7] This is a far higher barrier than is observed for diamagnetic alkoxybenzenes;[8] *p*-dimethoxybenzene has a methoxy rotational barrier of only 0.88 kcal/mol.[8a] A conjugative interaction of the sort shown in **11** ↔ **12** was invoked to rationalize the increase in barrier height.[7] Such delocalization might be predicted to be more favorable in the case of **11** ↔ **12** than for **13** because of the anionic oxygen substituent, which should electrostatically favor charge separation in the sense of **12**.

At higher applied potentials and longer electrolysis times, all of the dialkyl maleates and fumarates studied gave a second mixture of spectra, for which the ESR data are summarized in Table II. The species designated II was present in smaller amount in all cases, and the ratio of I/II varied from about 2.4:1 for methyl and ethyl to about 1.3:1 for *tert*-butyl. Since the monoalkyl maleates give the same species (I and II) as the second one from the dialkyl maleates and fumarates, and the spectra show only splittings for the quite inequivalent vinyl hydrogens and one alkyl group, we assign these spectra to monoalkyl fumarate dianion radicals. We have previously observed exactly analogous formation of benzaldehyde-*o*-carboxylate radical dianions directly from the acid, or as second species from the esters or pseudo-esters.[2] The dimeric species proposed by Il'yasov and coworkers[3] would certainly show additional splittings.

We have been unable to observe these monoalkyl fumarate dianion radicals in DMF or butyronitrile, and believe their lifetimes to be far shorter in these solvents. Since the *g* factors are quite similar for the two isomers observed in each case, and only two isomers were distinguished even for the methyl and ethyl cases, we assign I and II as "inner" and "outer" oxygen isomers **15** and **16**. As was the case in the *o*-carboxylate benzaldehyde dianion radicals, the carboxylate has a relatively minor effect on the spin distribution, and is probably substantially twisted out of conjugation with the rest of the molecule. Ethylacrylate anion radical has vinyl splittings of 12.18 (2 H_β) and 1.57 (H_α) G,[6]



15 **16**

compared to around 10 and 2.8 G for our radicals, which bear a β-carboxylate substituent. We see no evidence for the added complexity of still more conformations, as was observed with methyl and ethyl dialkyl fumarate anions. The presence of the carboxylate would be expected to increase the C–OR rotation rate, so we do not find this surprising. We do not have a plausible rationale for the significantly smaller alkyl splitting for the II conformations.

Ester exchange is easily noted if excess alcohol is mixed with the DMSO used as the reducing medium, as it was with the aromatic systems.[2] When 2-propanol–DMSO was used for reduction of dimethyl maleate, the first mixture species observed was an ill-resolved mixture of diisopropyl fumarate radical anions, and at longer reduction times, **15–16** (R = *i*-Pr) was observed. The exchange may well proceed by attack of electrolytically generated alkoxide upon starting ester. Another mechanism is suggested by the results of Il'yasov and coworkers,[3,4] who found that diphenyl maleates and fumarates did not give stable enough radical anions for observation, even at low temperature, and proposed "phenoxide stripping", loss of PhO from the radical anion, to account for this unstability. The ketene thus formed could capture either alcohol or adventitious water, and this is an alternative mechanism for **15–16** formation. The mixed ester **10** gave only the *tert*-butyl substituted **15–16**, as would be expected by either pathway.

Experimental Section

Di-*tert*-butyl maleate (**9**) was prepared by reaction of maleic acid and methyl maleate with isobutylene in methylene chloride in the presence of sulfuric acid.[9] Crystallization from ether gave **9**, mp 68° (lit.[10] mp 68°).

tert-Butyl methyl maleate (**10**) was prepared by stirring 10 g of maleic anhydride in 150 ml of methylene chloride with 3.6 g of anhydrous methanol and a trace of sodium methoxide overnight, and then *tert*-butylating as above. The residue was distilled at 5 mm (bp 50–85°), yielding 7 g of a mixture of **10** and dimethyl maleate (ca. 3:1), from which **10** was isolated by redistillation [bp 80–82° (5 mm)]. Dimethyl maleate or other impurities were not detected by NMR. The empirical formula was established by high-resolution mass spectroscopy.

ESR measurements were carried out on a Varian E-15 spectrometer using intra muros reduction with a mercury pool cathode in a flat quartz cell to generate the radical anions.[2]

Acknowledgment. We thank the National Science Foundation and the donors of the Petroleum Research

Fund, administered by the American Chemical Society, for partial financial support of this work. We thank Professor Bard for communication of his results prior to their publication.

Registry No.—**1**, 624-48-6; **2**, 624-49-7; *cis*-**9**, 18305-60-7; *trans*-**9**, 7633-38-7; *cis*-**10**, 55556-65-5; *trans*-**10**, 55556-66-6; butenedioic acid, dimethyl ester radical ion, 55569-40-9; butenedioic acid, di-*tert*-butyl ester radical ion, 55569-41-0; butenedioic acid, methyl, *tert*-butyl ester radical ion, 55569-42-1.

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Selective Lithiation of Bromoarylalkanoic Acids and Amides at Low Temperature. Preparation of Substituted Arylalkanoic Acids and Indanones[1]

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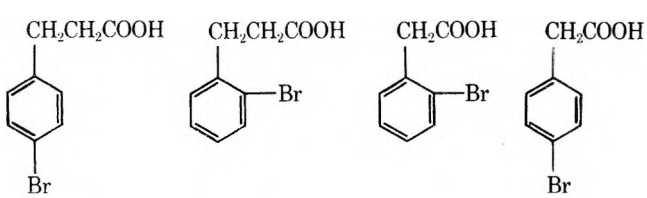
Studies of *p*-bromophenylpropanoic acid suggest that *p*-, and presumably *m*-, bromoarylalkanoic acids can be conveniently elaborated by selective halogen–metal exchange with *n*-butyllithium at −100° followed by reaction with E^+. Metal–halogen exchange is also selective for ortho-substituted acids; however, *o*-bromoarylpropanoic acids lead directly to indanones in high yield. Amide anions have been shown to be less reactive toward organolithium derivatives than carboxylate; consequently, by masking the carboxylic acid group by conversion to the amide anion, indanone formation can be obviated and elaboration of o-bromophenylpropanoic acid can be achieved. *o*-Bromophenylacetic acid (**3**) reacts with *n*-butyllithium at −100 or at −78° to give the dilithio derivative **21** and the trilithio derivative **23**. The trilithio derivative undergoes anion decay, with time, by reaction with solvent, to give **21**; consequently, by control of conditions, products can be obtained selectively from either **21** or **23**. Similar results were obtained with *p*-bromophenylacetic acid (**4**); however, in contrast to the results obtained with **3**, alkylation of intermediate anions with *n*-butyl bromide, formed during metal interchange, occurs which detracts from synthetic applications in the latter case.

Although Grignard (or lithium) reagents of aryl halides are useful intermediates for formation of aryl–carbon bonds, utilization of such derivatives has been of limited value for aromatic nuclei containing sensitive electron-withdrawing groups. Meyers and Temple[2] have obviated problems associated with aromatic carboxylic acids by disguising the carboxylic function as the corresponding oxazoline derivative. Recently we have shown[3a,b] that the lithium salt of aryl carboxylic acid function provides adequate protection of the carboxylic acid group at −100° to lithium reagents, and that high yields of elaborated arylcarboxylic acids can be obtained directly from *o*-, *m*-, and *p*-bromobenzoic acids.

We have now examined the reaction of acids **1**–**4** with *n*-butyllithium at −100° as part of a program designed to test

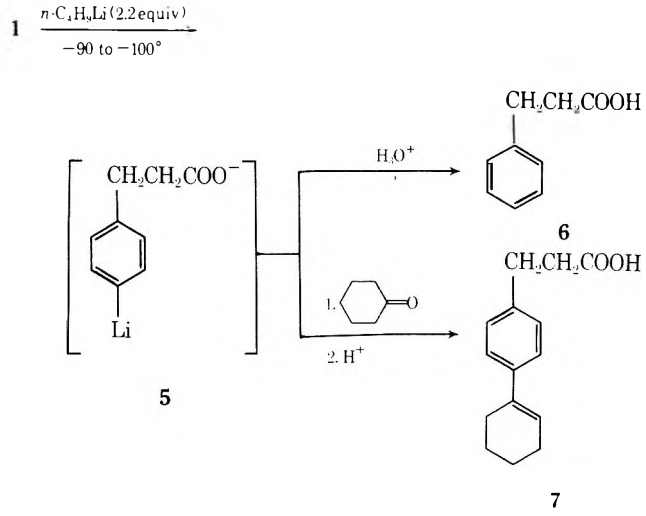


1 **2** **3** **4**

the generality of the above method for the elaboration of alkanoic acids. Acid **1** was selected as a model for the behavior expected for a broad series of para- and meta-substituted bromoarylalkanoic acids. Limitations for utilization of bromoarylalkanoic acids were anticipated where favorable entropy relationships might result in intramolecular reaction of derived aryllithium reagents with carboxylate functions (as in **2**), and in phenylacetic acids (**3** and **4**) where the methylene group α to the carboxylate function is more acidic. In all cases, progress of metal–halogen exchange was followed by quenching aliquots[4] with dilute acid and determining the ratio (by NMR) of recovered bromo acid to acid derived by replacing bromine with hydrogen.

A. β-(*p*-Bromophenyl)propanoic Acid (1). Two equivalents of *n*-butyllithium was added rapidly to a solution of **1** in THF–hexane at −100° at such a rate that the temperature did not exceed −90°. Examination of an aliquot showed that halogen–lithium exchange was ~80% after 30 min and the ratio did not change appreciably after an additional 90 min at −100°. Additional *n*-butyllithium (up to 0.4 to 1 equiv) increased the degree of exchange only slightly (ratio of **1**:**6** was ~85%); however, with excess *n*-butyllithium and time, small quantities of butylated products were detected (NMR) in the neutral component of the aliquots. In subsequent experiments 2.2 equiv of *n*-butyllithium was employed and the mixture was stirred at −100° for 45 min prior to quenching. In one experiment (see Scheme I) the mixture was quenched with water; the yield

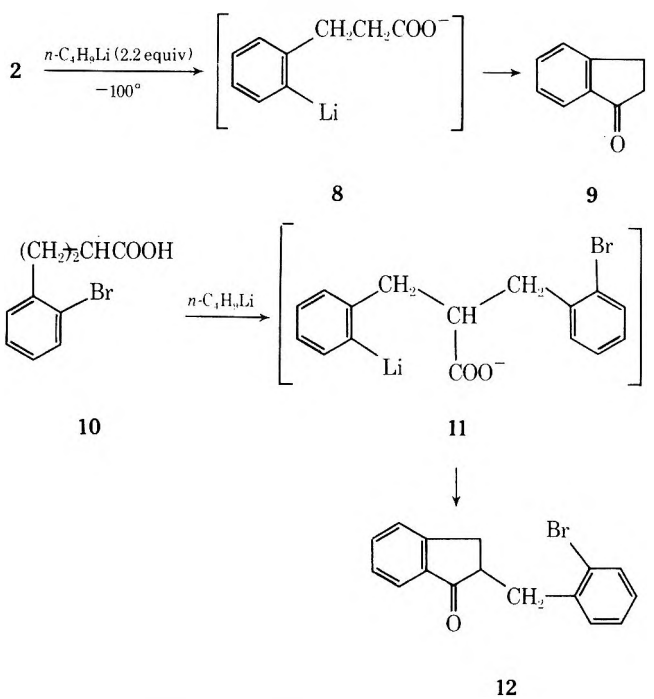
Scheme I



of **6**, isolated pure by distillation, was 86%. The residual acidic product was a mixture of **1**, **6**, and a trace of butylated acid.[5] In another experiment **5** was quenched with cyclohexanone;[6] the yield of nearly pure **7** was 67% (59% pure). In no case was there any evidence that **5** self-condensed at −100°. It was concluded, therefore, that, except for the limitations described in B and C (below), the procedure described should prove to be a useful one for the elaboration of *m*- and *p*-arylalkanoic acids.

B. β-(*o*-Bromophenyl)propanoic Acid (2). This acid was chosen for study since it was anticipated that favorable entropy considerations may lead to self-condensation of **8**, leading to indanone (**9**).

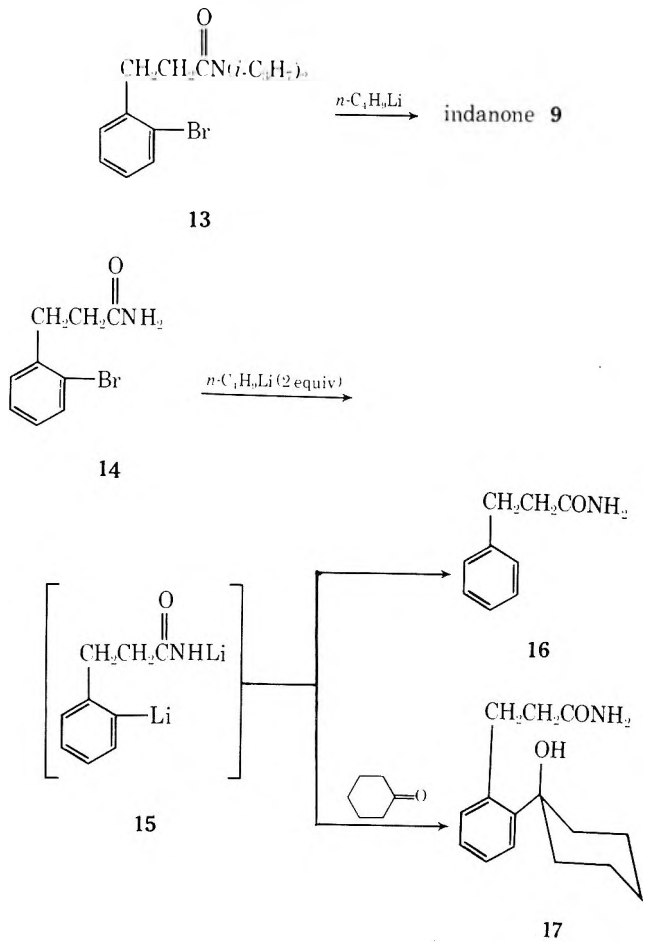
Scheme II



Reaction of **2** with *n*-butyllithium was indeed selective at −100° in that halogen–metal exchange occurred without proton abstraction from the methylene group or without addition of *n*-butyllithium to carboxylate; however, as anticipated, cyclization occurred at −100° to give indanone. Studies of aliquots[4] showed that cyclization was appreciable after 60 min at −100°. The mixture was stirred at −100° for 3 hr; the yield of indanone,[6] isolated pure by distillation, was 76%. While this observation defines a limitation to the general elaboration of bromoarylalkanoic acids suggested in A (above), this new synthesis should be of value for the preparation of indanones not easily available by more conventional routes.[7] In a similar experiment, reaction of **10** (Scheme II) with 2 equiv of *n*-butyllithium afforded a good yield of **12** (66%). Significantly, reaction of **10** with 3 equiv of *n*-butyllithium leads to 2-benzylindanone (72% yield).[8]

Amide ions were found to be less reactive than carboxylate ions toward organolithium reagents; consequently, cyclization of o-bromoarylpropanoic acids to indanones can be obviated by utilizing certain amides derived from the acid (Scheme III). Reaction of the dialkylamide **13** with 1

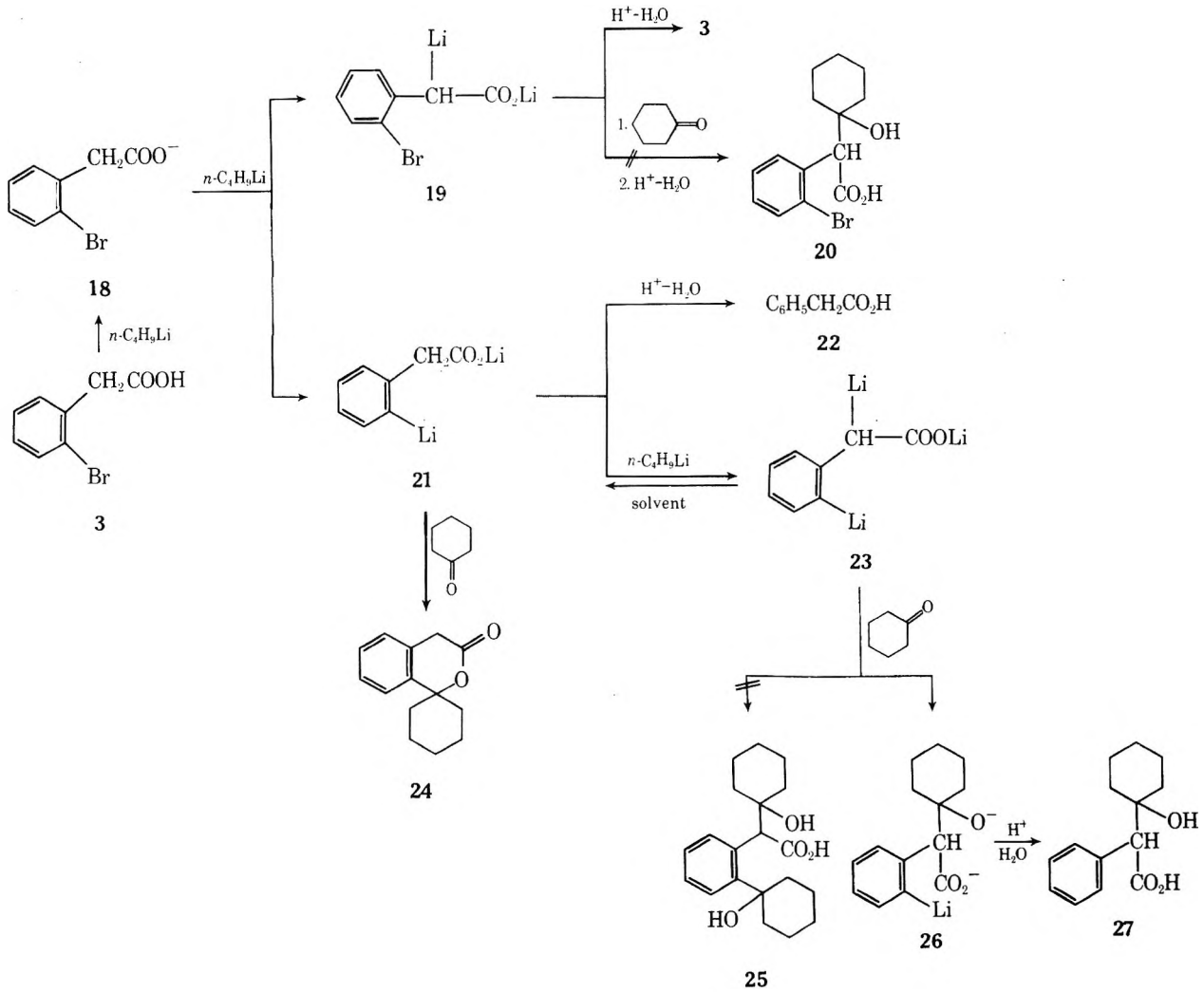
Scheme III



equiv of *n*-butyllithium at −100° leads directly to indanone (61% yield by isolation). By contrast, reaction of the unsubstituted amide **14** with 2 equiv of *n*-butyllithium leads to the dilithio derivative **15**, which does not cyclize at −100°. Reaction with acid gave **16** in 81% yield (isolated); amide **17** was isolated pure in 40% yield when **15** was quenched with cyclohexanone. Use of such amides appears attractive as masking agents of carboxyl functions in such reactions.

C. *o*-Bromophenylacetic Acid (3). Halogen–metal interchange in *o*-bromophenylacetic acid is more complex owing to trianion formation (**23**) and incomplete halogen–metal exchange; however, by utilizing "anion decay" (see below), reasonable yields of elaborated products (**24**) can be obtained. Results of these studies, which are summarized in Scheme IV, have led us to the following conclusions and comments.

Scheme IV



1. Metalation of the rapidly formed salt **18** with the second equivalent of *n*-butyllithium was slow at −100°[4e] and leads to the dilithio derivative **21** and presumably to the trilithio derivative **23**. Whether **19** is formed at all, or whether it was unreactive owing to solubility or steric reasons, was not determined; however, no products derived from **19**, other than recovered **3**, were obtained in subsequent reactions. Examination of aliquots which were quenched with dilute acid showed no change in degree of metalation (ratio of *o*-bromophenylacetic acid to phenylacetic acid 36:64) after 4 hr.[4b]

2. The salt **19**, if formed, does not undergo appreciable further metalation. Addition of a third equivalent of *n*-butyllithium changed the above ratio to 30:70; however, further addition of *n*-butyllithium (up to 6 equiv) caused no appreciable further change in this ratio, and in the amount of *o*-bromophenylacetic acid recovered.

3. The dilithio derivative **21** does react with *n*-butyllithium to give the trilithio derivative **23**; however, **23** is unstable at −100° and reacts with solvent to regenerate **21**. Thus, addition of additional *n*-butyllithium has little effect on the ultimate composition of the mixture; **23** is formed from **21**, which decays back to **21**, and this process is repeated by addition of additional *n*-butyllithium.

4. The dilithio derivative **21** reacts with cyclohexanone by addition to give, subsequent to acidification, lactone **24**, and undoubtedly some phenylacetic acid by enolate formation with the ketone. Maximum yield of lactone **24** (42%, 60% based on converted **3**) was obtained when a mixture of *o*-bromophenylacetic and 3 equiv of *n*-butyllithium was stirred at −100° for 5 hr, to permit decay of **23** to **21**, prior to addition of excess cyclohexanone. The only other acids formed in this reaction were *o*-bromophenylacetic acid and phenylacetic acid (ratio 40:60).

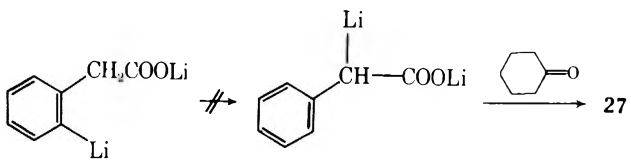
5. The trilithio derivative **23** reacts with cyclohexanone to give hydroxy acid **27**; in no case was hydroxy acid **25** detected. The anion **23** rapidly decays to **21** and after 4–5 hr at −75 to −100° is completely converted to **21**. Thus, if cyclohexanone is added only 1 hr after addition of the third equivalent of *n*-butyllithium to the reaction mixture obtained from **3** and 2 equiv of *n*-butyllithium (7 hr, −100°), **23** is present. Under these conditions hydroxy acid **27** is formed which was isolated in 39% yield; lactone **24** was isolated in 24% yield. If this solution is aged prior to addition of cyclohexanone (see 4, above), no hydroxy acid **27** is produced. The lifetime of **23** was examined (in separate experiments) by adding cyclohexanone after different time intervals following the addition of the third equivalent of *n*-butyllithium. The maximum yield of **27** (54%, 77% based on converted **3**) was obtained by adding excess cyclohexanone to an aged mixture (14 hr) prepared from **3** and 3 equiv of *n*-butyllithium 15 min after addition of a fourth equivalent of *n*-butyllithium; 10% yield of lactone **24** was also isolated in this case. Failure to isolate the disubstituted product **25** from the trilithio derivative is interpreted to mean that either (1) reaction with ketone occurred preferentially at the anion adjacent to carboxylate, and that the derived aryllithium intermediate **26** does not react further with cyclo-

hexanone for steric reasons, or (2) that the aryllithium in **26** is lost and converted to the salt of **27** by reaction with solvent. It is of interest to note that the corresponding trilithio derivative **30** derived from the para isomer reacts with cyclohexanone at both carbon anionic centers.

6. Loss of trilithio derivative **23** is a function of concentration and temperature. Reaction of **3** under identical conditions described in 5 (above), but at one-fourth the molar concentration (i.e., more concentrated in solvent tetrahydrofuran), led to greater loss of **23.** The yield of **27** decreased from 39% to 26% while the yield of lactone derived from **24** increased from 24% to 30% (by isolation). Furthermore, addition of cyclohexanone to a mixture prepared from **3** (2 equiv of *n*-butyllithium) 3 hr after adding the third molar equivalent of *n*-butyllithium at −100° led to a 13% yield of **27,** but to no **27** when the extra 3 hr of aging was at −75°.

7. An alternate pathway for the formation of **27** as shown in Scheme V is rejected. If this process was of signif-

Scheme V



icance, then aging prior to addition of cyclohexanone should result in an increase in yield of **27,** which is in complete contradiction to the results observed.

Studies of metalation of *p*-bromophenylacetic acid (**4**) gave similar results and provided more conclusive evidence for formation of products derived from the trilithio derivative **30** (Scheme VI); however, the reaction products were more complex than those obtained from **3.** The following observations were made.

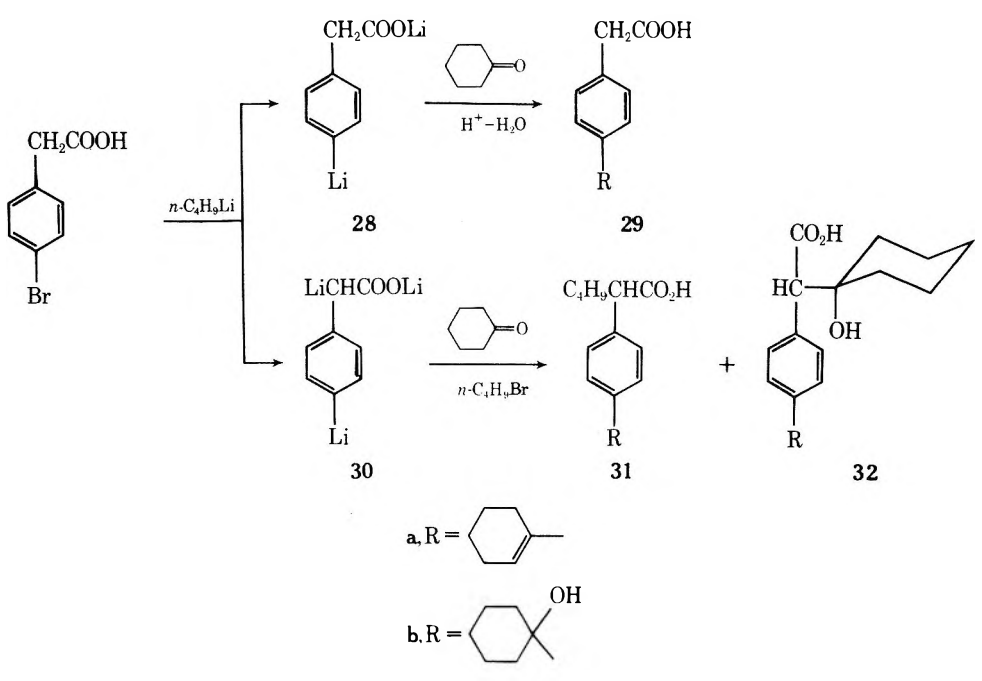
1. The degree of halogen–lithium interchange was 40% with 2 equiv of *n*-butyllithium after 2 hr and this value was unchanged after an additional 4 hr.[4c] The degree of halogen–lithium interchange decreased in more concentrated solutions. Thus, under similar conditions but at four times the molar concentration of **4** in solvent, the degree of halogen–lithium interchange was only 20%. This decrease is attributed to insolubility of the carboxylate salt of **4.** The maximum degree of halogen–lithium interchange (60%) was achieved by addition of 3 equiv of *n*-butyllithium to **4** and stirring the resulting mixture (~17 hr). The solution was a mixture containing **28** and **30.** The degree of halogen–lithium interchange was unchanged by addition of a fourth equivalent of *n*-butyllithium.

2. The trilithio derivative **30,** like the analogous salt **23,** decays to dilithio derivative **28** with time by reaction with solvent. Thus, addition of a fourth equivalent of *n*-butyllithium to a mixture prepared from **4** and 3 equiv of *n*-butyllithium gave a mixture rich in **30** relative to **28.** When excess cyclohexanone was added 15 min after addition of the fourth equivalent of *n*-butyllithium, the product mixture contained little **29**[9] which would be derived from the dilithium derivative **28.** The acidic products were separated by preparative plate chromatography. The principal products were (a) an oil (~25% crude yield), the NMR spectrum of which was consistent with **31a** (this product could not be induced to crystallize and was not characterized by composition analysis),[10] and (b) alcohol **32a** (~25% crude yield) which was obtained pure.

In contrast, when the above solution was aged for 12 hr at −75°, there was considerable loss of trilithio derivative **30** to dilithio derivative **28.** In this case, addition of excess cyclohexanone led to a significant quantity (~33% crude yield) of **29b.** Chromatography of the mixed acids gave, in addition to **29b,** products derived from the trilithio derivative **30** but in reduced yields: (a) diol **31b** (~16% yield) which was obtained pure, and (b) a mixture (by NMR spectral analysis) of **32a** and **32b** (~16% total yield) which was not resolved.

3. Alkylations of lithium derivatives derived from **4** by *n*-butyl bromide formed during halogen–lithium exchange, to give products of type **31,** detract from the synthetic utility of such syntheses with *p*-bromophenylacetic acid, an observation in sharp contrast to that observed with o-bromo-

Scheme VI



phenylacetic acid. We currently believe, but have not established, that alkylation at −100° occurs only with the very reactive trianion **30**, a process which is sterically inhibited with the ortho isomer **23**; consequently, we believe that significant amounts of alkylation at −100° will be encountered only in the phenylacetic acid series (meta or para).

While some exceptions have been defined, notably *p*-bromophenylacetic acid, the procedures described in A–C (above) offer useful routes for the elaboration of a seemingly broad variety of types of bromoalkanoic acids.

Experimental Section

A. Conversion of β-(*p*-Bromophenyl)propanoic Acid (1) to Phenylacetic Acid. β-(*p*-Bromophenyl)propanoic acid[11a] (2.29 g, 0.01 mol), mp 137–138° (lit.[11b] mp 136°), tetrahydrofuran (~125 ml, freshly distilled over lithium aluminum hydride), and dry hexane[13] (25 ml) were introduced, under nitrogen, into a three-neck flask equipped with a low-temperature thermometer, addition funnel, and nitrogen inlet tube. The reaction mixture was cooled to −100° (liquid nitrogen–diethyl ether bath) and *n*-butyllithium (9.2 ml, 0.022 mol, 2.4 *M* solution) was added rapidly (the rate of addition was adjusted such that the temperature did not exceed −90°). The reaction mixture was stirred at −100° for 45 min and poured into dilute aqueous hydrochloric acid (~50 ml). The organic layer was separated and the aqueous layer was extracted with four 100-ml portions of ether. The ether extracts were combined and extracted with two 50-ml portions of 10% aqueous sodium hydroxide. The aqueous basic extracts were combined, cooled, and added to cold dilute aqueous hydrochloric acid; the resulting mixture was extracted with four 100-ml portions of ether. The ether extracts were combined, dried ($MgSO_4$), and concentrated (rotary evaporation) to afford 1.55 g of light yellow semisolid. This material was distilled to give 1.29 g (86% yield, mp[12] and mmp 45–46°) of pure phenylacetic acid (**6**). The residue (0.26 g) was shown (NMR) to be a mixture of **1**, **6**, and a small amount of butylated acid (position of butyl group undetermined).

B. Preparation of β-(*p*-1-Cyclohexenylphenyl)propanoic Acid (7). Reaction of **1** (0.02 mol) in a mixture of THF (250 ml)–hexane[13] (50 ml) with *n*-butyllithium (0.044 mol) was carried out as in A. Cyclohexanone (0.10 mol) in dry hexane[13] (10 ml) was added; the mixture was warmed to 25° and poured into dilute hydrochloric acid (250 ml). The organic layer was extracted (four 150-ml portions) with ether. The acid, obtained by extraction of the ether extract with alkali, weighed 3.9 g (white solid, mp 105–112°). This material was sublimed [80° (0.01 Torr), 24 hr] to remove unchanged **1** (0.49 g, mp[11] and mmp 133–135°); the residue (3.1 g, 67% yield, mp 114–117°) was nearly pure **7**. Pure **7** (2.7 g, 59% yield from petroleum ether[14a]–chloroform) had mp 117–118°; NMR ($CDCl_3$) δ 1.72 (m, 4, aliphatic CH_2), 2.28 (m, 4, allylic CH_2), 2.72 (m, 2, CH_2Ar), 3.00 (m, 2, CH_2COOH), 6.23 (m, 1, vinyl H), 7.40 (m, 4, aromatic H), ~11.0 (broad s, 1, OH).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.32; H, 7.80.

The residue (0.55 g) from the recrystallization of **7** was a mixture of phenylpropanoic acid (0.4 g, 13%) and unchanged **1**.

C. Indanones. 1. From β-(*o*-Bromophenyl)propanoic acid[15] (2). Reaction of **2** [0.01 mol, mp 99–101° (lit[17] mp 98°)] in THF (125 ml)–hexane[13] (25 ml) with *n*-butyllithium (0.02 mol) was carried out as in A; the reaction mixture was stirred for 3 hr at −100°. From the neutral component of the reaction product there was obtained 1.0 g [76% yield; bp 60–65° (0.2–0.15 Torr); mp and mmp[16a] 42°; mp of 2,4-dinitrophenylhydrazone 256–257° (lit.[16b] mp 258°)] of pure indanone (**9**).

The reaction was repeated at −78°; examination of aliquots showed that the reaction was faster and complete after only 30 min. The yield of isolated indanone was 77%.

2. From 3-*o*-Bromodiisopropylamide (13). Amide **13** [0.01 mol, bp 130–140° (0.02–0.01 Torr); 96% yield from 3-*o*-bromophenylpropanoyl chloride[17] and diisopropylamine in ether] in THF (125 ml)–hexane[13] (25 ml) was allowed to react with *n*-butyllithium (0.01 mol) as in A. Examination of aliquots[4] by NMR showed that after 1 hr at −100° the reaction product was indanone contaminated with a small amount of butylated material. The mixture was quenched with water and the dried material obtained from the ether extract was distilled to give 0.8 g (61% yield) of pure indanone.

3. 2-(*o*-Bromobenzyl)-1-indanone (12). The starting acid **10** (mp 152–153°) was prepared in high yield from crude diethyl di(*o*-bromophenyl)malonate (by hydrolysis and decarboxylation of the derived malonic acid) obtained as a by-product in the synthesis of **2** from *o*-bromobenzyl bromide and diethyl malonate.

Anal. Calcd for $C_{16}H_{14}Br_2O_2$: C, 48.27; H, 3.54; Br, 40.15; neut equiv, 398. Found: C, 48.03; H, 3.67; Br, 39.94; neut equiv, 396.

Reaction of **10** (0.02 mol) with *n*-butyllithium (2 equiv) in THF (300 ml) and hexane[13] (50 ml) was carried out as in C-1 and gave 4.1 g (66% yield) of pure 2-(*o*-bromobenzyl)-1-indanone (**12**), bp 165–170° (0.05–0.04 Torr).

Anal. Calcd for $C_{16}H_{13}BrO$: C, 63.80; H, 4.35; Br, 26.54. Found: C, 63.96; H, 4.28, Br, 26.61.

4. 2-Benzyl-1-indanone. Reaction of **10** with *n*-butyllithium (3 equiv) was carried out as described in C-3 above. Distillation of the crude product gave 3.2 g (72% yield) of pure 2-benzyl-1-indanone, bp 135–140° (0.03 Torr).

Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 87.70; H, 6.35.

D. Reactions of β-(*o*-Bromophenyl)propionamide (14). 1. Conversion to Phenylpropionamide. Amide **14**[18] (0.01 mol) was treated with *n*-butyllithium (0.02 mol) in THF (125 ml)–hexane[13] (25 ml) as described in A. An aliquot (25 ml) taken after 30 min at −100° was quenched with water; NMR analysis showed only 3-phenylpropionamide.[4d] The mixture was quenched with water, and the crude product obtained by extraction with ether was recrystallized from water to give 1.22 g (81% yield) of pure 3-phenylpropionamide (mp and mmp[19] 104–105°).

2. Conversion to o-(1-Hydroxycyclohexyl)-3-phenylpropionamide (17). The reaction was carried out as in D-1 above, and quenched after 30 min with cyclohexanone (0.04 mol) in dry hexane[13] (20 ml) at −100°. The crude product (5.5 g) obtained after addition of water and extraction with ether and containing cyclohexanone was recrystallized from petroleum ether[14a] to give 2.1 g of white solid which was a mixture of **16** and **17**. This material was chromatographed on silica gel (200 g). Elution of the column with petroleum ether[14a]–ether (70:30) gave 0.88 g (59% yield) of 3-phenylpropionamide; elution with petroleum ether[14a]–ether (50:50) gave 1.1 g of white solid which was recrystallized from chloroform–petroleum ether to give 0.97 g (40% yield) of pure **17** (mp 148–150°).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.00; H, 8.42; N, 5.49.

E. Metalation of o-Bromophenylacetic Acid (3) with *n*-Butyllithium. 1. Degree of Metal–Halogen Exchange. Reaction of **3**[20] (0.025 mol) with *n*-butyllithium (0.05 mol) in THF (150 ml) and hexane[13] (30 ml) was carried out as in B. Examination of an aliquot[4c] (10 ml) taken after 30 min at −100° showed that the degree of halogen–metal exchange [ratio of *o*-bromophenylacetic acid (**3**) to phenylacetic acid (**22**)] was 50:50. The ratio of **3** to **22** was 40:60 after an additional 1 hr; after an additional 2.5 hr the ratio was 36:64 and this ratio did not change after an additional 2 hr at −100°.

A third molar equivalent of *n*-butyllithium was added to the reaction mixture at −100°; and the mixture was stirred for an additional 1 hr at −100°. Examination of an aliquot (10 ml) showed that the ratio of **3** to **22** was 30:70. Additional reaction time (at −100°) and/or further addition of *n*-butyllithium (up to a total of 6 molar equiv) caused no appreciable change in the above ratio (30:70).

Examination of aliquots from a similar reaction but at −78° (instead of −100°) showed no appreciable change in the progress and/or degree of metalation.

Synthesis of Spirolactone 24. Metalation of *o*-bromophenylacetic acid[21] (5.4 g, 0.025 mol) was effected with *n*-butyllithium (0.075 mol) as described above. The mixture was aged for 5 hr at −95 to −100° (ratio of *o*-bromophenylacetic acid to phenylacetic acid 30:70 by NMR spectral analysis)[4c] and cyclohexanone (9.8 g, 0.1 mol) in hexane (20 ml) was added to the mixture maintained at −100°. The resulting mixture was allowed to warm to room temperature and was added to a mixture of ether (200 ml) and aqueous sodium hydroxide (200 ml, 5%). The two layers were separated and the aqueous layer was extracted with ether (four 100-ml portions). The basic layer containing the salt of **24** was acidified (hydrochloric acid), brought to boil, cooled, and extracted with ether (400 ml). The ether extract was cooled (0–5°) and extracted with cold (0–5°) aqueous sodium hydroxide (100 ml, 3%). The ether layer was washed with cold water (50 ml), dried ($MgSO_4$), and concentrated to give nearly pure **24** (2.3 g, 42% yield, mp 95–105°; 2.1 g, 39% yield, mp 105–106° from petroleum ether[14b]).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.96; H, 7.40.

The NMR spectrum of the acid material (2.2 g) obtained from the alkaline extract showed it to be a mixture of *o*-bromophenylacetic acid (**3**) and phenylacetic acid (**22**) in the ratio 40:60 (20 and 33% yield, respectively).

Preparation of Hydroxy Acid 27. The reaction was conducted as described for **25** with the following modifications. The mixture was stirred for 7 hr after addition of 2 equiv of *n*-butyllithium, but only 15 min after addition of the third equivalent of *n*-butyllithium prior to addition of cyclohexanone. The yield of lactone **24** (mp and mmp 105–106°) was 10%.

Concentration of the dried ether extract obtained from the acidified alkaline extract gave a mixture of **27**, o-bromophenylacetic acid (**3**), and phenylacetic acid (**22**). Fractional crystallization of the product from chloroform–petroleum ether[14c] gave 2.92 g of pure **27** (54% yield, mp 114–146°).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.95; H, 8.00.

F. Reactions of *p*-Bromophenylacetic Acid (4). 1. Reaction of *p*-bromophenylacetic acid (5.4 g, 0.025 mol) was carried out exactly as described for **3** except the temperature was −78°[4b] (Dry Ice–acetone bath). Progress of metalation was followed as for **3**.[4c]

The ratio of recovered *p*-bromophenylacetic acid to phenylacetic acid was 60:40 after 2 hr and the ratio did not change after an additional 2–4 hr. An additional molar equivalent of *n*-butyllithium was added and the mixture was stirred at −78° for 17 hr. An aliquot showed the above ratio of acids to be 40:60. A fourth equivalent of *n*-butyllithium was added, and after 15 min at −78° an excess of cyclohexanone (5 equiv) dissolved in hexane (35 ml) was added rapidly. The mixture was allowed to warm to room temperature and was then partitioned between aqueous sodium hydroxide (100 ml, 10%) and ether (100 ml). Acidification of the alkaline layer (hydrochloric acid) gave 6.22 g of acidic product as a semisolid which was collected by ether extraction. Elution of the mixed acids (600 mg) from a preparative silica gel plate (fluorescent indicator) with a mixture of petroleum ether[14a] and ether (80:20) gave two major fractions. (1) 160 mg (~25%, higher R_f) of an oil. The NMR spectrum ($CDCl_3$) of this product was consonant with slightly impure **31a**: δ 0.9 (t, 3, CH_3), 1.25–2.3 (m, 1, aliphatic H), 3.55 (broad t, 1, benzylic methine), 6.2 (m, 1, vinyl H), 7.4 (broad, 4, aromatic H). This material could not be induced to crystallize and was not purified.[10] (2) 300 mg (lower R_f) of an oil. This product was rechromatographed as above, to give one major fraction (180 mg, ~25% yield) of an oil, the NMR spectrum ($CDCl_3$–DMSO-d_6) of which suggested that it was **32a** [δ 0.9–2.0 (m, 16, aliphatic H), 2.15–2.58 (m, 2, allylic H)]. The material crystallized from chloroform and melted at 193–200° dec.

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.17; H, 8.49.

2. The reaction was carried out as above except that the mixture was aged for 12 hr prior to addition of excess cyclohexanone. Analysis of an aliquot, as discussed in the text, showed that the ratio of acids remained constant at 40:60. A portion (580 mg) of the mixed acids (5.8 g, yellow semisolid) was purified by preparative plate chromatography (as in F-1) to give three major bands. (1) 180 mg (~33% yield) of an oil (higher R_f), the NMR spectrum of which was consistent with alcohol **29b**: NMR ($CDCl_3$) δ 1.4 (broad m, 10, aliphatic H), 3.6 (broad s, 2, benzylic methylene), 7.4 (broad m, H, aromatic H). The material crystallized from chloroform, mp 134–136°.

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.00; H, 8.00.

(2) 120 mg (~16% yield) of an oil (medium R_f) whose NMR spectrum was consistent with **31b**: NMR ($CDCl_3$) δ 1.0 (t, 3, $-CH_3$), 1.6 (m, 16, aliphatic H), 3.7 (t, 1, benzylic methine), 6.8 (broad s, 1, –OH), 7.6 (m, 4, aromatic H). This material crystallized from chloroform, mp 110–114°.

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.66; H, 8.86.

(3) 130 mg (~16% yield) of an oil (lower R_f) which was not resolved; however, the NMR spectrum was consistent with **32b** contaminated with **32a**. Compound **32a** was characterized in the preceding experiment.

Registry No.—**1**, 1643-30-7; **2**, 15115-58-9; **3**, 18698-97-0; **4**, 1878-68-8; **7**, 55223-22-8; **9**, 83-33-0; **10**, 55223-23-9; **12**, 55223-24-0; **13**, 55223-25-1; **14**, 55223-26-2; **17**, 55223-27-3; **24**, 55223-28-4; **27**, 5449-68-3; **29b**, 55223-29-5; **31a**, 55223-30-8; **31b**, 55223-31-9; **32a**, 55223-32-0; **32b**, 55223-33-1; diethyl di-(o-bromophenyl)malonate, 55223-34-2; 2-benzyl-1-indanone, 16307-30-5.

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(3) (a) W. E. Parham and Y. A. Sayed, *J. Org. Chem.*, **39**, 2051 (1974); (b) *ibid.*, **39**, 2053 (1974).
(4) In general, 0.02 mol of acid in ~300 ml of solvent was employed; aliquots of 10 ml were quenched with water and the organic material was extracted with ether. The extract was concentrated to give sample for NMR analysis. In many cases, neutral components were separated from acids by conventional extraction procedures and analyzed separately by NMR. (a) *p*-Bromophenylpropanoic acid (A, A′, B, B′ aromatic pattern) could easily be differentiated from phenylpropanoic acid (simple singlet for aromatic protons); however, the absorptions overlapped so that only estimates of composition were possible. (b) *o*-Bromophenylacetic acid and phenylacetic acid show benzylic methylenes at δ 3.8 and 3.60 (60 MHz), respectively. The ratio of these two acids is based on integrations of these two absorptions. (c) *p*-Bromophenylacetic acid shows benzylic methylene at δ 3.56, sufficiently resolved from phenylacetic acid (δ 3.60) to permit accurate analysis. (d) 3-(o-Bromophenyl)propionamide shows a complex pattern for the aromatic protons (δ 6.9–7.7) while 3-phenylpropionamide shows only a single peak at δ 7.1. (e) Similar results were obtained at −78°. (f) Similar results were obtained at −100°.
(5) The position of the butyl group was not determined.
(6) Part of the aryllithium reagent is reduced by proton abstraction to give the enolate of cyclohexanone; cyclohexanone was chosen for elaboration of **5** since we felt that the yields of products would provide a more realistic evaluation of the synthetic utility of the process than would use of nonenolizable carbonyl functions.
(7) (a) Possible application of this reaction for the syntheses of tetralones and related materials is being investigated. (b) Indanones are usually prepared by cyclization of arylpropanoic acids. The method described in this report obviates isomers encountered by direct cyclization of unsymmetrically substituted arylpropanoic acids; furthermore, Friedel–Crafts type cyclization cannot be employed when the aryl group is substituted with meta-directing groups.
(8) This observation supports the conclusion that both bromine atoms in **10** undergo metal exchange prior to cyclization when 3 equiv of *n*-butyllithium is employed. The product (**12** with bromine replaced by lithium) reacts with itself by enolization of carbonyl rather than addition to carbonyl, probably because of unfavorable entropy considerations for addition.
(9) (a) Compounds **29a,b** were not detected upon preparative plate chromatography; however, conversion of an aliquot of the products to the methyl esters (with diazomethane) with subsequent GLC and NMR analysis showed that **29a** and/or **29b** (detected as **29a**) was present in very low yield.
(10) In a subsequent experiment the hydroxy acid **31b** was obtained pure and was characterized by compositional analysis (see Experimental Section).
(11) (a) This acid was prepared from *p*-bromobenzyl chloride by a malonic ester synthesis similar to that reported for the preparation of α-bromo-β-phenylpropionic acid: C. Marvel, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 705. (b) S. Gabriel and J. Zimmerman, *Chem. Ber.*, **13**, 1683 (1880).
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(13) Practical grade stored over molecular sieves.
(14) (a) bp 30–60°; (b) bp 90–110°; (c) bp 60–90°.
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Notes

Preparation of 9-α-D-Idofuranosyladenine[1]

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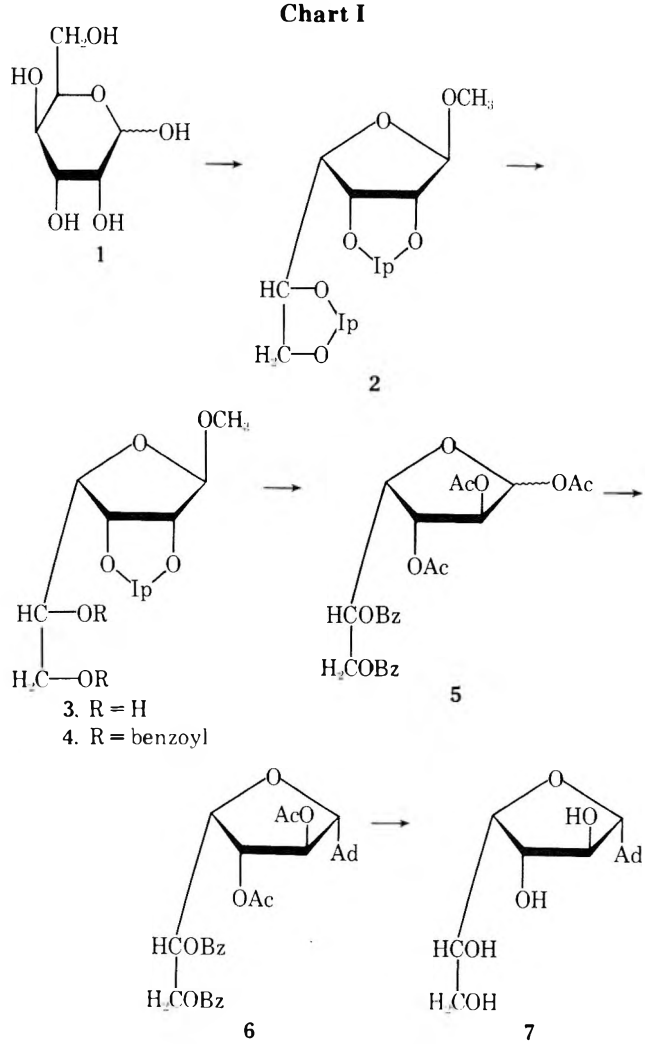
Hexofuranosyl nucleosides have been prepared as analogs[2] of the naturally occurring nucleosides with the intent of producing compounds of biological interest[3] as antitumor or antimicrobial agents. The only D-hexose which has not been transformed into a nucleoside of this type is D-idose, although the preparation of 9-α-L-idofuranosyladenine was reported a few years ago.[4] The problem with the preparation of the D nucleoside was that the route used[5] did not yield well-defined, characterizable intermediates that could be utilized for synthetic purposes. Although a simple method for preparing D-idose from D-glucose was developed some years ago,[6] the use of this source was considered impractical because the rather unstable free sugar would then have to be converted to the 1,2:5,6-di-*O*-isopropylidene derivative,[7] and this in turn transformed into a utilizable penta-*O*-acyl furanose derivative in a stepwise series of reactions similar to the route used by Baker and coworkers for the synthesis of 9-β-D-glucofuranosyladenine.[8]

A practical synthesis of a D-idofuranosyl nucleoside has now been accomplished by taking advantage of the commercial availability of D-gulono-1,4-lactone and the epimerization of C-2 of certain furanose derivatives when these are subjected to acetolysis conditions. In the present case, the conversion of a D-gulofuranose derivative to a penta-*O*-acyl-D-idofuranose derivative has been carried out and the latter converted to the title compound.

D-Gulose (1), which was prepared by reduction of D-gulono-1,4-lactone, was treated with a mixture of acetone, methanol, and 2,2-dimethoxypropane under acid conditions and subsequently subjected to partial hydrolysis to yield crystalline methyl 2,3-*O*-isopropylidene-β-D-gulofuranoside (3) in 59% yield[7] (Chart I). No particular advantage was accrued by isolation of the intermediate, methyl 2,3:5,6-di-*O*-isopropylidene-β-D-gulofuranoside (2), because no additional conditions of partial hydrolysis were found that would increase the yield of 3 any better than that reported here. The 5 and 6 hydroxyls were blocked by benzoylation, giving crude 4. This was subjected to acetolysis under conditions which are known to cause epimerization of the C-2 position of glycofuranoses having three contiguous hydroxyl groups with the ring hydroxyls in a cis relationship.[10] The crude acetolysis product (5) was coupled with 6-benzamidochloromercuripurine by the titanium tetrachloride method[11] and the blocked nucleoside was isolated as a solid picrate of 6 after boiling with an ethanolic picric acid solution.[12] The picrate ion was removed with an anion exchange resin,[13] the blocking groups of 6 were removed with sodium methoxide in methanol, and the nucleoside, 9-α-D-idofuranosyladenine (7), was crystallized and found to have properties identical with those of the previously reported L enantiomer,[4] except for the sign of the optical rotation.

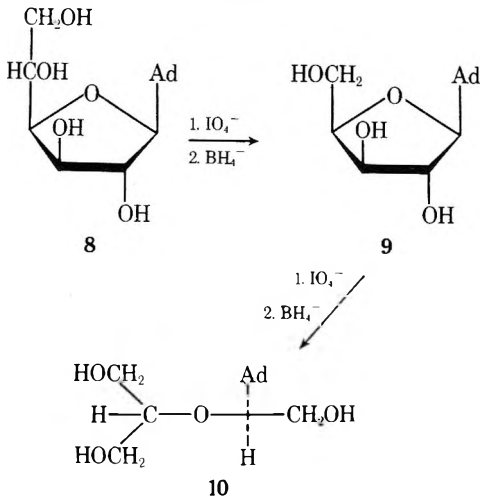
Previously, the anomeric configuration of 9-α-L-idofuranosyladenine (8)[4] had been assumed on the basis of the trans rule, in which the incoming base would form a bond trans to the hydroxyl group at C-2. Because of the greater availability of the L form 8 in this laboratory, it was used in the following experiment in order to determine the nature of the anomeric configuration. The reaction pathway utilized is shown in Chart II. It is generally recognized that vicinal hydroxyl groups in the trans configuration in furanose rings are very slowly oxidized in comparison to the exocyclic glycol group.[14] The former may require 4–7 days for completion, whereas the latter is completely oxidized in a matter of minutes. Therefore, 8 was subjected to periodate oxidation for a short time and then reduced with sodium borohydride to give a glassy substance, presumably 9-β-D-xylofuranosyladenine (9). Because the physical properties of this compound appeared to differ with each laboratory that prepared it,[15] the picrate was prepared which had a melting behavior similar to the literature value,[16] but whose optical rotation differed slightly. Therefore, compound 9 was regenerated from the picrate and the trialcohol 10 was prepared by extensive treatment of 9 with sodium periodate followed by reduction. The specific rotation of the final solution was +53° and was a good indication that the anomeric configuration of 9 was β-D, which meant

Chart I



Ad = adenine. Bz = benzoyl, Ip = $C(CH_3)_2$

Chart II



that the configuration of 8 was α-L. In the original work,[16] the anomeric configuration of **9** had not been proved directly, but was demonstrated using its precursor, 2,8-dichloro-9-β-D-xylofuranosyladenine. The latter was oxidized with periodate to a dialdehyde and its molecular rotation was compared to that of the dialdehyde derived from 2,8-dichloro-9-β-D-ribofuranosyladenine, treated the same way. Proof of the configuration of 8 meant that the configuration of the new nucleoside **7** must be assigned as α-D.

Experimental Section[17]

D-Gulose (1). D-Gulono-1,4-lactone (Pfanstiehl Laboratories, 30 g) was reduced to D-gulose (23 g) according to the general method of Wolfrom and Thompson.[18] The sugar was used as a clear, colorless syrup.

Methyl 2,3:5,6-Di-*O*-isopropylidene-β-D-gulofuranoside (2). D-Gulose (2.39 g) was dissolved in a refluxing mixture containing 13 ml of 2,2-dimethoxypropane, 8 ml of acetone, 8 ml of methanol, and 0.24 ml of concentrated hydrochloric acid. After 2 hr, the solution was cooled and poured slowly into 20 ml of saturated sodium bicarbonate solution. The organic solvents were evaporated and a white solid precipitated in the water. This was extracted with chloroform (3 × 25 ml) and dried, and the chloroform was evaporated. The syrup crystallized to afford 2.9 g (79%). Recrystallization from *n*-hexane gave the analytical sample as large, prismatic rods, mp 78.5–79°, $[\alpha]^{26}D$ −44.9° (*c* 1.39, chloroform). This compound was previously prepared by methylation of 2,3:5,6-di-*O*-isopropylidene-D-gulofuranose,[19] mp 75–76°, $[\alpha]D$ −44.9° (chloroform).

Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.09. Found: C, 56.88; H, 8.02.

Methyl 2,3-*O*-Isopropylidene-β-D-gulofuranoside (3). A mixture containing 20 g of D-gulose, 80 ml of 2,2-dimethoxypropane, 66 ml of methanol, 66 ml of acetone, and 2 ml of concentrated hydrochloric acid was heated at reflux for 2 hr. The solution was cooled to room temperature, 200 ml of water was added, and the organic solvents were removed by evaporation at 35°. A white precipitate formed in the aqueous layer which dissolved upon addition of 200 ml of methanol. Concentrated hydrochloric acid (5 ml) was added and after 1 hr the pH was adjusted to neutrality with saturated sodium bicarbonate solution (ca. 150 ml). The solution was evaporated to ca. 100 ml and extracted with chloroform (3 × 25 ml). The aqueous layer was then saturated with sodium chloride and extracted again with chloroform (3 × 25 ml). The extracts were combined and dried. Evaporation of the chloroform gave a white solid, 14.4 g (59%), of sufficient purity for further reactions. A small portion was recrystallized from ethyl acetate–*n*-hexane to give tiny needles, mp 77.5–79.5°, $[\alpha]^{20}D$ −83.5° (*c* 1.18, methanol). The compound had an ir spectrum identical with that of the L form, which was prepared from methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methanesulfonyl-α-D-mannofuranoside by the method of Evans and Parrish,[9] mp 76.5–77°, $[\alpha]D$ +82.3° (*c* 1.17, methanol) [obtained mp 78.5–80°, $[\alpha]^{22}D$ 2.5° (*c* 1.10, methanol)].

Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.74. Found: C, 51.18; H, 7.56.

9-α-D-Idofuranosyladenine (7). A solution of **3** (3.39 g) in 40 ml of dry pyridine was treated with 4.7 ml of benzoyl chloride and after 45 hr at room temperature the reaction mixture was poured into 300 ml of ice and saturated sodium bicarbonate solution. A gum formed which was extracted with chloroform (2 × 40 ml). The chloroform solution was washed with saturated sodium bicarbonate (100 ml) and water (100 ml), dried, and evaporated to a thin syrup. This was triturated with hot petroleum ether (bp 60–110°) and, after chilling, the solvent was decanted. This process was repeated one time and traces of solvent were evaporated to give 4 as a thick, orange syrup, 5.36 g (84%). The ir showed no hydroxyl peak, ir (film) 1718 (carbonyl), 1370 (*gem*-dimethyl), and 708 cm^{-1} (monosubstituted phenyl).

The entire sample was dissolved in a mixture containing 80 ml of acetic acid and 8 ml of acetic anhydride, and 4.4 ml of concentrated sulfuric acid was slowly added, dropwise, while the temperature of the solution was maintained below 20° with an ice bath. After 67 hr at room temperature, the dark solution was poured into 300 ml of ice and stirred until the ice melted. The milky mixture was extracted with chloroform (3 × 60 ml) and the chloroform solution was washed successively with saturated sodium chloride solution (2 × 150 ml), saturated sodium bicarbonate (200 ml), and again with saturated sodium chloride, and dried. All of the dark color was removed in the aqueous portions so that the chloroform solution was colorless. The chloroform was removed by evaporation and the syrup was coevaporated three times with benzene to afford a stiff gum of **5**, 3.6 g.

The gum was dissolved in 1,2-dichloroethane and coupled with 4.0 g of 6-benzamidochloromercuripurine in a reaction mixture containing 4 g of Celite 545, 1.2 ml of titanium tetrachloride, and 250 ml of 1,2-dichloroethane.[11] After work-up, as previously described,[4,11] a syrup was obtained which was dissolved in 30 ml of ethanol. To this solution was added 25 ml of 10% ethanolic picric acid, and the mixture was refluxed. After 5 min, an orange gum settled out of solution and additional ethanol was added to the boiling mixture until complete dissolution occurred again. Upon cooling to room temperature, a yellow solid slowly precipitated and the flask was stored in the refrigerator overnight. The product was obtained by filtration and immediately treated with Bio-Rad AG1-X8 (CO_3^{2-}) ion exchange resin in a solution of 80% aqueous acetone to remove the picrate ion. After filtration and treatment with Darco G-60, the solvents were evaporated to give a gum (1.49 g), which was dissolved in 50 ml of methanol, treated with 6 ml of 1 *N* methanolic sodium methoxide, and refluxed for 2 hr. The solution was neutralized with CG-120 (H^+) resin, filtered, and concentrated on a steam bath, during which crystallization occurred. After cooling, the product was filtered to yield 601 mg of **7** (14% yield from 3), mp 219–224°. Recrystallization from methanol raised the melting point to 226–226.5°, $[\alpha]^{26}D$ +38.1° (*c* 1.06, 1 *N* HCl). The L form 8 was reported[4] to have mp 228–228.5°, $[\alpha]^{26}D$ −39° (*c* 1.0, 1 *N* HCl). The ir spectra of **7** and 8 were identical.

Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.47; H, 5.11; N, 23.48.

Anomeric Configuration of 9-α-L-Idofuranosyladenine (8). A solution containing 100 mg of 8 in 2.5 ml of hot water was cooled to room temperature and 79 mg of sodium periodate in 2.5 ml of water was added. The mixture was kept in the dark for 1 hr and then poured into 60 ml of ethanol and stirred for 15 min, and the precipitate was removed by filtration. The solvents were evaporated, and the residue was dissolved in 5 ml of water and treated with 60 mg of sodium borohydride. The reaction proceeded for 1 hr, the solution was brought to pH 7 with Amberlite IR-120 (H^+) resin and filtered, and the water was evaporated, leaving a glass, 91 mg, $[\alpha]^{23}D$ −53°, presumably **9**.

The glass was dissolved in water and converted to a picrate with a saturated solution of picric acid in water, and recrystallized from boiling water, mp 210–220° with slow decomposition and sublimation, the sublimate forming star-like clusters on the cover slip which melted and further sublimed over 260°, $[\alpha]^{22}D$ −54.1° (*c* 0.74, pyridine).

Anal. Calcd for $C_{16}H_{16}N_8O_{11}$: C, 38.71; H, 3.25; N, 22.58. Found: C, 38.84; H, 3.35; N, 22.38.

The picrate ion was removed in hot water with Bio-Rad AG1-X8 (CO_3^{2-}) resin. Evaporation of the water gave 30.6 mg of a glass which was dissolved in 2.5 ml of 0.098 *M* aqueous sodium periodate solution and stored in the dark for 5 days. The solution was treated with 180 mg of sodium borohydride for 1 hr and neutralized with 20% aqueous acetic acid. The volume was adjusted to 5 ml, $[\alpha]^{23}D$ +53°. Considering inaccuracies involved in weighing the glass and the lengthy exposure to the oxidizing agent, this value is quite reasonable. When adenosine was treated in a similar manner,

a value of +66° was obtained,[20] but the pure trialcohol **10** had a value of +59°.[21]

Registry No.—**1**, 4205-23-6; **2**, 55520-69-9; **3**, 55520-70-2; **4**, 55520-71-3; **5**, 55520-72-4; **7**, 55555-40-3; **8**, 32653-60-4; **9**, 524-69-6; 9 picrate, 55520-73-5; 2,2-dimethoxypropane, 77-76-9; 2,3-*O*-isopropylidene-5,6-di-*O*-methanesulfonyl-α-D-mannofuranoside, methyl, 50692-25-6.

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A Simple $RuCl_2(PPh_3)_3$-Catalyzed Synthesis of the 3,5,6,7-Tetrahydro-4(2*H*)-benzofuranone System

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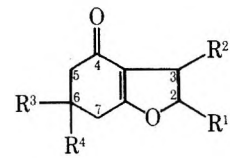
In a previous communication[1] we reported the selective transfer hydrogenation of one carbonyl group in cyclohexane-1,3-diones using ethylene glycol as hydrogen donor and $RuCl_2(PPh_3)_3$ as catalyst. The reduction is effective under conditions in which the dehydrogenated carbinol, the glycol aldehyde, is continuously removed from the reaction mixture during the process. (See footnote 5, ref 1). When the aldehyde is allowed to accumulate these cyclic diketones undergo a remarkable catalytic reaction whereby the title system is formed.

With the exception of the Claisen rearrangement of 3-allyloxy-2-cyclohexen-1-ones[2] that yields 2-methylated 3,5,6,7-tetrahydro-4(2*H*)-benzofuranones (isolated as semicarbazone derivatives), the known syntheses of **1**, and of its simple alkyl derivatives, are low yielding and give, in general, impure products.[3-7]

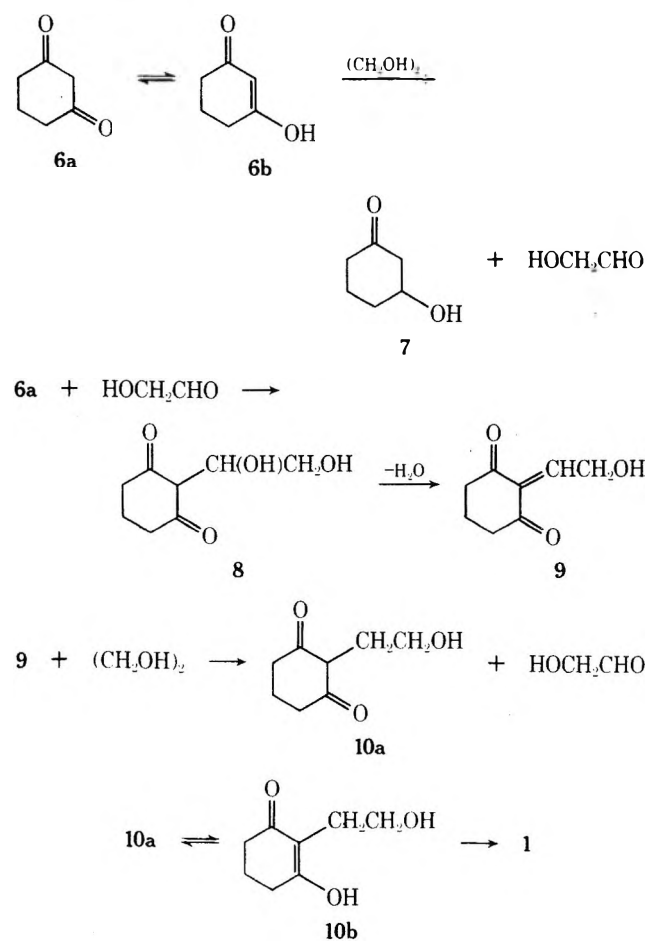
Our new one-pot synthesis of **1** is accomplished simply by refluxing cyclohexane-1,3-dione with excess ethylene glycol in the presence of some $RuCl_2(PPh_3)_3$. The method is not only extremely facile, but permits the isolation of the analytically pure bicyclic compound in a reasonable yield (64%). Similarly alkylated cyclohexane-1,3-diones can be converted to the corresponding substituted 3,5,6,7-tetrahydro-4(2*H*)-benzofuranones. 5,5-Dimethylcyclohexane-1,3-dione (dimedone) and 5-*tert*-butylcyclohexane-1,3-dione[8] give **2** and **3** in 40 and 27% yields, respectively.



1, $R^1 = R^2 = R^3 = R^4 = H$
2, $R^1 = R^2 = H; R^3 = R^4 = CH_3$
3, $R^1 = R^2 = R^3 = H; R^4 = C(CH_3)_3$
4, $R^2 = H; R^1 = R^3 = R^4 = CH_3$
5, $R^1 = H; R^2 = R^3 = R^4 = CH_3$

The reaction of dimedone with propane-1,2-diol afforded a mixture of 2,6,6- and 3,6,6-trimethyl-3,5,6,7-tetrahydro-4(2*H*)-benzofuranone (**4** and **5**, respectively) in a ratio of 3:1. Compounds **4** and **5**, however, proved difficult to separate.[9]

The catalysis is assumed to proceed by the following mechanism.



Transfer hydrogenation of the starting diketone (in the enol form) gives enough glycolaldehyde[10] to start a *$RuCl_2(PPh_3)_3$-catalyzed condensation* with **6**. The slow rate in this step is presumably the reason for an induction period recorded in the catalysis. Further molecules of the aldehyde are formed by transfer hydrogenation of the α,β-unsaturated ketone **9**. The bicyclic compound **1** results then via Ru(II)-catalyzed ether formation from **10b**.[11,12]

The very high ratio of **1**:**7** (including the transformation products of **7**) indicate that glycol aldehyde formation in step **9** → **10a** is considerable faster than in **6b** → **7**.

At the elevated temperature of the catalysis the proposed reaction intemediates could not be isolated. We found, however, that in the initial stages of the catalysis (with dimedone as starting ketone) an unstable keto alcohol of mass 184 is formed. This compound may be the 5,5-dimethyl analog of **10**.

Finally it should be recalled that in the presence of *piperidine*, glycol aldehyde reacts with *two* molecules of dimedone to give 3,5,6,7-tetrahydro-3-(2-hydroxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)-6,6-dimethyl-4(2*H*)-benzofuranone,[14] which is not formed in our catalytic process.

Experimental Section

6,6-Dimethyl-3,5,6,7-tetrahydro-4(2*H*)-benzofuranone (2). In a 150-ml flask equipped with an *efficient* condensor, a mixture of 4.2 g of dimedone, 70 mg of $RuCl_2(PPh_3)_3$,[15] and 60 ml of ethylene glycol was refluxed for 4 hr. The clear solution was cooled to room temperature and the products were extracted (four times) with 100 ml of benzene. The benzene extract was washed with water, dried ($MgSO_4$), and concentrated and the residue (4.6 g) was analyzed by the aid of a 2-m GLC column packed with 10% SE-30 on Chromosorb W, operated at 130°. (Dimedone methyl enol ether served as internal standard.) The mixture was found to consist of 3.5% **3,3-dimethylcyclohexanone**, 15% **3,3-dimethylcyclohexanol**, 24% **3,3-dimethylcyclohexanone ethylene ketal**, and 42% of the bicyclic compound **2**. The first two compounds were identified by comparison with authentic samples.[16,17] The ethylene ketal: NMR ($CDCl_3$) δ 0.98 (s, 6), 1.3–2.0 (m, 8), 3.86 (s, 4); mass spectrum (70 eV) *m/e* (rel intensity) 170 (3), 155 (3), 152 (10), 127 (100), 101 (27), 99 (94), 96 (27), 81 (25), 78 (25). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.6; H, 10.6. Found: 70.3; H, 10.6. The **dimethyltetrahydrobenzofuranone 2**: uv max (EtOH) 274 mμ (ϵ 12,800); ir 1630 cm^{-1}; NMR[6] ($CDCl_3$) δ 1.10 (s, 6), 2.24 (s, 2), 2.30 (t, 2, J = 1.5 Hz), 2.83 (t, 2, J = 9 Hz), 4.55 (t, 2, J = 9 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 166 (21), 151 (4), 123 (4), 111 (11), 110 (100), 80 (9). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.3, H, 8.4. Found: C, 72.1; H, 8.4. The 2,4-dinitrophenylhydrazone derivative of **2** melted at 168–169° (lit.[6] mp 167–169).

The reaction mixture was distilled at 0.9 mm. The fraction of bp 89–90° was further purified by preparative GLC to give 2.0 g (40%) of analytically pure **2**.

6-*tert*-Butyl-3,5,6,7-tetrahydro-4(2*H*)-benzofuranone (3). By the same method 5.04 g of 5-*tert*-butylcyclohexane-1,3-dione[8] was converted into 1.57 g (27%) of **3**. The GLC analysis was accomplished by a 2-m long column packed with 10% FAAB on Chromosorb W at 160°: uv max (EtOH) 269 mμ (ϵ 11,000); ir 1635 cm^{-1}; NMR ($CDCl_3$) δ 0.85 (s, 9), 1.3–2.3 (m, 4), 2.68 (t, 2, J = 9 Hz), 3.80 (m, 1), 4.50 (t, 2, J = 9 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 194 (16), 179 (6), 155 (8), 138 (20), 137 (51), 110 (100), 57 (25). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.2; H, 9.3. Found: C, 73.9; H, 9.0.

The **3-*tert*-butylcyclohexanone**[18] and **3-*tert*-butylcyclohexanol**[19] were compared with authentic samples. **3-*tert*-Butylcyclohexanone ethylene ketal:** NMR ($CDCl_3$) δ 0.89 (s, 9), 1.0–1.8 (m, 9), 3.87 (s, 4); mass spectrum (70 eV) *m/e* (rel intensity) 1.98 (1), 155 (15), 141 (98), 137 (18), 99 (100), 57 (38). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.6; H, 11.1. Found: C, 72.5; H, 11.0.

3,5,6,7-Tetrahydro-4(2*H*)-benzofuranone (1) was prepared similarly from cyclohexane-1,3-dione in 46% yield. The unsubstituted bicyclic compound **1** is less stable than **2** and **3**, and therefore had to be freshly distilled [bp 100° (4 mm)] or gas chromatographed (on 15% QF-1 on Chromosorb W at 120°) prior to each spectroscopic recording and the elementary analysis: uv max (EtOH) 272 mμ (ϵ 15,600); ir 1630 cm^{-1};[7] NMR[7] ($CDCl_3$) δ 1.88–2.58 (m, 6), 2.81 (t, 2, J = 9.5 Hz), 4.55 (t, 2, J = 9.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 138 (32), 124, (19), 111 (11), 110 (100), 80 (27), 67 (31). Anal. Calcd for $C_8H_{10}O_2$: C, 69.6; H, 7.2. Found: C, 69.2; H, 7.6.

The **cyclohexanone ethylene ketal:** NMR ($CDCl_3$) δ 1.50 (s, 10), 3.80 (s, 4); mass spectrum (70 eV) *m/e* (rel intensity) 142 (22), 113 (62), 99 (100), 86 (60). Anal. Calcd for $C_8H_{14}O_2$: C, 67.5; H, 9.9. Found: C, 67.5; H, 10.0.

Acknowledgment. We are grateful to the Central Fund of the Hebrew University for financial support.

Registry No.—**1**, 42858-96-8; **2**, 19225-65-1; **3**, 55401-07-5; **6a**, 504-02-9; $RuCl_2(PPh_3)_3$, 15529-49-4; ethylene glycol, 107-21-1; dimedone, 126-81-8; 3,3-dimethylcyclohexanone ethylene ketal, 49673-67-8; 5-*tert*-butylcyclohexane-1,3-dione, 49673-64-5; 3-*tert*-butylcyclohexanone ethylene ketal, 49673-70-3; cyclohexanone ethylene ketal, 177-10-6.

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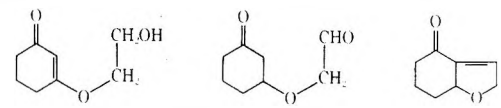

11 12 13

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Intramolecular and Intermolecular 1,3-Dipolar Cycloadditions of Nitrile Oxides Bearing an Alkenyl Substituent

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Oxidation of 2-allyloxybenzaldoxime by nitrogen dioxide has been recently reported[1] to give the fused ring compound **2a**, the product of an intramolecular cycloaddition of the intermediate nitrile oxide **1a**. The stereochemistry of the latter molecule reasonably accounts for the intramolecular process as well as for the unusual orientation, leading to 5-unsubstituted 2-isoxazoline.[2]

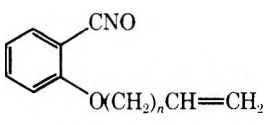
This result led us to examine whether the intramolecular reaction proceeds as the chain length between the dipole

Table I
Yields, Physical Data, and Spectral Properties of Aldehydes 3 and Oximes 4[a]

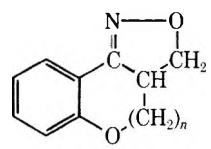
Compd	Yield, %	Bp, °C (mm) (mp, °C)	Ir spectrum (film), cm^{-1}	NMR spectrum ($CDCl_3$), δ (J, Hz)
3a	41	90–92 (0.3)	1690 (C=O)	2.4–2.8 (2 H, m, CH_2CH=), 4.12 (2 H, t, J = 6 Hz, CH_2O), 4.95–5.35 (2 H, m, CH_2=), 5.6–6.2 (1 H, m, CH=), 6.8–7.9 (4 H, m, aromatics), 10.50 (1 H, s, CHO)
3b	43	119–121 (0.7)	1690 (C=O)	1.6–2.6 [4 H, m, $(CH_2)_2CH$=], 4.08 (2 H, t, J = 6 Hz, CH_2O), 4.85–5.25 (2 H, m, CH_2=), 5.5–6.1 (1 H, m, CH=), 6.8–7.9 (4 H, m, aromatics), 10.53 (1 H, s, CHO)
3c	60	111–113 (0.1)	1690 (C=O)	1.5–2.4 [6 H, m, $(CH_2)_3CH$=], 4.09 (2 H, t, J = 6 Hz, CH_2O), 4.8–5.2 (2 H, m, CH_2=), 5.6–6.2 (1 H, m, CH=), 6.8–8.0 (4 H, m, aromatics), 10.52 (1 H, s, CHO)
4a	85	145–150 (0.1) (40–41)	3280 (OH) 1650 (C=N)	2.3–2.7 (2 H, m, CH_2CH=), 4.00 (2 H, t, J = 6 Hz, CH_2O), 4.9–5.3 (2 H, m, CH_2=), 5.5–6.2 (1 H, m, CH=), 6.7–7.9 (4 H, m, aromatics), 8.55 (1 H, s, CH=N), 9.3 (1 H, broad s, OH)
4b	75	170–175 (0.5) (49–50)	3270 (OH) 1650 (C=N)	1.6–2.4 [4 H, m, $(CH_2)_2CH$=], 3.96 (2 H, t, J = 6 Hz, CH_2O), 4.8–5.2 (2 H, m, CH_2=), 5.5–6.1 (1 H, m, CH=), 6.7–7.8 (4 H, m, aromatics), 8.57 (1 H, s, CH=N), 9.0 (1 H, broad s, OH)
4c	82	155–160 (0.4)	3270 (OH) 1640 (C=N)	1.5–2.3 [6 H, m, $(CH_2)_3CH$=], 4.02 (2 H, t, J = 6 Hz, CH_2O), 4.8–5.2 (2 H, m, CH_2=), 5.5–6.2 (1 H, m, CH=), 6.8–8.0 (4 H, m, aromatics), 8.60 (1 H, s, CH=N), 9.2 (1 H, broad s, OH)

[a] All the compounds listed gave correct elemental analyses.

and dipolarophile functions is increased, and, if so, which of the two possible orientations the product acquires. In this context, an exploratory investigation on the behavior of the structurally related nitrile oxides **1b–d** was undertaken. By analogy with **1a**, compounds **1b–d** were generated in situ from the corresponding aldoximes by NO_2 oxidation.

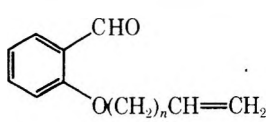


1a, $n = 1$
b, $n = 2$
c, $n = 3$
d, $n = 4$

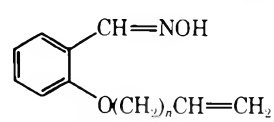


2a, $n = 1$
b, $n = 2$

The hitherto unknown aldehydes **3a–c** were synthesized by allowing equimolar amounts of salicylaldehyde, sodium hydroxide, and the proper ω-bromo-1-alkene to react in aqueous ethanol. From them, oximes **4a–c** were easily ob-



3a, $n = 2$
b, $n = 3$
c, $n = 4$

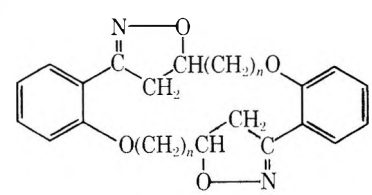


4a, $n = 2$
b, $n = 3$
c, $n = 4$

tained by the standard procedure. Yields, physical data, and spectral properties are collected in Table I.

The treatment of the above aldoximes with nitrogen dioxide was carried out in 0.05 *M* ethereal solutions. In all cases, the crude reaction product was a very complex mixture; however, somewhat different results were obtained for the different substrates, as is illustrated below.

When starting from **4a**, the column chromatography of the product mixture afforded, besides some **3a** and **4a**, 3,3a,4,5-tetrahydro[1]benzoxepino[5,4-*c*]isoxazole (**2b**, 17% yield) and 3,17-dioxa-13,14,27,28-tetrahydrobis([3]orthocyclo[0](3,5)isoxazolo)phane (**5a**) (2% yield). A sizable quantity of uncharacterized resinous material was also obtained.



5a, $n = 2$
b, $n = 3$
c, $n = 4$

In the case of **4b** and **4c**, the reaction led predominantly to resinous material, as found for **4a**; however, in addition to trivial compounds such as the starting aldoximes and the corresponding aldehydes, the macrocyclic compounds **5b** and **5c** were isolated in 13 and 19% yield, respectively.[3]

The structures **2b** and **5a–c** were assigned on the basis of elemental analysis, molecular weights measured by mass spectrometry, and ir and NMR spectra (see Table II). In particular, the unsubstituted positions of the isoxazoline rings in these compounds were established on the basis of the following evidence.

The NMR spectrum of **2b** shows a double doublet centered at δ 4.60 (1 H, J = 8 and 10 Hz) which may well be regarded as half of the signal of the isoxazoline methylene group; the other half of this signal appears to be overwhelmed by the signal due to the OCH_2 grouping of the seven-membered ring (δ 4.1–4.3). The multiplet centered at δ 3.7 should then be attributed to the isoxazoline methynic group. This interpretation is supported by the literature data on 3,4-disubstituted 2-isoxazolines, whose ring protons gave ABC systems with δ values for 5-H_2 in the range 4.5–4.8 ($J_{gem} \simeq 8.5$, $J_{4,5cis} \simeq 11$, and $J_{4,5trans}$ = 5.92–8.45 Hz).[4]

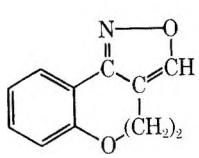
Table II
Physical and Spectral Properties of Heterocyclic Compounds 2b, 5a–c, 6, and 7b,c[a]

Compd	Mp, °C (recrystn solvent)	Mass spectrum, M^+ m/e	NMR spectrum, δ (J, Hz)
2b	57 (*n*-pentane)	189	$CDCl_3$: 1.6–2.7 (2 H, m, CH_2CH_2O), 3.4–4.8 (5 H, m, CH_2O and $CHCH_2O$),[b] 6.8–7.5 and 7.6–7.9 (3 H and 1 H, m, aromatics)
5a	293–295 (pyridine)	378	C_5D_5N: 2.0–2.4 (4 H, m, CH_2CH_2O), 3.3–3.7 (4 H, m, $CH_2C=$), 4.0–4.4 (4 H, m, CH_2O), 4.7–5.2 (2 H, m, CH), 6.8–7.55 and 7.65–8.0 (6 H and 2 H, m, aromatics)
5b	218–219 (acetone)	406	C_5D_5N: 1.6–2.1 [8 H, m, $(CH_2)_2CH_2O$], 3.2–3.6 (4 H, m, $CH_2C=$), 3.8–4.1 (4 H, m, CH_2O), 4.4–4.9 (2 H, m, CH), 6.8–7.4 and 7.6–8.0 (6 H and 2 H, m, aromatics)
5c	233–234 (chloroform)	434	$CDCl_3$: 1.5–2.1 [12 H, m, $(CH_2)_3CH_2O$], 3.1–3.5 (4 H, m, $CH_2C=$), 3.9–4.2 (4 H, m, CH_2O), 4.4–4.9 (2 H, m, CH), 6.8–7.6 and 7.8–8.0 (6 H and 2 H, m, aromatics)
6	(bp 128–130, 0.2 mm)	187	$CDCl_3$: 3.02 (2 H, dt, J = 5 and 1 Hz, CH_2CH_2O), 4.25 (2 H, t, J = 5 Hz, CH_2O), 6.9–7.4 and 8.15–8.4 (3 H and 1 H, m, aromatics), 8.24 (1 H, t, J = 1 Hz, CH)
7b	236–237 (pyridine)	402	C_5D_5N: 1.8–2.4 (4 H, m, CH_2CH_2O), 2.8–3.2 (4 H, m, $CH_2C=$), 3.8–4.1 (4 H, m, CH_2O), 6.85 (2 H, s, CH), 6.9–7.5 and 8.1–8.4 (6 H and 2 H, m, aromatics)
7c	168 (toluene)	430	$CDCl_3$: 1.6–2.0 [8 H, m, $(CH_2)_2CH_2O$], 2.5–2.9 (4 H, m, $CH_2C=$), 3.8–4.1 (4 H, m, CH_2O), 6.44 (2 H, s, CH), 6.7–7.5 and 7.6–7.9 (6 H and 2 H, m, aromatics)

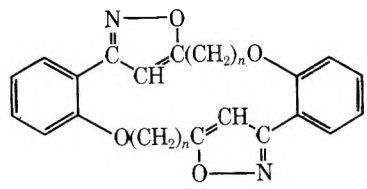
[a] All the compounds listed gave correct elemental analyses and showed, in the ir spectrum, a band of moderate intensity at ca. 1600 cm^{-1} ($\nu_{C=N}$). [b] At 100 MHz: 3.5–3.9 (1 H, m), 4.1–4.3 (3 H, m), 4.60 (1 H, dd, J = 8 and 10 Hz) (see text).

For compounds **5a–c**, the presence of only one hydrogen at the 5 position of each isoxazoline ring was inferred from the intensity (2 H) of the furthest downfield NMR signal. In fact, isoxazoline 5 hydrogens resonate downfield from those in the 4 position.[4–7]

The above structural assignments were confirmed for **2b** and **5b,c** by converting them into the corresponding isoxazole derivatives **6** and **7b,c** with *N*-bromosuccinimide under



6



7a, $n = 2$
b, $n = 3$
c, $n = 4$

free-radical conditions.[8] In addition to correct elemental analyses, molecular weights (from mass spectra), and ir absorptions, compounds **6** and **7b,c** gave NMR spectra (Table II) of unequivocal interpretation. In fact, the isoxazole proton of **6** resonates at δ 8.24 while those of **7b,c** give signals at δ 6.85 and 6.44, respectively. These data agree with the reported δ values of variously substituted isoxazoles, which are in the range of 8.0–9.8 for the 5 hydrogens[1,4,9–12] and 6–7.5 for the 4 hydrogens.[4,11–16]

Analogous oxidation of **5a** to **7a** was not performed because of the small amount of the available material.

The reported results show the effect of the chain length between the dipole and dipolarophile groups on the intramolecular cycloadditions. Thus, while nitrile oxide **1a** gave **2a** in 42% yield,[1] formation of **2b** from **1b** occurred to a minor extent (17%) and no compound of formula **2** was present, within the detection limits, among the products arising from **1c,d**. On the other hand, the formation of the large ring compounds **5a–c** involves an intermolecular cycloaddition to originate long-chain intermediates capable of undergoing an intramolecular ring closure to the final products.

The above results confirm that nitrile oxides add to terminal double bonds preferably giving 5-substituted rather than 4-substituted 2-isoxazolines, as amply shown in intermolecular reactions.[2] The existence of geometrical restraints to such orientation can force the reaction to occur in the opposite manner, as observed in the intramolecular cycloadditions of **1a,b**.

Experimental Section

All melting points and boiling points are uncorrected. Ir spectra were taken on a Perkin-Elmer Model 377 spectrophotometer. NMR spectra were recorded on a Varian A-60A instrument with Me_4Si as internal standard. Mass spectra were obtained on a Hitachi Model RMU-6L spectrometer.

Preparation of Aldehydes 3. General Procedure. A solution of salicylaldehyde (0.20 mol), ω-bromo-1-alkene (0.20 mol), and sodium hydroxide (0.20 mol) in 75% aqueous ethanol (300 ml) was heated at 70° during 30 hr. The mixture was then poured into ice–water and extracted several times with ether. The organic solution was dried over $MgSO_4$ and evaporated. Distillation in vacuo of the residue afforded aldehyde **3** (see Table I).

Preparation of Oximes 4. General Procedure. A solution of sodium carbonate (0.06 mol) in water (50 ml) was added dropwise to a stirred solution of aldehyde **3** (0.10 mol) and hydroxylamine hydrochloride (0.12 mol) in 50% aqueous ethanol (100 ml). The mixture was then heated at 70° for 1 hr. After removal of the solvent, water was added and the mixture was extracted several times with ether. The organic layer was dried over $MgSO_4$ and evaporated; the residue was distilled in vacuo to give oxime **4** (see Table I).

Treatment of Oximes 4 with Nitrogen Dioxide. Typical Procedure. A slow current of gaseous NO_2 (99.5%, J. T. Baker) was bubbled into a solution of oxime **4a** (5.75 g, 0.030 mol) in anhydrous ether (600 ml) under cooling at 0°, until all the starting material practically disappeared [TLC analysis with ether–*n*-hexane (3:2), 6 hr]. The resulting mixture was refluxed during 48 hr. The solvent was then removed under reduced pressure and the residue was chromatographed on a silica gel column (600 g) using benzene–ethyl acetate (9:1) as eluent. The following compounds were isolated in order of elution, the volume of eluent and yield being given in parentheses: aldehyde **3a** (200 ml, 0.45 g), oxime **4a**

(280 ml, 0.50 g), isoxazoline **2b** (550 ml, 0.97 g), bisisoxazoline **5a** (100 ml, 0.11 g), and a uncharacterized pale yellow solid (700 ml, 1.7 g).

Treatment of oximes **4b,c** with nitrogen dioxide was carried out under identical conditions.

Oxidation of 5b,c to 7b,c. A mixture of compound **5b** or **5c** (1 mmol), *N*-bromosuccinimide (2 mmol), and a trace of 2,2′-azobis(2-methylpropionitrile) in carbon tetrachloride (50 ml) was refluxed for 12 hr. The solvent was removed and the residue was taken up by dry triethylamine (15 ml). After 12 hr of refluxing, the mixture was poured into water and extracted several times with carbon tetrachloride (200 ml). The organic solution was dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column (40 g) using benzene–ethyl acetate (9:1) as eluent to give compound **7b** or **7c** (see Table II), yield ca. 30%.

Oxidation of 2b to 6. Treatment of compound **2b** (1 mmol) with *N*-bromosuccinimide (1 mmol) according to the above procedure afforded compound **6** (see Table II) in 62% yield.

Acknowledgment. We wish to thank Mr. Giorgio Tuan (Lepetit SpA) for determining the mass spectra.

Registry No.—**2b,** 55400-93-6; **3a,** 55400-94-7; **3b,** 55400-95-8; **3c,** 55400-96-9; **4a,** 55400-97-0; **4b,** 55400-98-1; **4c,** 55400-99-2; **5a,** 55401-00-8; **5b,** 55401-01-9; **5c,** 55401-02-0; **6,** 55401-03-1; **7b,** 55401-04-2; **7c,** 55401-05-3; salicylaldehyde, 90-01-7; sodium hydroxide, 1310-73-2; ω-bromo-1-butene, 5162-44-7; ω-bromo-1-pentene, 1119-51-3; ω-bromo-1-hexene, 2695-47-8; hydroxylamine hydrochloride, 5470-11-1; nitrogen dioxide, 10102-44-0; *N*-bromosuccinimide, 128-08-5.

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Comparison of Photochemical Reactions of $(C_6H_5)_2CHXCH(C_6H_5)_2$ (X = NH, CH_2, O, S) Systems

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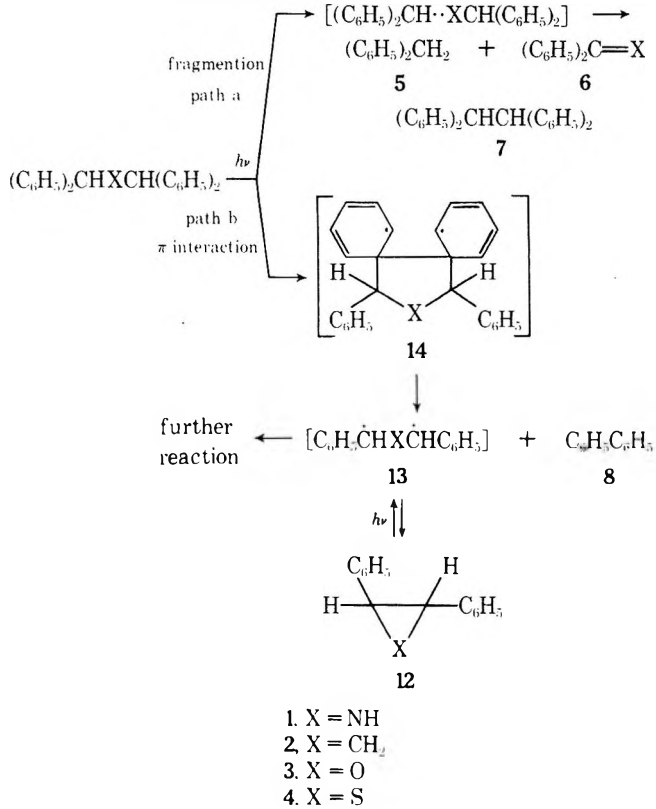
Several years ago it was reported that photochemical reaction of 1,1,1′,1′-tetraphenyldimethylamine (**1**) resulted in formation of diphenylmethane (**5**), benzophenone imine (**6**), and a small amount of 1,1,2,2-tetraphenylethane (**7**).[1]

Scheme I
Proposed Reaction Pathways

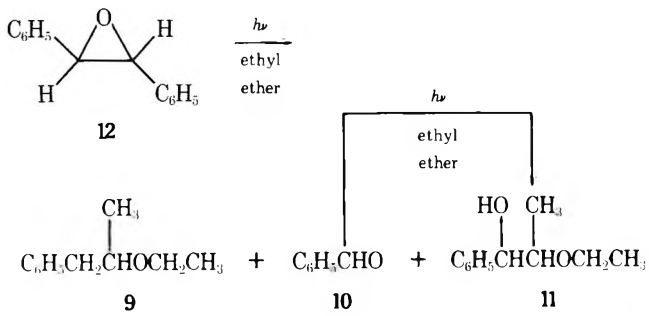


1. X = NH
2. X = CH_2
3. X = O
4. X = S

Mechanistic studies led to the proposed reaction sequence shown in Scheme I (path a). More recent investigation has uncovered a quite different reaction (Scheme I, path b) for a structurally similar compound, 1,1,3,3-tetraphenylpropane (**2**).[2] An understanding of this difference in reactivity is now possible as a result of further investigation of the photochemistry of **1** as well as study of two related systems, bis(diphenylmethyl) ether[3] (**3**) and bis(diphenylmethyl) sulfide (**4**).[4]

Results

Corex-filtered irradiations of compounds **1–3** were conducted in ethyl ether (1 mmol/350 ml) for both preparative runs and quantum yield determinations.[5] Reaction mixture separations were achieved by adsorption chromatography on Florisil followed by preparative GLC of fractions containing photoproduct mixtures. Product analysis from irradiation of **1** agreed with that reported earlier[1] except for the isolation of biphenyl (**8**) as an additional photoproduct. This new product is quite significant, however, since it suggests that the initially observed nitrogen–carbon bond fragmentation process (path a) is accompanied by a π-interaction reaction[6] (path b). The primary reaction process previously described for 1,1,3,3-tetraphenylpropane (**2**) was unaffected by the change in reaction solvent.[2] The reactivity of bis(diphenylmethyl) ether (**3**) was similar to that of **2** in that products characteristic of π interaction were the only ones observed. Irradiation of **3** gave biphenyl (**8**, 40%) and, although no stilbene oxide (**12**) was isolated, 2-ethoxy-1-phenylpropane (**9**, 35%), benzaldehyde (**10**, 31%), and 2-ethoxy-1-phenyl-1-propanol (**11**, 12%)[7] were produced. The intermediacy of stilbene oxide (**12**) or its precursor **13** (X = O) in the formation of **9**, **10**, and **11** is clearly suggested by the fact that compounds **9–11** arise from irradiation of **12**[8] in the same relative amounts as from **3**. Also, photolysis of benzaldehyde (**10**) in ether produced **11**, indicating **10** to be an intermediate in the formation of **11**.



Irradiation of bis(diphenylmethyl) sulfide (4) produced no detectable amount of biphenyl, although diphenylmethane (5, 28%), 1,1,2,2-tetraphenylethane (7, 44%), and bis(diphenylmethyl) disulfide (14%) were observed.

Discussion

The quantum yields for π-interaction reaction of compounds 1–3 (Table I) and piperylene quenching of this process (Figure 1) are particularly informative since they reveal that (a) the π-interaction process alone is quenched; (b) this quenching is similar in all three systems (1–3); and (c) quenching produces linear Stern–Volmer plots.[9] These experiments implicate a triplet excited state and suggest a π-interaction pathway in which the heteroatom does not play a significant role. Consistent with this information is a transition state resembling 14 (Scheme I) where the heteroatom is insulated from the reactive centers.

Table I
Quantum Yields for Photoreaction of Compounds 1–4 in Ether

Compd	Quantum yields[a]		
	Φ_{dis}	Φ_{π}	Φ_{fra}
1 (X = NH)	0.40	0.030	0.13
2 (X = CH_2)	0.06	0.046	<0.001[b]
3 (X = O)	0.11	0.040	0.002
4 (X = S)	0.95	<0.010[b]	0.40

[a] Φ_{dis}, Φ_{π}, and Φ_{fra} are the quantum yields for disappearance of starting material, π interaction (determined from biphenyl yields), and fragmentation (determined from diphenylmethane and 1,1,2,2-tetraphenylethane yields combined), respectively. [b] None detected. Number represents detection limit.

In contrast to the π-interaction reaction, the quantum yields for fragmentation, a process which is not quenched by piperylene, vary considerably among compounds 1–3; thus, the fragmentation process is critically dependent upon the identity of atom X (Scheme I). One clear way in which atom X causes compounds 1–3 to differ is in the C–X bond energy.[10,11] 1,1,1′,1′-Tetraphenyldimethylamine (1) is more reactive toward fragmentation than 2 and 3 and it has a weaker C–X bond. This factor suggests that a correlation may exist between photofragmentation and bond energy. Such a prediction is in agreement with the finding that fragmentation alone is observed from irradiation of bis(diphenylmethyl) sulfide (4).

A minimum-complexity picture for understanding the reactivity of compounds 1–4 involves two excited states. Excitation produces an excited singlet state which must undergo intersystem crossing to a triplet state in order for π-interaction reaction to occur. The fate of unquenchable excited states appears to be a function of the strength of the C–X bond. For compounds with stronger bonds (X = O, CH_2) return to starting material is most important; however, as the C–X bond energy decreases, fragmentation begins to compete with return to starting material.

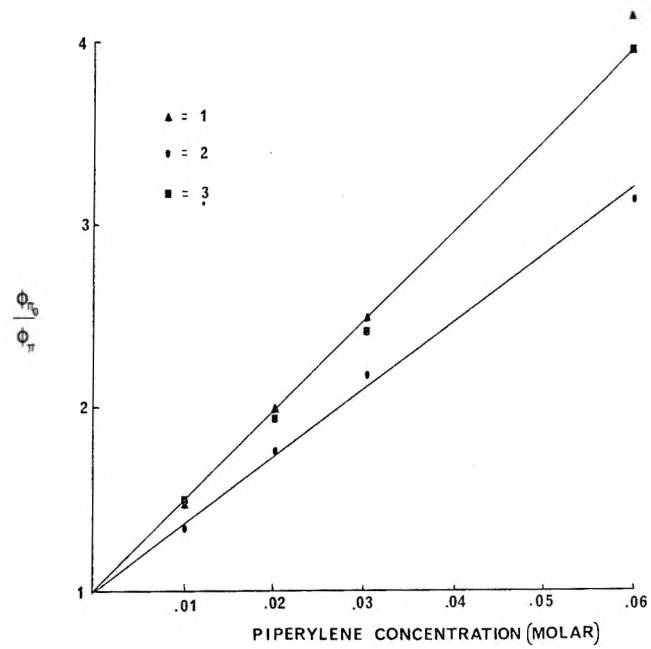


Figure 1. Quenching of π-interaction product formation. π interaction reaction is determined from biphenyl formation. Plots for 1 and 3 are the same within experimental error, ϕ_{π_0} is the π-interaction quantum yield with no quencher added. ϕ_{π} is the π-interaction quantum yield at various quencher concentrations.

Experimental Section

NMR spectra were run on a Varian T-60 NMR spectrometer and mass spectra were determined using a Finnigan 6000 mass spectrometer.

General Irradiation and Chromatography Procedure. In a typical reaction 1 mmol of material was irradiated in 350 ml of ethyl ether with a 450-W Hanovia medium-pressure mercury-vapor lamp which had been lowered into a water-cooled quartz immersion well. Prepurified nitrogen was passed through the solution for 1 hr prior to irradiation and a slow stream of nitrogen was continued during photolysis.

After irradiation, the solvent was removed by distillation in vacuo below 15° and the residual material was chromatographed on a 90 × 2.5 cm Florisil column slurry packed in 1:9 ether–hexane; 60-ml fractions were collected. The column was eluted as follows: 0.5 l. of hexane, 0.5 l. of 1:49 ether–hexane, 0.5 l. of 1:24 ether–hexane, and 0.5 l. of 1:9 ether–hexane.

Vycor-Filtered Irradiation of Bis(diphenylmethyl) Ether (3). Bis(diphenylmethyl) ether[3] (350 mg, 1.00 mmol) was irradiated for 1 hr under the standard conditions described above. Fraction 7 afforded 31 mg (0.20 mmol, 40%) of biphenyl (8), identified by NMR and mass spectral analysis. Fractions 10–13 gave 29 mg (0.17 mmol, 35%) of 2-ethoxy-1-phenylpropane (9), identified by NMR and GC–MS comparison with an authentic sample.[12] Fractions 18–23 contained 178 mg of unreacted starting material. Fractions 25–28 yielded 20 mg (0.16 mmol, 31%) of benzaldehyde (10), identified by NMR and ir. Fractions 31–33 gave 11 mg (0.06 mmol, 12%) of 2-ethoxy-1-phenyl-1-propanol (11).

Vycor-Filtered Irradiation of *trans*-Stilbene Oxide. *trans*-Stilbene oxide (196 mg, 1.00 mmol) was irradiated for 0.25 hr and chromatographed under the standard conditions described above. Fractions 10–13 produced 62 mg (0.35 mmol, 35%) of 2-ethoxy-1-phenylpropane (9). Fractions 18–23 gave 35 mg (0.29 mmol, 29%) of benzaldehyde (10) and fractions 30–34 afforded 24 mg (0.12 mmol, 24%) of 2-ethoxy-1-phenyl-1-propanol (11).

Vycor-Filtered Irradiation of Benzaldehyde (10). Benzaldehyde (120 mg, 1.00 mmol) was irradiated for 0.25 hr and chromatographed according to the standard conditions described above. Fractions 18–25 gave 63 mg of benzaldehyde (0.52 mmol) and fractions 30–34 gave 51 mg (0.26 mmol, 54%) of 2-ethoxy-1-phenyl-1-propanol (11).

Vycor-Filtered Irradiation of 1,1,1′,1′-Tetraphenyldimethylamine (1). Irradiation for 0.25 hr and chromatography of

1,1,1′,1′-tetraphenyldimethylamine (349 mg, 1.00 mmol) under the conditions described above resulted in a confirmation of the produce identity and yields described by a previous researcher[1] except for the isolation of biphenyl in 9% yield. It was necessary to separate biphenyl and diphenylmethane by preparative GLC (10% OV-1 on 80/100 mesh Chromosorb W at 170°).

Vycor-Filtered Irradiation of Bis(diphenylmethyl) Sulfide (4). Irradiation of bis(diphenylmethyl) sulfide[4] (366 mg, 1.00 mmol) for 0.25 hr was conducted under the conditions described above. Fractions 18–20 produced 102 mg (0.31 mmol, 44%) of 1,1,2,2-tetraphenylethane (7), identified by NMR and melting point comparison with an authentic sample. Fractions 21–28 afforded a mixture of two compounds which upon rechromatography in the manner described above gave in fractions 21–22 110 mg of unreacted starting material and in fractions 23–25 31 mg (0.10 mmol, 14%) of bis(diphenylmethyl) disulfide.[13]

Quantum Yield Determinations and Quenching Experiments. The apparatus and procedures used in conducting these experiments have been previously described.[2a] The quantum yields are recorded in Table I. The results of the quenching experiments are plotted in Figure 1.

Acknowledgment. The authors wish to thank Drs. T. W. Flechtner and A. H. Andrist for their helpful discussion of this work.

Registry No.—**1**, 5350-71-0; **2**, 36171-50-3; **3**, 574-42-5; **4**, 1726-03-0; **7**, 632-50-8; **8**, 92-52-4; **9**, 17953-97-8; **10**, 100-52-7; **11**, 55520-57-5; **12**, 1439-07-2; bis(diphenylmethyl) disulfide, 27080-90-6.

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(5) Quantum yield determinations were made as described in ref 2a.
(6) See ref 2 for the definition of the π-interaction reaction.
(7) Percent yields may exceed a total of 100 since reaction can cleave 3 into two compounds.
(8) H. Kristinsson and G. W. Griffin, *J. Am. Chem. Soc.*, **88**, 1579 (1966), have found that photolysis of stilbene oxide in methanol gives benzyl methyl ether in high yield.
(9) This fact has been described previously for irradiation of **2** in methanol.
(10) The following ranges for bond-energy values (kilocalories per mole) have been assembled by J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill, New York, N.Y., 1968, p 26: C–O, 85–91; C–C, 83–85; C–N, 69–75; C–S, 66.
(11) A referee has suggested that a correlation might also exist between reactivity and lowest excited singlet state energy. This is not the case, however, since compounds **1–3** have the same lowest excited singlet state energy but experience different reactivity.
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Reactions of Dichloroketene with 2-Protio- and 2-Methyl-Δ²-oxazolines

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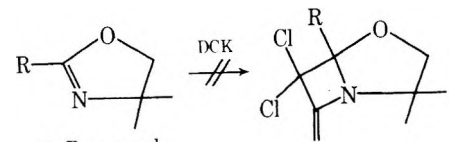
Recent reports on the syntheses of active[1] β-lactam-containing antibiotics in which the ring sulfur had been replaced by oxygen,[1,2] together with the interest[3,4] in azetidine-2,3-dione modifications of penicillins as synthons for other β-lactam-containing systems, prompt us to report our approach toward molecules containing both structural features.

In a previous study,[5] we showed that the reaction of dichloroketene[6] (DCK) with 2-aryl-Δ²-oxazolines (**1**) did not form the desired azetidinone **2** (R = aryl) as is generally the case when dichloroketene is treated with acyclic imines,[7] but rather formed 2:1 ketene:oxazoline adducts.



1, R = aryl
3a, R = CH_3
3b, R = H

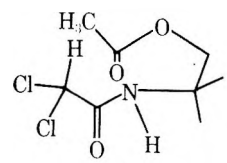
2

In these studies, it was postulated that the initially formed zwitterionic adducts were stabilized via charge delocalization due to the aromatic substituents at the 2 position,[7] and hence discouraged from ring closure to give β-lactam-containing products, but not from further reaction with the dichloroketene. In order to prevent delocalized zwitterion formation, thus hopefully encouraging β-lactam formation, the reactions of dichloroketene with 2-methyl and 2-protio oxazolines were studied.

Results

Monoaddition of dichloroketene to 2,4,4-trimethyloxazoline (**3a**) was attempted using three methods of reaction. The first method involved formation of the ketene via dehydrohalogenation of dichloroacetyl chloride with triethylamine[6b] in dry ether at −78° followed by addition of the oxazoline. The second method, which entailed formation of the ketene in the presence of the oxazoline, was accomplished by the addition of the acid chloride to a cool solution of oxazoline containing triethylamine. The third mode of reaction involved formation of the ketene in the presence of the oxazoline via dehalogenation of trichloroacetyl chloride using zinc powder.[6a]

Reaction of **3a** by either method 1 or method 2 led to the same products, amido ester **4** and vinylogous amide **5** (and small amounts of diadduct **6**), but in ratios which varied greatly with the method used. While reaction of **3a** with preformed ketene resulted in formation of **4** and **5** in a 7:1 ratio, reaction of **3a** with ketene formed in situ gave **4** and **5** in a 1:4 ratio. The zinc procedure gave a poor (13%) yield of **5** as the only isolable product.



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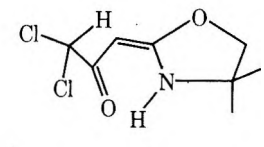

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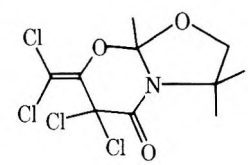
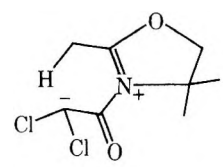
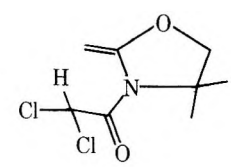


6

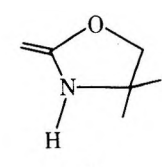
We feel that products **4** and **5** are formed by two pathways whose relative importance depends upon the experimental conditions. Pathway 1 would involve reaction of **3a** and preformed DCK to give a zwitterion[8] **7a**, which would be expected to undergo a rapid "ene" reaction[9,10] forming **7b**. Attempted isolation of **7b** by column chromatography



7a



7b



7c

gave hydrolysis product **4**. Attempted GLC isolation or distillation of **7b** after anhydrous removal of salts and in

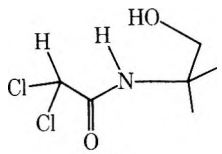
vacuo removal of solvent resulted in polymerization. ^{1}H NMR spectra of the crude reaction mixture, however, were compatible with a syn–anti mixture of **7b** (=CH_2, δ 5.8 → 6.1, 2 AB patterns). Addition of dichloroacetyl chloride to the mixture did not affect the olefinic portion of the ^{1}H NMR spectrum, indicating that **7b** was not reactive to further acylation under mild conditions. This is not surprising, as **7b** is an en*amide* and not an en*amine*.

Pathway 2, we believe, involves an equilibrium between imine **3a** and enamine **7c**[9-11] promoted by the excess base (triethylamine) and longer reaction times. Reaction of **7c** with either the acid chloride or DCK would give **5**. Attempts to methylate **5** on either nitrogen or carbon (enamine reaction) resulted in no reaction, supporting our view that **5** should be looked upon as a relatively unreactive vinylogous amide and not as an enamine. Our results do not rule out other possible mechanisms, however.

Compound **5** was identified on the basis of its spectral and analytical data, while **4** was synthesized via intermediate **8** (see Experimental Section).

The identification of the diadduct **6** was based on its spectral data. The mass spectrum of **6**, which shows a parent ion at *m/e* 333 containing four chlorine atoms, indicates a 2:1 stoichiometry. Comparison of the carbonyl portion of the ir spectrum of **6** (1725 cm^{-1}) with those of similar diadducts[5] strongly indicated the structure given. No attempt was made to further characterize **6**.

Dichloroacetic acid was found to react with **3a** to give the ether-soluble adduct **9**[10] in nearly quantitative yield.



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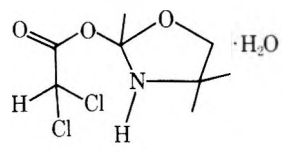
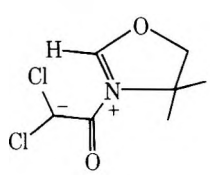


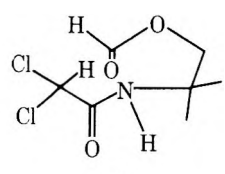
9

The presence of **9** in a few of the reaction mixtures was taken as evidence that totally anhydrous conditions had not been realized, and such runs were ignored.

Reaction of dichloroketene with 4,4-dimethyloxazoline (**3b**) would be expected to proceed via N-acylation of the substrate to give zwitterion **10**.[8] Adduct **10** is apparently stable and closure to β-lactam **2** (R = H) was not observed, but rather amido ester **11** was isolated upon work-up followed by chromatography. Longer reaction times, higher temperatures, and varying solvents did not alter the course of this reaction.



10



11

That zwitterionic intermediates of type **10** (and **7a**) were involved in this reaction was demonstrated by reducing **10** with sodium borohydride followed by mild hydrolysis[9] to yield the previously formed amido alcohol **8** which could be formylated to yield **11** or acetylated to yield **4**. Compound **11** was shown not to revert to **8** under the conditions used for the work-up of the $NaBH_4$ reduction reaction.

Experimental Section

Melting points were taken with a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 grating instrument, while ^{1}H NMR data were collected on a Jeol MH-100 spectrometer utilizing Me_4Si as internal standard. Mass spectra were taken with a Hitachi RMU 6-D mass spectrometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Flame-dried glassware and nitrogen atmospheres were used for all reactions involving dichloroketene.

2,4,4-Trimethyloxazoline (**3a**) and 4,4-dimethyloxazoline (**3b**) were prepared by the method of Allen and Ginos[12] but were observed to codistill with water. Distillation from sodium hydride into dried containers provided dry material which could be kept for several weeks in a desiccator.

Reaction of 3a with Dichloroketene. Method 1. Freshly distilled dichloroacetyl chloride (1.47 g, 0.01 mol) dissolved in dry ether was dripped slowly into a solution containing 1 equiv of freshly distilled triethylamine in ether at −78°. The immediate appearance of triethylamine hydrochloride indicated the formation of dichloroketene. After the mixture was allowed to stir for 30 min at −78°, 1.13 g (0.01 mol) of freshly dried oxazoline **3a** was added to it over a period of 30 min. The mixture was warmed to 25° and allowed to stir for 1–4 hr. Vacuum filtration of the slurry followed by evaporation of the solvent in vacuo resulted in the isolation of a yellow oil which, when chromatographed on silicic acid (hexane–ether eluent), gave **4** (60–80%), **5** (5–15%), and **6** (2–5%).

Method 2. Freshly distilled dichloroacetyl chloride (1.47 g, 0.01 mol) in dry ether was added to a stirred solution of 0.01 mol each of dry oxazoline and triethylamine at −78°. The immediate formation of a white precipitate was observed. The mixture was stirred at −78° for 1 hr, warmed at 25°, and allowed to stir for another 1–48 hr. The solid was removed via vacuum filtration and the filtrate was concentrated in vacuo to yield a pale yellow oil which, when chromatographed on silicic acid, alumina (acidic or basic), or Florisil (hexane–ether eluent), provided **4** (10–20%), **5** (55–65%), and **6** (3–5%).

Method 3. To 50 ml of dry ether under nitrogen was added 1.13 g (0.01 mol) of freshly dried oxazoline and 1.5 g of finely powdered zinc. Freshly distilled trichloroacetyl chloride (1.13 g, 0.01 mol) was added to the mixture with vigorous stirring over a period of 3 hr. After 12 hr of further stirring at 25°, the dark mixture was vacuum filtered and concentrated in vacuo to give a tarry oil. Chromatography on Florisil (hexane–ether eluent) provided **5** (13%) as the only isolated product.

For 6: mp 128°; ir (CCl_4) 2995, 1725, 1380, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 3), 1.56 (s, 3), 1.76 (s, 3), 3.90 (AB, 2); mass spectrum (70 eV) *m/e* 333 (parent, 4 Cl), 298 (3 Cl), 270 (3 Cl), 262 (3 Cl), 223 (2 Cl).

For 5: mp 123°; ir (CCl_4) 3300, 2990, 1639, 1545, 1390, 1370 and 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 6), 4.08 (s, 2), 5.14 (s, 1), 5.70 (s, 1); mass spectrum (70 eV) *m/e* 223 (parent, 2 Cl), 208 (2 Cl), 140, 72.

Anal. Calcd for $C_8H_{11}NO_2Cl_2$: C, 42.89; H, 4.91. Found: C, 43.05; H, 4.91.

Reaction of 3b with Dichloroketene. Methods 1 and 2 described above were utilized substituting **3b** for **3a** and giving after work-up **11** as a semisolid in yields from 70 to 90%.

Synthesis of Dichloroacetamido-2-methylpropanol (8). Alcohol **8** was synthesized in 80% yield from 2-amino-2-methylpropanol and dichloroacetyl chloride using Schotten–Baumann conditions. For **8**: mp 125–125.5°; ir ($CHCl_3$) 3420, 2995, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 6), 2.96 (s, 1, Br), 3.62 (s, 2), 5.76 (s, 1) 6.54 (s, 1, Br).

Synthesis of 2-Dichloroacetamido-2-methylpropanol Acetate Ester (4). Compound **4** was synthesized by acetylation of alcohol **8** with 1.2 equiv of acetic anhydride in pyridine. Acid–base work-up gave a pale yellow oil which solidified upon standing to give **4** in 80% yield.

For **4**: mp 81–82°; ir (CCl_4) 3440, 3380, 2995, 1752, 1711, 1520, 1378, 1240, and 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 6), 2.04 (s, 3), 4.12 (AB, 2, J = <1 Hz), 5.72 (s, 1), 6.5 (s, 1, broad); mass spectrum (70 eV) *m/e* 241 (parent, 2 Cl), 184 (2 Cl), 168 (2 Cl), 116, 72.

Anal. Calcd for $C_8H_{13}Cl_2NO_3$: C, 39.70; H, 5.38. Found: C, 39.85; H, 5.26.

Synthesis of 2-Dichloroacetamido-2-methylpropanol Formate Ester (11). A solution of formic–acetic anhydride[13] was prepared by adding 0.02 mol of acetic anhydride to 50 ml of 88% formic acid. To this mixture was added 0.01 mol of alcohol **8** in formic acid. After stirring for 1 hr, the solution was added to an ice-cold carbonate solution, which was extracted with $CHCl_3$, dried, and evaporated in vacuo to give a residual oil which was found to be in excess of 95% **11** by ^{1}H NMR. This material could not be recrystallized in our hands and distillation resulted in an O to N formyl shift and decomposition.

For **11**: ir (CCl_4) 3420, 2985, 2940, 1780, 1720, 1540, 1155 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.36 (s, 6), 4.28 (s, 2), 5.84 (s, 1), 6.60 (Br, 1), 8.10 (s, 1); mass spectrum (70 eV) *m/e* no parent ion, 181 (2 Cl), 168 (2 Cl), 116, 101, 72, 58.

Synthesis of 2-Dichloroacetoxy-2,4,4-trimethyloxazolidine (9) Monohydrate. Dichloroacetic acid (1.29 g, 0.01 mol) was added dropwise to 1.13 g (0.01 mol) of **3a** in ether to yield an initial precipitate which later dissolved. Concentration of the solution in vacuo produced a pale yellow oil which crystallized upon standing at 5°. Recrystallization with ether–hexane gave **9** monohydrate in 85% yield.

For **9** monohydrate: mp 110°; ir (CCl_4) 3000, 1755, 1680, 1390, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 6), 2.13 (s, 3), 4.12 (s, 2), 5.82 (s, 1), 7.6 (Br, 3); mass spectrum (70 eV) *m/e* no parent ion, 113, 98, 83, 70, 57.

Anal. Calcd for $C_8H_{15}Cl_2NO_4$: C, 36.94; H, 5.81; Cl, 27.26; N, 5.38. Found: C, 37.05; H, 5.84; Cl, 27.43; N, 5.40.

Reduction of 10 by Borohydride. Zwitterion **10** was formed by reaction of dichloroketene and **3b** using either methods 1 or 2 described above and treated with a threefold excess of sodium borohydride. The resulting slurry was stirred for 3 days under nitrogen, quenched with ice water acidified to pH 5, and extracted with ether which was then dried (Na_2SO_4) and evaporated in vacuo to yield a pale yellow oil. The oil, when saturated with ether, produced 65% of a white, crystalline material shown to be amido alcohol **8.**

Some ester **11** resulting from incomplete reduction of **10** was also recovered. Compound **11** was shown not to be hydrolyzed to **8** under the work-up conditions employed.

Acknowledgment. We thank the National Institutes of Health (AI 10389) for support of this work.

Registry No.—**3a,** 1772-43-6; **3b,** 30093-99-3; **4,** 55428-39-2; **5,** 55428-40-5; **6,** 55428-41-6; **8,** 55428-42-7; **9,** 55428-43-8; **10,** 55428-44-9; **11,** 55428-45-0; dichloroacetyl chloride, 79-36-7; triethylamine, 121-44-8; dichloroketene, 4591-28-0; oxazoline, 504-77-8; 2-amino-2-methylpropanol, 124-68-5; formic–acetic anhydride, 2258-42-6; dichloroacetic acid, 79-43-6; sodium borohydride, 16940-66-2.

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Synthesis of 3,11-Dimethyl-2-nonacosanone, a Sex Pheromone of the German Cockroach

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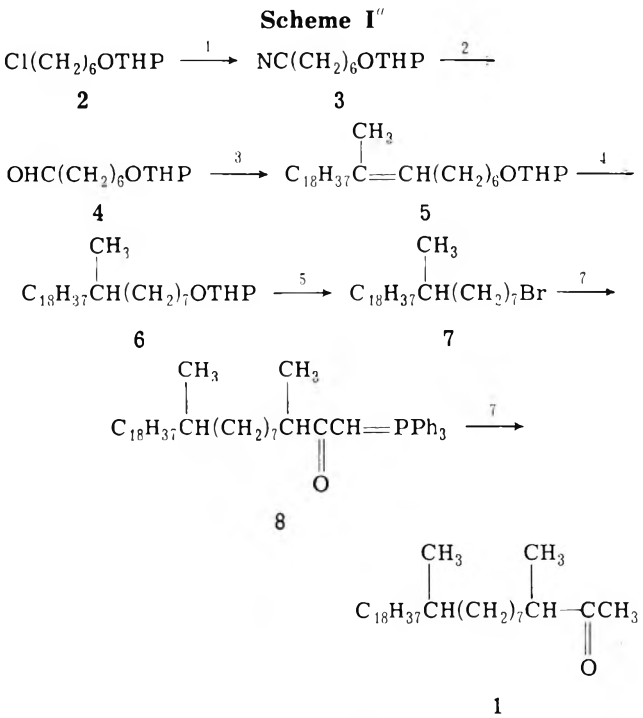
Recently Nishida et al.[1] reported the isolation of a sex pheromone of the German cockroach, *Blattella germanica* (L.), from its cuticular waxes. The compound was identified as 3,11-dimethyl-2-nonacosanone (1) with no information given concerning its absolute configuration. We wish to report a synthesis of the mixture of diastereomers of **1** as outlined in Scheme I.[2]

Scheme I[a]



[a] 1, NaCN–NaI–DMSO; 2, $Li(EtO)_2AlH_2$; 3, $C_{18}H_{37}C(CH_3)=PPh_3$; 4, H_2–Pd/C; 5, PPh_3Br_2; 6, $C_2H_5C(=O)CH=PPh_3$; 7, OH^-.

6-Chlorohexyl tetrahydro-2-pyranyl ether[3] **2** was converted to the corresponding cyanohexyl tetrahydropyranyl ether (**3**) with sodium cyanide in Me_2SO in the presence of a catalytic amount of sodium iodide. Reduction of **3** with lithium diethoxyhydroaluminate[4] yielded the corresponding aldehyde **4.** The Wittig reaction between **4** and (1-methylnonadecylidene)triphenylphosphorane (see Experimental Section) afforded presumably a cis and trans mixture of 8-methyl-7-hexacosenyl tetrahydropyranyl ethers (**5**) which was hydrogenated to compound **6.** Treatment of tetrahydropyranyl ether **6** with dibromotriphenylphosphorane[5] in methylene chloride gave 1-bromo-8-methylhexacosane (**7**) in excellent yield.[6] (2-Oxobutylidene)triphenylphosphorane,[7] prepared according to Cooke,[8] was converted to its anion by treatment with *n*-butyllithium and was alkylated with bromide **7.** Title compound **1**[9] was finally obtained by the hydrolysis of the crude alkylation product **8.** This extension of Cooke's procedure[8] thus represents a useful method for the preparation of α-branched methyl ketones.

Experimental Section[10]

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Ir spectra were obtained with CCl_4 solutions on a Perkin-Elmer Model 457A grating spectrophotometer. NMR spectra were obtained on a Varian Model T-60 spectrometer with tetramethylsilane (Me_4Si) as an internal standard. Reported chemical shifts are in δ, parts per million downfield from Me_4Si. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

6-Cyanohexyl Tetrahydropyranyl Ether (3). A heterogeneous mixture of 6-chlorohexyl tetrahydropyranyl ether[3] (50 g, 0.227 mol), NaCN (17.2 g, 0.35 mol), and NaI (4.5 g, 0.03 mol) in dry DMSO (50 ml) was stirred at ambient temperature for 16 hr. The mixture was diluted with water and extracted with petroleum ether. The organic phase was washed with H_2O (2 × 100 ml) and dried ($MgSO_4$). Concentration followed by distillation afforded 44.0 g (90%) of **3:** bp 105–115° (0.7 mm); n^{25}D 1.4550; ir 2260 cm^{-1}; NMR δ 2.30 (m, 2, CH_2CN), 3.2–4.0 (m, 4, CH_2O), 4.47 (s, 1,

OCHO). Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 67.98; H, 9.80; N, 6.80.

7-Oxoheptyl Tetrahydropyranyl Ether (4). Ethyl acetate (4.5 g, 0.05 mol) was added dropwise to a stirred suspension of $LiAlH_4$ (1.95 g, 0.05 mol) in ethyl ether at 0°. Then **3** (10.55 g, 0.05 mol) was added dropwise over a 10-min period and the reaction mixture was stirred for an additional 50 min at ice-bath temperature. Water (2 ml), 15% NaOH (2 ml), and water (6 ml) were added dropwise in that order, the mixture was filtered, and the filtrate was concentrated. The crude imine was stirred for 1 hr at room temperature in a mixture of 40 ml of water, 40 ml of ethyl alcohol, and 20 ml of glacial acetic acid;[11] then the mixture was diluted with water and extracted with petroleum ether. The organic layer was washed with brine, saturated sodium bicarbonate, and brine and dried. After removal of the solvent, **4** (5.0 g, 45%) was purified by short-path distillation: bp 95–100° (0.05 mm); ir 1729 cm^{-1}; NMR δ 2.35 (m, 2, $-CH_2CHO$), 3.2–4.0 (m, 4, $-CH_2O-$), 4.48 (broad s, 1, OCHO), 9.67 (t, 1, -CHO). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.24, H, 10.22.

***(Z)*- and *(E)*-8-Methyl-7-hexacosenyl Tetrahydropyranyl Ethers (5).** Ethylidenetriphenylphosphorane was prepared from ethyltriphenylphosphonium bromide in THF using 2.0 *M* *n*-butyllithium in hexane in the usual manner. One equivalent of 1-bromooctadecane was added to the ylide solution (ca. 10°) and 10 min later HMPA, 1 ml/ml THF, was added. The deep red solution remained homogeneous. After 2 days the solution, lighter in color but still red, was diluted with 1,2-dichloroethane and washed with H_2O several times. The organic phase was dried ($MgSO_4$) and concentrated. The oily salt, (1-methylnonadecyl)triphenylphosphonium bromide, was freed of traces of 1,2-dichloroethane by washing with anhydrous Et_2O several times and then concentrating the residue on a flash evaporator. A solution of the salt was prepared in dry THF and used as soon as possible.

The secondary alkylphosphonium salt (0.045 mol) was converted to its ylide at 5° in 100 ml of THF with *n*-butyllithium (23 ml of 2.0 *M* in hexane) and the aldehyde **4** (8.2 g, 0.038 mol) was added dropwise. The ice bath was removed and after 1 hr the reaction mixture was worked up in the usual manner with petroleum ether to extract the olefin **5**. The crude product was deposited on a column of silica gel (100 g) and then eluted with 200 ml of petroleum ether and 200 ml of 15% Et_2O in petroleum ether. The combined eluates were then rechromatographed (silica gel, 100 g) and eluted with 200 ml of petroleum ether and 400 ml of 15% Et_2O in petroleum ether. Compound **5** was obtained in the last 200 ml and weighed 18.3 g (56%); $n^{25}D$ 1.4625; NMR δ 0.88 (t, ca. 3, CH_3), 3.2–4.0 (m, 4, CH_2), 4.48 (s, 1, OCHO), 5.03 (t, 1, -CH). Anal. Calcd for $C_{32}H_{62}O_2$: C, 80.26; H, 13.05. Found: C, 80.50; H, 13.30.

8-Methylhexacosanyl Tetrahydropyranyl Ether (6). Olefin **5** (10.0 g, 0.021 mol) was hydrogenated at atmospheric pressure in hexane (150 ml) with 10% Pd/C (1 g). Filtration and concentration provided **6** quantitatively: $n^{25}D$ 1.4577; NMR δ 0.87 (t, ca. 3, CH_3), 3.2–4.0 (m, 4, CH_2O), 4.45 (s, 1, OCHO). Anal. Calcd for $C_{32}H_{64}O_2$: C, 79.93; H, 13.42. Found: C, 79.74; H, 13.22.

1-Bromo-8-methylhexacosane (7). A solution of triphenylphosphine dibromide was prepared by adding bromine (7.0 g, 0.0436 mol) dropwise to a chilled, stirred solution of triphenylphosphine (11.4 g, 0.0436 mol) in 120 ml of CH_2Cl_2 maintained at 0–10°. The THP ether **6** (9.5 g, 0.0198 mol) in 10 ml of CCH_2Cl_2 was then added at once. The mixture was allowed to stir for 16 hr under nitrogen at room temperature. The black solution was washed with H_2O (2 × 100 ml), dried ($MgSO_4$), and deposited on 45 g of alumina (Fisher, neutral). The resulting mixture was placed onto a column of silica gel (125 g) and eluted with petroleum ether (500 ml). Concentration of the eluate provided the bromide as a colorless liquid, 8.1 g (91%): $n^{25}D$ 1.4641; NMR δ 0.88 (t, ca. 3, CH_3), 3.30 (t, 2, CH_2Br). Anal. Calcd for $C_{27}H_{55}Br$: C, 70.55; H, 12.06; Br, 17.39. Found: C, 70.75; H, 12.08; Br, 17.16.

(2-Oxobutylidene)triphenylphosphorane. To a cooled solution (−78°) of 10.5 g (0.033 mol) of (2-oxopropylidene)triphenylphosphorane[12] in 250 ml of dry THF was added under nitrogen 20 ml (0.033 mol) of 1.6 *N* *n*-butyllithium in hexane. The deep red solution of the ylide anion was stirred at −78° for 15 min, then 6.0 g (0.042 mol) of methyl iodide was added slowly. The color of the anion was discharged at the end of the addition. The reaction mixture was allowed to warm to room temperature and a clear solution resulted. Excess solvents were removed with a flash evaporator and the remaining solid was filtered to yield 10 g of crude (2-oxobutylidene)triphenylphosphorane. Recrystallization from chloroform–ethyl acetate gave 8 g (75%) of product, mp 218–219° (lit.[7] mp 221–222°).

3,11-Dimethylnonacosan-2-one (1). A solution of (2-oxobutylidene)triphenylphosphorane (0.33 g, 0.001 mol) in THF (10 ml) was cooled to −78° under nitrogen and treated with 1.2 ml (0.002 mol) of 1.6 *M* *n*-butyllithium in hexane. The resulting deep red solution was stirred for 15 min, and then a solution of 1-bromo-8-methylhexacosane (**7**, 0.40 g, 0.00087 mol) in THF (15 ml) was added (**7** separated from solution at the low temperature). The cooling bath was removed, stirring was continued for 20 hr at room temperature, then water (ca. 5 ml) was added (color discharged) and the mixture was refluxed for 24 hr. The solvent was evaporated and the residue was partitioned between ether and water. Alumina (ca. 6 g) was added to the dried ether solution, the ether was evaporated, and the residue was added to a column of silica gel (20 g). After eluting with petroleum ether, the ketone **1** (0.11 g, 28%) was obtained by elution with 10% ether in petroleum ether.

The reaction was repeated with a twofold excess of the phosphorane with no increase in the yield of **1**.

The products of the two reactions (0.21 g) were combined and rechromatographed on silica gel to give an analytical sample: ir 1716 cm^{-1}; NMR δ 2.0 (s, CH_3CO), 0.83 (*t*-CH_3).

Anal. Calcd for $C_{31}H_{62}O$: C, 82.59; H, 13.86. Found: C, 82.82; H, 13.77.

Registry No.—**1**, 53623-10-2; **2**, 2009-84-9; **3**, 33803-59-7; **4**, 34335-17-6; (*E*)-**5**, 55590-31-3; (*Z*)-**5**, 55590-32-4; **6**, 55590-33-5; **7**, 55590-34-6; **8**, 55590-35-7.

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(10) Mention of a trade name or proprietary product does not constitute a USDA endorsement.
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Cephem-*N*-methylnitrones

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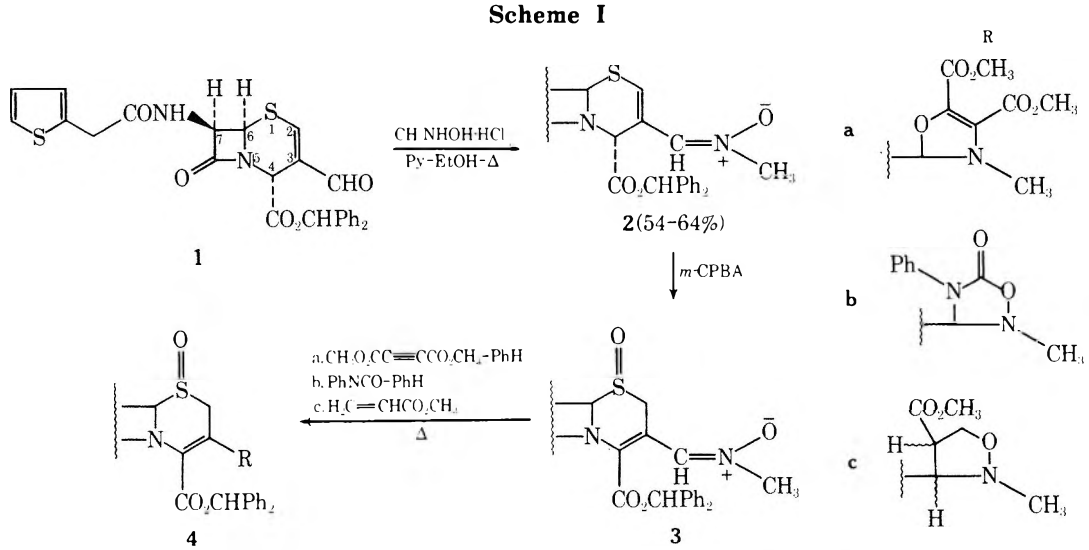
Our interest in the synthesis of 2-C–3-C-tricyclic cephalosporins,[1] of cephem-3-*C*-carboxamides,[2] and in the synthesis of cephalosporins with ring substituents attached directly at 3-C vs. 3-C'[3a,3b] led us to explore some of the chemistry of the *C*-3-*C*-cephem-*N*-methylnitrones. Thus aldonitrones are known to undergo rearrangement with a variety of reagents (acetic anhydride, acetyl chloride, sulfur dioxide, etc.) to give amides and to undergo inter- and intramolecular cycloaddition reactions to give heterocyclic ring systems.[4]

Treatment of the Δ^2-3-*C*-formyl derivative (**1**) with *N*-methylhydroxylamine followed by chromatography on silica gel gave the *N*-methylnitrone (**2**) in moderate yield (Scheme I). Sulfur oxidation with *m*-chloroperbenzoic acid

Scheme I



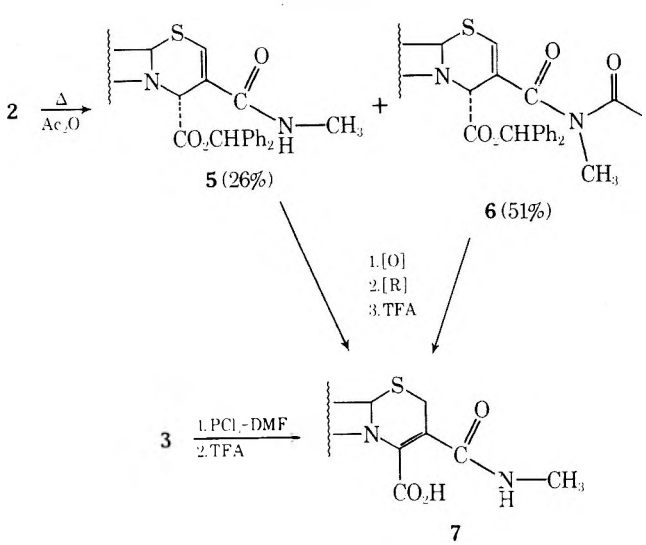
(*m*-CPBA) with concomitant double bond isomerization then gave **3** in 90% crude yield.

Cycloaddition reactions of **3** with dimethyl acetylenedicarboxylate gave what we believe to be the 4′-oxazoline **4a** (70%) via the 4′-isoxazoline by thermal rearrangement via the acyl aziridine.[5] Reaction of **3** with phenyl isocyanate gave a single product (52%) believed to be the 1′,2′,4′-oxadiazolin-5′-one (**4b**), while methyl acrylate gave two different products (**4c**, 32 and 20%). Structural assignments in the latter reaction are complicated by the fact that the mechanism of such cycloaddition reactions is not known with certainty but can be subject to both kinetic and thermodynamic control. The conditions of the reaction (80°, 1 hr) should favor conjugate addition, thus leaving the question of whether the process is stereospecific cis addition as well as the obvious creation of two new asymmetric centers.

The sulfoxides **4a–c** were reduced (PCl_3–DMF) and the esters cleaved to give the corresponding acids. The acids retain gram positive, but show loss in gram negative activity relative to sodium cephalothin.

The 3-*C*-*N*-methyl carboxamides were synthesized via the PCl_3–DMF reaction on **3** (21%) followed by ester cleavage to give **7** or alternatively by the reaction of **2** with acetic anhydride to give the amide **5** (26%) and the imide **6** (51%) (Scheme II). Although the presence of acetic acid reverses the amide/imide ratio (26:51 to 52:27), double bond isomerization followed by ester cleavage with strong acid (TFA) results in deacetylation of the imide to give the corresponding *N*-methyl amide.

Scheme II



Biological tests show that the *N*-methyl amide **7** retains gram positive, but shows reduced gram negative activity relative to sodium cephalothin.

Although aldonitrones can theoretically exist in two different geometric configurations, it is known that under thermodynamic conditions the trans or *Z* form exists exclusively.[4b,6] Consequently the nitrone oxygen in **2** is oriented correctly for an intramolecular 1,3-dipolar cycloaddition. Pyrolysis of **2** in toluene at 110° for 3 hr results in the formation of two products (**8a**, isomer I, and **8b**, isomer II) (72%) (Scheme III) which are isomeric with starting material. Similar pyrolysis on **3** gave starting material, thus showing the necessity of a Δ^2 double bond and corroborating an intramolecular 1,3-dipolar type reaction. Changing the 4-C ester changed the ratio of isomer I to II as shown: CH_3 (74%), I:II = 7:1; $CHPh_2$ (72%), I:II = 2.3:1.0; $CH_2C_6H_4NO_2$-*p* (58%), I:II = 1.2:1.0.

Ir studies of **8a** and **8b** show that both rearrangement products contain the β-lactam, while the NMR spectra were characterized in both cases by an *N*-methyl doublet (ca. δ 2.9, J = 4 Hz) and two low-field protons, one a singlet at ca. δ 8.9 and the other a multiplet at ca. δ 11.5. D_2O wash caused the *N*-methyl doublet to become a singlet and showed the δ 11.5 peak to be an NH, thus ruling out a tricyclic isoxazoline.

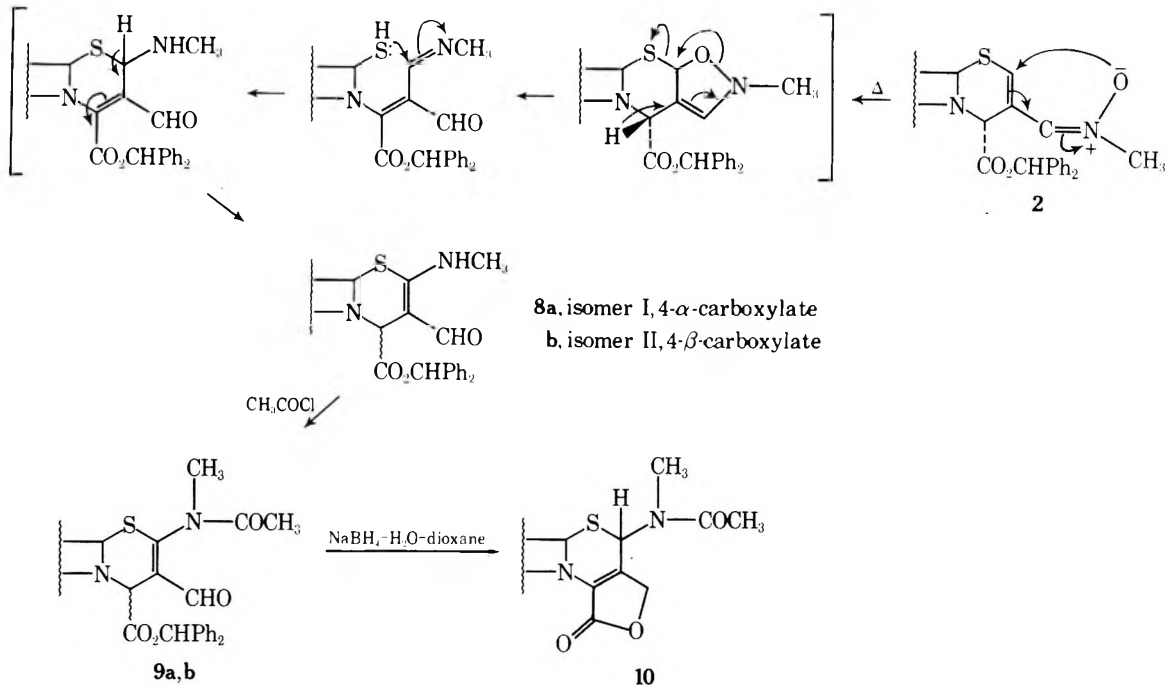
Both rearrangement products **8a** and **8b** can be acylated with either CH_3COCl or $ClCO_2CH_2CCl_3$ (isomer I, mp 166–168°) to give different acyl derivatives. Borohydride reduction of the *N*-acetyl derivatives **9a** and **9b**, however, gave a common lactone, thereby explaining the δ 8.9 peak in the NMR as belonging to the hydrogen of a 3-*C*-aldehyde.

We believe that the intramolecular dipolar addition products have structure **8**, being isomeric at 4-C (isomer I is thought to have the α-carboxylate while isomer II is the β) and are derived by fragmentation of the intermediate tricyclic isoxazoline (O–N fragmentation, rotation about 3-C–4-C, followed by abstraction of the 4-H to give the conjugated imine.)

That the double bond in **8** is Δ^2 is indicated by the NMR, which shows the NH in isomer I to have an AB pattern and the 4-C proton to be a singlet. The NMR of isomer II shows H_4 to H_7 coupling (2 Hz) which has previously been used to distinguish abnormal (β-carboxylate) stereochemistry at 4-C.[7] The uv absorption, showing λ_{max} at 325 (**8a**) and 332 nm (**8b**), confirms the double bond assignment. Similar uv data on the *N*-acyl derivatives show that acylation does not shift the double bond.

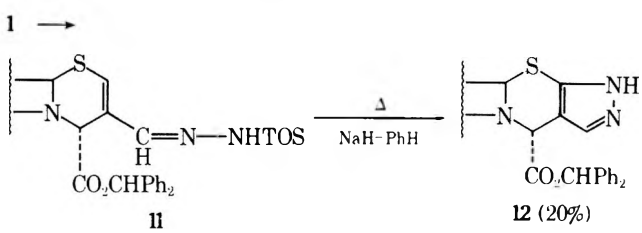
Running the intramolecular dipolar addition rearrange-

Scheme III



ment at lower temperatures failed to allow isolation of the fused isoxazoline, apparently a result of the propensity of the N–O bond to thermally fragment. This type of approach to 2-C–3-C triheterocyclic derivatives, however, has been successfully demonstrated by treatment of the tosylhydrazone **11** with NaH in a Bamford–Stevens[8] type reaction to give the tricyclic pyrazole **12** (198–199°) in 20% yield (Scheme IV). (Double bond orientation has not been determined.)

Scheme IV



Experimental Section

Diphenylmethyl-3-[(dehydroxymethyl-*aci*-nitro)methyl]-7-[2-(2-thienyl)acetamido]-2-cephem 4α-Carboxylate (2). The Δ^2-aldehyde (1) (0.519 g, 1.0 equiv), 0.184 g (2.2 equiv) of *N*-methylhydroxyamine hydrochloride, and 0.237 g (3.0 equiv) of pyridine in 2 ml of CH_2Cl_2 and 40 ml of 2B EtOH was refluxed for 6 hr and then evaporated to dryness. It was taken up in EtOAc, washed with 1 *N* HCl and brine, dried (Na_2SO_4), and chromatographed on silica gel using a toluene–ethyl acetate gradient to give 0.347 g (63.5%) of nitrone as a pale yellow froth: ir ($CHCl_3$) 1780 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 3.52 (s, 3, *N*-Me), 3.85 (s, 2, thiophene methylene), 5.07 (s, 1, H_4), 5.20 (d, J = 4 Hz, 1, H_6), 5.59 (q, J = 4, 8 Hz, 1, H_7), 6.87 (s, 1, H_2), 9.12 (s, 1, nitrone proton).

Cephem-*N*-methylnitrone Sulfoxide (3). Oxidation was done in $CHCl_3$ at 5° by dropwise addition of 1.1 equiv of *m*-chloroperbenzoic acid. After 1 hr the solution was washed with $NaHCO_3$, H_2O, and brine, dried, and evaporated to 98% of an amorphous gel: NMR (DMSO-d_6) δ 3.35 (s, 3, *N*-Me), 3.90 (s, 2, thiophene methylene), 3.72, 4.43 (AB, J = 18 Hz, 2, H_2), 5.00 (d, J = 5 Hz, 1, H_6), 6.00 (q, J = 5, 8 Hz, 1, H_7), 7.60 (s, 1, nitrone proton).

Cephem-3-(4′-oxazoline) (4a). A solution of the nitrone (0.282 g, 5.0 mmol) and 1 ml (ca. 20 equiv) of dimethyl acetylenedicarboxylate in 30 ml of benzene was refluxed for 45 min and then evaporated to dryness and chromatographed on silica gel using a toluene–ethyl acetate gradient to give 0.248 g (70.2%) of pale yellow froth: ir ($CHCl_3$) 1800 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 2.85 (s, 3, *N*-Me), 3.00, 4.15 (AB, J = 18 Hz, 2, H_2), 3.43 (s, 3, CO_2CH_3), 3.86 (s, 3, CO_2CH_3), 3.90 (s, 2, thiophene methylene), 4.45 (d, J = 4 Hz, 1, H_6), 5.75 (s, 1, 2′-oxazoline proton), 6.00 (q, J = 4, 9 Hz, 1, H_7).

Cephem-3-(1′,2′,4′-oxadiazolin-5′-one) (4b). A solution of the nitrone (0.564 g, 1.0 mmol) and 2 ml of phenyl isocyanate in 40 ml of ethylene dichloride and 10 ml of DMF was refluxed for 1 hr. It was then evaporated to dryness and chromatographed on silica gel using a toluene–ethyl acetate gradient to give 0.351 g (51.3%) of froth: ir ($CHCl_3$) 1808 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 2.67, 4.12 (AB, J = 18 Hz, 2, H_2), 2.95 (s, 3, *N*-Me), 3.78 (s, 2, thiophene methylene), 4.17 (d, J = 4 Hz, 1, H_6), 5.90 (q, J = 4, 9 Hz, 1, H_7), 6.16 (s, 1, 3′-oxadiazoline ring proton).

Cephem-3-(isoxazolidine) (4c). A solution of the nitrone (1.18 g, 2.09 mmol) in 60 ml of methyl acrylate was gently refluxed for 1 hr. It was then evaporated to dryness and chromatographed on silica gel using a toluene–ethyl acetate gradient to give 0.429 g (32%) of isomer I and 0.265 g (20%) of isomer II.

Isomer I: ir ($CHCl_3$) 1800 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 2.55 (s, 3, *N*-Me), 3.42 (s, 3, CO_2CH_3), 3.85 (s, 2, thiophene methylene), 3.0–4.5 (m, 5), 5.30 (d, J = 9 Hz, 1), 6.02 (q, J = 4, 10 Hz, 1, H_7).

Isomer II: ir ($CHCl_3$) 1800 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 2.59 (s, 3, *N*-Me), 3.76 (s, 3, CO_2CH_3), 3.86 (s, 2, thiophene methylene), 2.0–3.0 (m, 2), 4.0–4.7 (m, 4), 6.0 (q, J = 4, 10 Hz, 1, H_7).

Sulfides of 4a–c. The sulfoxides were reduced using 2–3 equiv of PCl_3 in DMF at room temperature for 45 min. Ethyl acetate was then added and the solution was washed with $NaHCO_3$ and NaCl, dried (Na_2SO_4), evaporated, and chromatographed on silica gel using a toluene–ethyl acetate gradient to give the corresponding sulfides.

Cephem-3-(4′-oxazoline) (30%): ir ($CHCl_3$) 1790 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 2.86 (s, 3, *N*-Me), 3.65 (s, 3, CO_2CH_3), 3.85 (s, 3, CO_2CH_3), 3.99 (s, 2, thiophene methylene), 5.00 (d, J = 4 Hz, 1, H_6), 5.65 (s, 1, oxazoline proton), 5.88 (q, J = 5, 9 Hz, 1, H_7).

Cephem-3-(oxadiazolin-5′-one) (35%): ir ($CHCl_3$) 1800 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 3.00 (s, 3, *N*-Me), 3.10, 3.74 (AB, J = 18 Hz, 2, H_2), 3.81 (s, 2, thiophene methylene), 4.70 (d, J = 4 Hz, 1, H_6), 5.80 (q, J = 4, 9 Hz, 1, H_7), 6.08 (s, 1, 3′-oxadiazoline ring proton), 6.78 (d, J = 9 Hz, 1, NH).

Cephem-3-(isoxazolidine). Isomer I (82%): ir ($CHCl_3$) 1790 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 2.54 (s, 3, *N*-Me), 3.44 (s, 3, CO_2CH_3), 3.80 (s, 2, thiophene methylene), 3.3–4.3 (m, 5), 4.85 (d, J = 4 Hz, 1, H_6), 5.20 (d, J = 9 Hz, 1), 5.80 (q, J = 4, 8 Hz, 1, H_7).

Isomer II (76%): ir ($CHCl_3$) 1788 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 3.80 (s, 3, CO_2CH_3), 3.59 (s, 2, H_2), 3.87 (s, 2, thiophene methylene), 4.0–4.7 (m, 2), 4.99 (d, J = 4 Hz, 1, H_6), 5.80 (q, J = 4, 9 Hz, 1, H_7), 6.80 (d, J = 9 Hz, 1, NH).

Cephem-3-*C*-carboxamide (5) and Imide (6). The nitrone **2** (0.548 g) was dissolved in 30 ml of distilled acetic anhydride, acetic acid (4 drops) was added, and the solution was heated at 80° for 10 min and then cooled in an ice bath. Evaporation to dryness followed by chromatography on silica gel using a toluene–ethyl acetate gradient gave 0.161 g (27%) of the faster moving imide **6** and 0.287 g (52%) of the amide **5**.

5: needles from CH_2Cl_2–hexane; mp 196–197°; ir ($CHCl_3$) 1788 cm^{-1} (β-lactam); NMR (DMSO-d_6) δ 2.73 (d, J = 4 Hz, 3, N-Me), 3.85 (s, 2, thiophene methylene), 5.09 (d, J = 4 Hz, 1, H_6), 5.55 (q, J = 4, 8 Hz, 1, H_7), 5.70 (s, 1, H_4), 8.21 (d, J = 4 Hz, 1, NHMe). Anal. Calcd for $C_{28}H_{25}N_3O_5S_2$: C, 61.41; H, 4.60; N, 7.67. Found: C, 61.20; H, 4.42; N, 7.54.

6: ir ($CHCl_3$) 1792 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 2.07 (s, 3, $COCH_3$), 2.87 (s, 3, N-Me), 3.75 (s, 2, thiophene methylene), 5.10 (d, J = 4 Hz, 1, H_6), 5.50 (q, J = 4, 7 Hz, 1, H_7), 5.70 (s, 1, H_4).

3-Formyl-2-(methylamino)-2-cephem (8). The nitrone **2** (2.45 g, 4.48 mmol) in 100 ml of dry toluene was refluxed for 3 hr, evaporated to dryness, and chromatographed on silica gel using a hexane–toluene–ethyl acetate gradient to give 1.22 g of isomer I (eluted first) and 0.54 g of isomer II.

8a **isomer I:** needles from toluene–hexane; mp 176–177° (4-C-PNB, mp 192–193°); ir ($CHCl_3$) 1782 cm^{-1} (β-lactam); NMR (60 and 220 MHz) ($CDCl_3$) δ 2.90 (d, J = 4 Hz, 3, N-Me), 3.91 (s, 2, thiophene methylene), 5.27 (s, 1, H_4), 5.44 (d, J = 4 Hz, 1, H_6), 5.52 (q, J = 4, 8 Hz, 1, H_7), 8.86 (s, 1, CHO), 11.53, 11.62 (AB, J = 4 Hz, 1, NH); λ_{EtOH} 325 nm (ϵ 14,700). Anal. Calcd for $C_{28}H_{25}N_3O_5S_2$: C, 61.40; H, 4.60; N, 7.67. Found: C, 61.65; H, 4.38; N, 7.77.

8b isomer II: ir ($CHCl_3$) 1780 cm^{-1} (β-lactam); NMR (60 and 100 MHz) ($CDCl_3$) δ 2.86 (d, J = 4 Hz, 3, N-Me), 3.75 (s, 2, thiophene methylene), 4.97 (d, J = 2 Hz, 1, H_4), 5.02 (d, J = 4 Hz, 1, H_6), 5.40 (m, 1, H_7), 8.90 (s, 1, CHO) (220 MHz on D_2O shake shows the multiplet at 5.40 as a q, J = 2, 4 Hz, and shows H_4 to H_7 coupling); λ_{EtOH} 332 nm (ϵ 11,000).

2-(*N*-Methyl,*N*-acetyl)-3-formyl-2-cephem (9). Acetylation of **8a** and **8b** was accomplished in cold (5°) THF using 1.1 equiv of acetyl chloride and 2.0 equiv of $NaHCO_3$ for 40 min. The reaction mixture was combined with ETOAc, washed with $NaHCO_3$, H_2O, and brine, evaporated, and chromatographed on silica gel to acetylated derivatives **9a** (79%) from **8a** and **9b** (69%) from **8b**. The NMR spectra are similar, both showing N-methyl singlets, the major difference being the H_4 proton (**9a** δ 5.67, **9b** δ 5.15).

2-(*N*-Methyl,*N*-acetyl)-3-cephem Lactone (10). **9a** (0.325 g) in 15 ml of dioxane plus 8 ml of water was cooled to ca. 5° and treated with 4 equiv of $NaBH_4$ in 2 ml of water for 15 min; 1 ml of 1 N HCl was added and when the reaction had ceased the mixture was diluted with EtOAc, washed with 1 N HCl and brine, evaporated, and chromatographed on silica gel to give 0.095 g (42%) of lactone. A similar run on **9b** gave 51% identical lactone: ir ($CHCl_3$) 1810 cm^{-1} (β-lactam); mass 407 (theory 407.46); NMR ($CDCl_3$) δ 2.12 (s, 3, N-Ac), 2.93 (s, 3, N-Me), 3.87 (s, 2, thiophene methylene), 4.85 (br s, 2, lactone methylene), 5.20 (d, J = 4 Hz, 1, H_6), 6.02 (q, J = 4, 9 Hz, 1, H_7), 6.70 (s, 1, H_2); λ_{EtOH} 255 nm (ϵ 10,500).

Tricyclic Pyrazole 12. The 3-formyl-2-cephem **1** was combined with 1.1 equiv of tosylhydrazine in 2B EtOH and refluxed for 1 hr. It was then evaporated to dryness and chromatographed on silica gel using a toluene–ethyl acetate gradient to give 88% tosylhydrazone as a white froth: 0.609 g (0.89 mmol) of tosylhydrazone in 50 ml of dry benzene was treated with 1.2 equiv of 50% NaH and refluxed for 15 min. It was then cooled to room temperature, washed with 1 N HCl and brine, evaporated, and chromatographed on silica gel using a toluene–ethyl acetate gradient to give 0.092 g (20%) of pyrazole as a crystalline white solid: needles from acetone–hexane: mp 198–199°; ir ($CHCl_3$) 1765 cm^{-1} (β-lactam); NMR (DMSO-d_6) δ 3.80 (s, 2, thiophene methylene), 5.37 (d, J = 4 Hz, 1, H_6), 5.57 (q, J = 4, 8 Hz, 1, H_7), 5.93 (s, 1, H_4), 7.79 (br s, 1, olefinic proton of pyrazole), 13.15 (br s, 1, NH of pyrazole). Anal. Calcd for $C_{27}H_{22}N_4O_4S_2$: C, 61.12; H, 4.18; N, 10.56; S, 12.09. Found: C, 60.96; H, 4.11; N, 10.53; S, 12.00.

Acknowledgment. We thank Mr. T. K. Elzey for running the 100-MHz and 220-MHz NMR spectra.

Registry No.—**1**, 55331-32-3; **2**, 55569-95-4; **3**, 55569-96-5; **4a**, 55569-97-6; **4a** sulfide, 55569-98-7; **4b**, 55569-99-8; **4b** sulfide, 55570-00-8; **4c**, 55570-01-9; **4c** sulfide, 55570-02-0; **5**, 55570-03-1; **6**, 55570-04-2; **7**, 55570-05-3; **8a**, 55570-06-4; **8b**, 55570-07-5; **9a**, 55570-08-6; **9b**, 55570-09-7; **10**, 55570-10-0; **11**, 55570-11-1; **12**, 55570-12-2.

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Nucleophilic Adducts of *N*-*tert*-Butyloxycarbonyl-1,1,1,3,3,3-hexafluoroisopropylimine. Facile Hydrolysis of Imidazole-Based Adducts[1,2]

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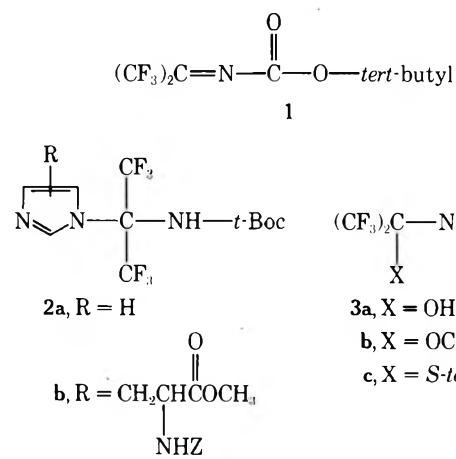
During the course of studies toward new blocking groups for the imidazole moiety of histidine,[3] we synthesized *N*-*t*-Boc-hexafluoroisopropylimine (**1**) and prepared its adducts with various nucleophiles including imidazole (adduct **2a**), N^{α}-Z-L-his-OCH_3 (adduct **2b**), water (adduct **3a**), methanol (adduct **3b**), and *tert*-butyl mercaptan (adduct **3c**). It

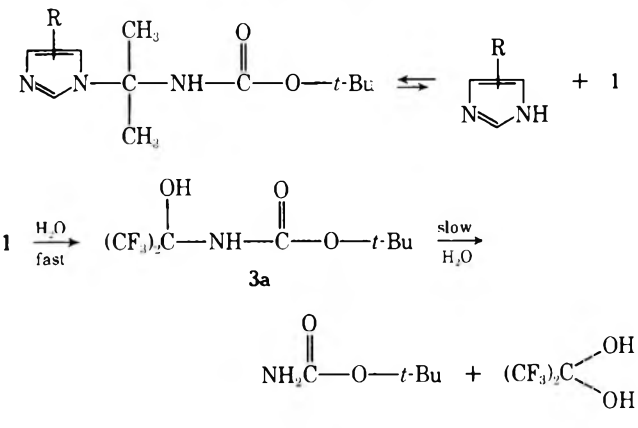


was found that although **3b** and **3c** are hydrolytically stable, the imidazole-based adducts **2a** and **2b** undergo facile hydrolysis; **2a** decomposes upon standing in air giving *O*-*tert*-butyl carbamate and **2b** cleaves in acetonitrile solution to which a small amount of water is added giving the carbamate and N^{α}-Z-his-OCH_3. This is surprising in view of the stability of many 1,1,1,3,3,3-hexahalopropanes bearing two heteroatoms at carbon 2 including **3b** and **3c** (unchanged after 124 and 179 hr in an aqueous environment), the incredible stability in both acid and base of ketals and *gem*-amino ethers of fluorinated ketones,[3-5] and the stability of analogs of **2b** containing a single trifluoromethyl group derived from trifluoroacetaldehyde.[6] Simple *gem*-diamines based on hexafluoroacetone have been reported to decompose with HCl in ether.[7] Details of the hydrolysis of **2b** were examined by NMR spectroscopy.

Water, 2–3 equiv, was added to a solution of **2b** in CD_3CN and the NMR spectrum monitored for 147.5 hr, during which time three separate resonances were seen for the *tert*-butyl protons. During the first 4.75 hr the resonance at δ1.42 of **1b** is seen to diminish while a resonance at δ1.48 appears along with a very small signal at δ1.43. After 18 hr the original resonance has disappeared and after 70 hr that at δ1.48 has been almost entirely replaced by that at δ1.43. This latter resonance belongs to *O-tert*-butyl carbamate which is isolated at the end of the experiment; moreover, the only Pauly position spot[8] on TLC is N^{α}-Z-his-OCH_3.[9] There are corresponding changes in the resonance of the imidazole C-2 and C-4 protons as deblocking occurs; the resonance of the former shifts from δ7.78 to δ7.72, and that of the latter at δ7.11 is replaced by a new band at δ6.90. This process parallels the formation of the δ1.48 *tert*-butyl resonance but is complete and stabilized within the 18-hr period.

We favor the hydrolytic mechanism shown in Scheme I; this scheme is directly supported by the NMR data, which show two observable reactions occurring at different rates and a *tert*-butyl-containing intermediate on the path from **1b** to *tert*-butyl carbamate. Assignment of the δ1.48 intermediate as compound **3a** is based on (1) its experimentally determined chemical shift as δ0.05 downfield of *tert*-butyl carbamate in a similar medium, (2) the precedented[7,10,11] equilibrium of fluorimines and addends with their adducts, and (3) the known hydration of fluorimines[10] including **1**.[12]

Scheme I



A hydrolytic mechanism involving water as a nucleophile in an SN2 displacement would not be acceptable at a tertiary center and is incompatible with the marked stability of the less hindered monotrifluoromethyl analogs. An SN1 mechanism is highly unlikely considering the carbonium ion destabilization by unattached trifluoromethyl groups, dramatically shown recently by the bimolecular displacement of nitrogen from hexafluoroisopropyldiazonium ion.[13] The need for a protic nitrogen is indicated by the hydrolytic stability of **3b** and **3c**; N^{α}-Z,N^{im}-[1,1,1,3,3,3-hexafluoro-2-(*p*-chlorophenoxymethoxy)propyl]-L-his-OCH_3[3] is stable to water, aqueous citric acid, and aqueous sodium hydroxide. Thus, the equilibrium in Scheme I probably requires prior ionization of the nitrogen proton. Steric hindrance may provide a driving force for the initial equilibrium of **2a,b** relative to trifluoroacetaldehyde-based derivatives, analogous to the unfavorable bisulfite addition equilibrium with ketones relative to aldehydes. Along these lines Banfield et al.[14] have shown that the addition of nucleophiles to aromatic *N*-acylimines is unsuccessful with sterically hindered compounds. The reactivity of **2a,b** may be enhanced by the leaving ability of imidazole relative to simple amines; e.g., compare the reactivity of acylimidazoles[15] relative to normal amides.

Finally, adduct **3b** is stable to 0.5 *M* citric acid and to cyclohexylamine. Thus imine **1** may be an effective acid-labile blocking agent for alcohol functionalities in general.

Experimental Section

Thin layer chromatograms were obtained on commercially prepared fluorescent silica gel coated plates. Proton magnetic resonance spectra were obtained on a Varian T-60 spectrometer; variable temperature ^{19}F spectra were obtained on a Bruker B-90C NMR spectrometer at 84.66 Hz.

***N*-*t*-Boc-hexafluoroisopropylimine (1).** To *tert*-butyl carbamate (2.34 g, 0.02 mol) dissolved in 100 ml of anhydrous ether in a 200-ml glass bomb fitted with a Dry Ice–acetone cold finger condenser and drying tube was added hexafluoroacetone (6.6 g, 0.04 mol). The sealed bomb was partially immersed in a 75–90° water bath for 2 hr. The cooled bomb was opened, the ether was removed by flash evaporation and the liquid residue, 1,1,1,3,3,3-hexafluoro-2-hydroxy-*N*-*tert*-butyloxycarbonylisopropylamine, (**3a**), was distilled: bp 80.5° (24 mm); mp 36.5–39°; 3.39 g (60%). The use of 10 equiv of hexafluoroacetone did not affect the yield; large-scale reactions were carried out in steel bombs.

Anal. Calcd for $C_8H_{11}NO_3F_6$: C, 33.91; H, 3.92; N, 4.95; F, 40.26. Found: C, 34.15; H, 4.08; N, 5.14; F, 39.99.

A round-bottom flask fitted with thermometer, drying tube, stirring bar, and pressure-equalizing dropping funnel containing the carbinol (56.2 g, 0.20 mol) in 50 ml of dry quinoline was charged with 80 ml of dry quinoline, 36.5 ml (0.40 mol) of $POCl_3$, and boiling stones. The alcohol solution was added dropwise over a 0.75-hr period and the reaction mixture was stirred for another 1 hr. The product was then vacuum distilled into a chilled receiver (−78°) until a pot temperature of 105° (23 mm) was reached. Redistillation through a porcelain-packed column gave 26.0 g (49%) yield of imine, bp 46–49° (24 mm). GLC showed the product to be free of $POCl_3$: ^1H NMR ($DCCl_3$) δ 1.57 (s); ^{19}F NMR (neat, 330 K) s, 720 Hz downfield from TFA; (neat, 255 K) q, 866 Hz from TFA, J = 6.5 Hz; q, 563 Hz from TFA, J = 6.5 Hz. Variable-temperature data[16] gave an activation energy for syn–anti isomerization of 16.83 kcal/mol, ir (CCl_4) 2967, 1760, 1730 (shoulder), 1235 cm^{-1}.

1,1,1,3,3,3-Hexafluoro-2-*N*-*t*-Boc-aminoisopropylimidazole (2a). Imidazole (68 mg, 1 mmol) dissolved in THF (1 ml) was treated with imine **1** (273 mg, 1 mmol) in ⅓ ml of THF. The reaction was mildly exothermic and complete in 10 min. Flash evaporation left an oil. An aliquot was dissolved in Skelly B and cooling to −78° caused oiling. The mother liquor was decanted and the oil crystallized on standing. These crystals were used to seed crystallization from 10% ethyl acetate in hexane, giving 157 mg (47%) of product, mp 96–102°.

Anal. Calcd for $C_{11}H_{13}N_3O_2F_6$: C, 39.65; H, 3.93; N, 12.61; F, 34.21. Found: C, 39.62; H, 3.89; N, 12.35; F, 33.20.

NMR (parts per million from THF downfield multiplet maximum) δ 5.49 (br s, 1.2 H, NH), 4.31 (br s, 1.1 H, C_2H), 3.61 (br s, 1.0 H, C_5H), 3.45 (br s, 1.0, C_4H), −2.27 (s, *O-tert*-butyl).

1,1,1,3,3,3-Hexafluoro-2-methoxy-*N*-*t*-Boc-isopropylamine (3b). Equimolar amounts of imine **1** and methanol were mixed at room temperature. The material solidified after a few hours. After 30 hr the solid was recrystallized from CS_2: yield 68%; mp 65–69°; NMR ($CDCl_3$) δ 5.32 (1 H, NH), 3.60 (3 H, OCH_3), 1.50 (9 H, *O-tert*-butyl).

1,1,1,3,3,3-Hexafluoro-2-*tert*-butylmercapto-*N*-*t*-Boc-isopropylamine (3c). The procedure was the same as for **3b** using *tert*-butyl mercaptan: yield 50%; mp 80.5°; NMR ($CDCl_3$) δ 5.18 (1.0 H, NH), 1.52, 1.50 (s, 18 H, *O-tert*-butyl, *S-tert*-butyl).

***N*$^{\alpha}$-Z,*N*^{im}-(1,1,1,3,3,3-hexafluoro-2-*t*-Boc-aminoisopropyl)-L-his-OCH_3 (2b).** N^{α}-Z-L-his-OCH_3 (153 mg, 0.5 mmol) in $CDCl_3$ was treated with imine **1** (142 mg, 0.54 mmol) at room temperature. After 20.5 hr the solution was added to cold (0°) Skelly B dropwise with swirling. A white, amorphous precipitate developed which became tacky on warming to room temperature. The mother liquor was decanted and the residue was high vacuum dried to a crisp foam: NMR (CD_3CN) δ 7.78 (br s, 1.0 H, C_2H), 7.39 (s, 5.4 H, phenyl), 7.11 (br s, 1.23 H, C_4H), 6.43 and 6.1 (1.95 H, Z-NH, *t*-BOC-NH), 5.09 (s, 2.0 H, benzyl), 4.53 (m, 0.92 H, $C_\alpha H$), 3.65 (s, 3.0 H, OCH_3), 3.03 (d, J = 6 Hz, 1.92 H, β-CH_2), 1.43 (s, 8.0 H, *O-t*-Bu); TLC (silica gel F-254, 5% CH_3OH in $CHCl_3$, detected by fluorescence quenching and Pauly reagent) R_f 0.75 with some tailing; R_f of N^{α}-Z-his-OCH_3 0.23.

Registry No.—**1**, 52786-55-7; **2a**, 55606-65-0; **2b**, 55648-91-4; **3a**, 52786-44-4; **3b**, 55606-66-1; **3c**, 55606-67-2; *tert*-butyl carbamate, 543-28-2; hexafluoroacetone, 684-16-2; imidazole, 288-32-4; methanol, 67-56-1; *tert*-butyl mercaptan, 513-44-0; N^{α}-Z-L-his-OCH_3, 15545-10-5.

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(1) We acknowledge the support of the U.S. Public Health Service (Grant AM 12970) and the Department of Chemistry in providing a teaching fellowship for H.H.S.
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Directive Effects in the Hydroboration of Vinylferrocenes

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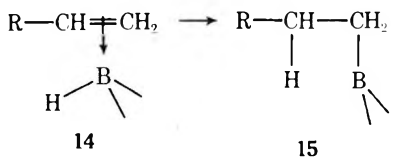
While examining possible synthetic applications of the hydroboration reaction in organometallic systems,[1] we observed that certain vinylmetallocenes, upon hydroboration–oxidation, were converted to a single alcohol product. By contrast, most aryl- and alkyl-substituted alkenes yield a mixture of two isomeric alcohols under similar reaction conditions. Since the positional selectivity of this reaction was so pronounced, a study was initiated in order to probe the nature of this directive ability.

Results and Discussion

A series of ferrocenyl-substituted alkenes (**1–6**, Table I) was prepared and allowed to react with borane in tetrahydrofuran. These alkenes reacted normally and produced the corresponding alcohols in high yields. The alcohols were isolated by column chromatography,[2] and percent yields of isolated products ranged from 60% with **4** to 79% with **3**. In addition, approximately 5% yields of the corresponding alkanes were obtained.

The distributions of the isomeric alcohols are indicated in Table I. By way of comparison, distributions in similar aryl- and alkyl-substituted alkenes are also shown. The distribution of ferrocenyl-substituted alcohols was determined by NMR analysis. The NMR spectra of the purified alcohol fractions from the hydroboration–oxidation procedure were recorded and unique areas of absorption for each of the possible alcohols were integrated repeatedly. Even though the accuracy of the distributions is limited by the accuracy of the integration procedure, these values are the average of several experiments. Variations in distribution among several experiments were found to be quite small (±3%).

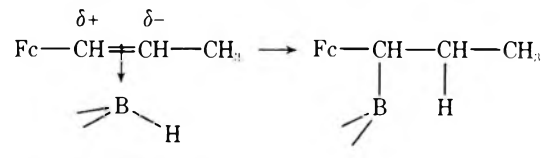
The various isomer distributions can be accounted for in terms of the presently accepted hydroboration mechanism. This mechanism, which is based on stereochemical[3] and thermodynamic[4] considerations, involves the formation of a triangular π complex (**14**) and its collapse via a concerted process[5] to product (**15**). Both steric and electronic factors



14 **15**

are involved in determining the carbon to which the boron moiety will become attached.[5] Upon hydroboration–oxidation the terminal alkenes **1** and **2** produce preponderant amounts of the terminal alcohols. In fact, vinylferrocene (**1**) produces a significantly greater amount of the terminal alcohol than does styrene (**7**) or *tert*-butylethylene (**10**). It is likely that the steric bulk of ferrocene and its powerful electron-releasing ability[6] combine to produce this increased preferential attachment of boron to the terminal carbon.

With disubstituted internal alkyl-substituted alkenes, Brown and Zweifel[7] observed that the boron moiety becomes attached in approximately equal amounts to each carbon of the double bond. When one of the substituents is the very bulky *tert*-butyl group (**12**) the distribution becomes 42:58 (Table I). However, the case of 1-phenylpropene (**9**) demonstrates the importance of electronic factors in the hydroboration reaction. Further, when substantial amounts of both isomers are formed one must consider the extent of hydroboration. Reactions of stoichiometric amounts of borane and of disubstituted alkenes such as **3**, **4**, or **5** indicate that these reactions proceed to the dialkylborane stage while with the trisubstituted alkene **6**, hydroboration apparently stops at the monoalkylborane stage. In the hydroboration of **3**, control by steric factors should cause a small preference for boron addition to the carbon β to the ferrocenyl group; however, the opposite result is observed. This suggests that some type of electronic control must also be involved. Ferrocene is generally regarded as a very strong electron-releasing group;[8] however, electron release by ferrocene would not favor the formation of the observed major product. An electron-withdrawing tendency (similar to the phenyl group's behavior in **9**) would lead to an intermediate such as **16**, but this tendency must be considerably less significant than in the phenyl case, since there is not a large deviation from the usual 50:50 distribution.



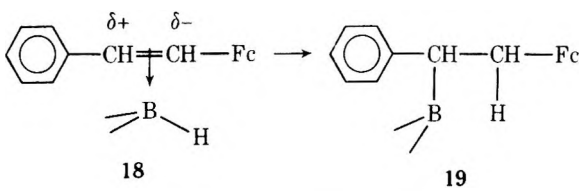
16 **17**

When the two substituents are the phenyl and the ferrocenyl systems (**4**), the boron displays a great preference for attachment to the carbon α to the phenyl group. This result occurs because of the very favorable combination of electronic factors in the intermediate (**18**) in which the ferrocenyl system is electron releasing and the phenyl group is

Table I
Distribution of Alcohol Products from Hydroboration–Oxidation

Ferrocenyl alkenes	Aryl alkenes[9]	Alkyl alkenes[9]
	Monosubstituted	
(1) Fc—CH=CH_2 2 98	(7) PhCH=CH_2 20 80	(10) $CH_3C(CH_3)_2$—CH=CH_2 6 94
	Disubstituted	
(2) Fc—$C(CH_3)$=CH_2 1 99	(8) Ph$C(CH_3)$=CH_2 100	(11) $CH_3CH_2C(CH_3)$=CH_2 1 99
(3) Fc—CH=CHCH$_3$ 63 37	(9) PhCH=CHCH$_3$ 85 15	(12) $CH_3C(CH_3)_2$—CH=CHCH$_3$ 42 58
(4) Fc—CH=CHPh 10 90		
(5) Fc—CH=CHC$_6$H$_4$-*p*-OCH$_3$ 28 72		
	Trisubstituted	
(6) Fc—CH=$C(CH_3)$—CH$_3$ 95 5		(13) $CH_3C(CH_3)_2$—CH=$C(CH_3)$—CH$_3$ 98 2

electron withdrawing. This distribution can be distorted by appropriate substitution on the benzene ring (5). In this case, the *p*-methoxy group lessens the ability of the phenyl system to withdraw electron density from the adjacent carbon.



18 19

In summary, the steric bulk of the ferrocene group tends to produce boron addition β to itself: however, in internal alkenes electronic factors become important in determining the product distribution.

Experimental Section

Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. The microanalyses were performed by Chemalytics, Inc., Tempe, Ariz. Infrared spectra were recorded on a Perkin-Elmer Model 457 spectrophotometer, and NMR spectra were determined with a Perkin-Elmer R12B spectrometer using tetramethylsilane as an internal standard.

Most of the alkenes and alcohols used in this study have been previously prepared and their physical and spectra properties fully described. The preparations of previously unreported compounds are described below.

Preparation of Ferrocenyl-*p*-methoxybenzyl Ketone. Ferrocene (7.4 g, 40 mmol) and *p*-methoxyphenylacetyl chloride (7.4 g, 40 mmol) were dissolved in 100 ml of CH_2Cl_2 under a nitrogen atmosphere at 0°. To this stirred mixture was added anhydrous $AlCl_3$ (5.4 g, 40 mmol) in small portions. The purple-colored mixture was then stirred for 0.5 hr at 0° and 2 hr at room temperature. At that time water was added and the mixture was extracted with CH_2Cl_2. . The combined CH_2Cl_2 extracts were washed with 5% $NaHCO_3$ and H_2O, and finally dried over $MgSO_4$. After filtration and solvent evaporation, 8.6 g (65%) of the desired compound was obtained. Recrystallization from hexane produced bright orange needles: mp 91–92°; NMR ($CDCl_3$) τ 2.9 (4 H, m), 5.2 (2 H, m), 5.5 (2 H, m), 5.86 (5 H, s), 6.08 (2 H, s), 6.21 (3 H, s); ir (CCl_4), 1663 cm^{-1} (s, ketone carbonyl).

Anal. Calcd for $C_{19}H_{18}O_2Fe$: C, 68.28; H, 5.44. Found: C, 68.28; H, 5.79.

Preparation of 1-Ferrocenyl-2-(*p*-methoxyphenyl)ethanol. A mixture of 8.0 g (24 mmol) of ferrocenyl-*p*-methoxybenzyl ketone and 1.5 g (38 mmol) of $LiAlH_4$ in 100 ml of anhydrous ether was refluxed for 2 hr. The reaction mixture was then cooled in an ice bath while 100 ml of ice water was cautiously added. The layers were separated and the aqueous layer was further extracted with ether. The combined ether layers were washed with water and dried over $MgSO_4$. Solvent removal revealed the crude product (4.8 g, 60%) as a dark orange solid. An analytical sample was produced by recrystallization from hexane; yellow crystals, mp 62–63°; NMR ($CDCl_3$) τ 3.05 (4 H, m), 5.25 (1 H, m), 5.85 (9 H, s), 6.24 (3 H, s), 7.08 (2 H, d), 8.08 (1 H, s).

Anal. Calcd for $C_{19}H_{20}O_2Fe$: C, 67.87; H, 6.01. Found: C, 67.70; H, 6.03.

Preparation of 1-Ferrocenyl-2-(*p*-methoxyphenyl)ethene (5). A mixture of 2.6 g of 1-ferrocenyl-2-(*p*-methoxyphenyl)ethanol, 3 g of acidic alumina, and 75 ml of benzene was stirred under reflux for 2 hr with continued removal of water by a Dean-Stark trap. The mixture was filtered and the solvent was evaporated. The crude residue was chromatographed over alumina and elution with pentane removed the desired product. The red-orange crystals (1.6 g, 65%) melted at 95–97° and appear to represent a cis–trans mixture; NMR (CCl_4) τ 3.0 (4 H, m), 3.4 (2 H, m), 5.70 (2 H, m), 5.88 (2 H, m), 6.00 (5 H, s), 6.26 (3 H, s).

Anal. Calcd for $C_{19}H_{18}CFe$: C, 71.71; H, 5.71. Found: C, 71.75; H, 5.58.

Preparation of 2-Ferrocenyl-1-(*p*-methoxyphenyl)ethanol. To a stirred suspension of ferrocenylmethyltriphenylphosphonium iodide (5.88 g, 10 mmol) in 100 ml of anhydrous ether was added 11 mmol of butyllithium. The resultant red solution was stirred for 1.5 hr and then 5.12 g (30 mmol) of anisoyl chloride was added. An

immediate precipitate formed. The mixture was stirred for an additional 2 hr and then filtered. The crude (α-ferrocenyl-p-methoxyphenacyl)triphenylphosphonium iodide weighed 7.0 g. A 250-ml three-necked flask was then equipped with a stirring bar, addition funnel, and condenser. Into the flask was placed 2.5 g of the iodide, 50 ml of chloroform, and 20 g of zinc dust. The reaction mixture was heated to boiling and 75 ml of glacial acetic acid added dropwise. After 1 hr the mixture was poured into water and the organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed in pentane over alumina. Pentane removed triphenylphosphine and ether removed 0.16 g of p-methoxyphenacylferrocene as an orange solid (mp 96–101°). The crude ketone was dissolved in ether (25 ml) and treated with 0.2 g of $LiAlH_4$. This mixture was refluxed for 1.5 hr and then excess $LiAlH_4$ was removed by dropwise addition of water. The resultant two-phase system was poured into water and the organic layer was separated. The aqueous phase was extracted with ether and the combined extract was dried ($MgSO_4$) and evaporated. The residue was recrystallized from hexane to produce the desired alcohol as pale yellow crystals: mp 52–54° (yield, 0.11 g); NMR ($CDCl_3$) τ 2.95 (4 H, m), 5.20 (1 H, m), 5.93 (9 H, s), 6.21 (3 H, s), 7.24 (2 H, d), 7.80 (1 H, s).

Anal. Calcd for $C_{19}H_{20}O_2Fe$: C, 67.87; H, 6.01. Found: C, 67.35; H, 5.94.

Preparation of 1-Ferrocenyl-2-methyl-2-propanol. A solution of 5.4 g (22 mmol) of 1-ferrocenyl-2-propanone in ether was prepared according to literature procedures[10] and added to a solution of 50 mmol of methylmagnesium iodide in 50 ml of ether. The solution was stirred for 1 hr at room temperature and then poured into water. The ether layer was separated and the aqueous phase was extracted with ether. The combined ether extracts were dried ($MgSO_4$) and concentrated to yield a dark red oil. This viscous oil was repeatedly chromatographed over alumina and eluted with ether. The resultant dark red oil weighed 1.3 g (24%); NMR ($CDCl_3$) τ 5.90 (9 H, s), 7.45 (2 H, s), 8.50 (1 H, s), 8.86 (6 H, s).

Anal. Calcd for $C_{14}H_{18}OFe$: C, 65.13; H, 7.08. Found: C, 65.04; H, 7.06.

Hydroboration–Oxidation of Substituted Vinyl Ferrocenes. A. Excess Borane. The alkene (2.5 g), 50 ml of tetrahydrofuran, and 0.85 g of $NaBH_4$ were placed in a three-neck, 100-ml flask equipped with a condenser, addition funnel, and nitrogen inlet-outlet tube. The flask was placed in a water bath and the solution was magnetically stirred. Into the addition funnel was placed 4.2 g of boron trifluoride etherate and 10 ml of THF. This solution was added to the alkene solution over a period of 20 min and after the addition was complete, stirring was continued for 1 hr. The solution was cooled in an ice bath and 5 ml of H_2O was added dropwise to destroy excess diborane.

Enough 3 *N* NaOH was then added to raise the pH of the solution to 8.0. An equal volume of 30% H_2O_2 was added and the solution was stirred for 1 hr after which it was poured into 100 ml of water and extracted with three 50-ml portions of ether. The combined ether extracts were washed with 5% $NaHCO_3$ and four 100-ml portions of water. The ether solutions were then dried over $MgSO_4$. Removal of the solvent left the crude product, which was chromotographed over alumina. Pentane removed unreacted alkene and any reduction products. Ether eluted the alcohol fractions.

B. Stoichiometric Borane. The alkene (4.5 mmol) was dissolved in 10 ml of tetrahydrofuran (distilled from $LiAlH_4$) and a commercial solution of BH_3-THF (1.7 mmol) diluted with 5 ml of THF was added dropwise over a period of 20 min. All operations were conducted at room temperature under a N_2 atmosphere. After addition of the borane, stirring was continued for 1.25 hr and then the reaction mixture was worked up as before.

The extent of alkylation of the borane was estimated from the amount of recovered unreacted alkene. With terminal and disubstituted internal alkenes used in this study, hydroboration apparently terminates at the dialkylborane stage. Trisubstituted alkene **6** proceeded to the monoalkylborane stage. The distribution of isomeric alcohols was found to be insensitive to the hydroboration procedure followed.

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Registry No.—*cis*-**5**, 55648-58-3; *trans*-**5**, 55700-24-8; ferrocenyl-p-methoxybenzyl ketone, 55648-59-4; ferrocene, 102-54-5; p-methoxyphenylacetyl chloride, 4693-91-8; 1-ferrocenyl-2-(p-methoxyphenyl)ethanol, 55648-86-7; 2-ferrocenyl-1-(p-methoxyphenyl)ethanol, 55648-87-8; ferrocenylmethyltriphenylphosphonium iodide, 32914-67-3; (α-ferrocenyl-p-methoxyphenacyl)-triphenylphosphonium iodide, 55648-88-9; p-methoxyphenacylferrocene, 55648-89-0; 1-ferrocenyl-2-methyl-2-propanol, 55648-90-3; 1-ferrocenyl-2-propanone, 12215-52-0.

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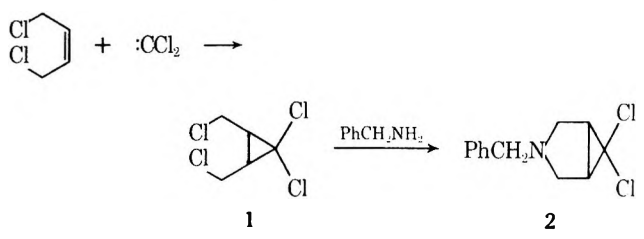
Synthesis and Reactions of Some Bicyclic Piperidine Analogs. Formation of the 4-Azatricyclo[2.2.1.0^{2,6}]heptane Ring System

Summary: The reaction of *n*-butyllithium with 3-benzyl-6-*exo*-chloro-3-azabicyclo[3.1.0]hexane (**3**) produced 3-phenyl-4-azatricyclo[2.2.1.0^{2,6}]heptane (**5**), a new heterotricyclic ring system.

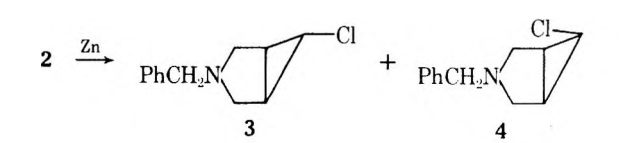
Sir: We are reporting the synthesis of several novel 3-azabicyclo[3.1.0]hexane derivatives and a new heterotricyclic ring system.[1] Dichlorocarbene added to 1,4-dichloro-*cis*-2-butene to produce 1,1-dichloro-*cis*-2,3-bis(chloromethyl)-cyclopropane (**1**, 45% yield): bp 123–126° (22 Torr); PMR ($CDCl_3$) δ 2.22 (2 H, m), 3.67 (4 H, m); ir (film) 1255 ($-CH_2Cl$ wag[2]), 988 cm^{-1} (cyclopropyl ring deformation[3]); uv (methanol) λ_{max} 239 nm (ϵ 87.5); mass spectrum *m/e* 171 (M − Cl). The dichlorocarbene was generated from $CHCl_3$ and 50% aqueous NaOH solution using the phase transfer reaction reported by Makosza.[4] Reaction at room temperature over a period of 2–3 days[5] using cetyltrimethylammonium bromide (CTABr)[6] as a catalyst gave the best yield (44.5%).

When **1**, benzylamine, and sodium bicarbonate were stirred together in 1-butanol and heated at reflux for 16–30 hr, 3-benzyl-6,6-dichloro-3-azabicyclo[3.1.0]hexane (**2**) was obtained. Chromatography on Florisil using increasing ratios of acetone to benzene gave pure **2** (51% yield): PMR ($CDCl_3$) δ 2.23 (2 H, m), 2.97 (4 H, m), 3.62 (2 H, s), 7.29 (5 H, s); ir (film) 2800 (s, tertiary alkylamine[7]), 1018 cm^{-1} (m, cyclopropyl ring deformation); uv (methanol) λ_{max} (HCl salt) 261 nm (ϵ 260); mass spectrum *m/e* 241 (M$^+$); mp (HCl salt) 198–199°.



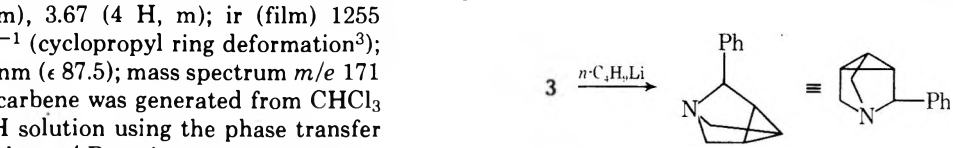
1 2

Reduction of **2** with zinc dust in refluxing acetic acid[8] yielded the *exo*-monochloro isomers **3** and the *endo*-monochloro isomer **4** in a 4:1 ratio. Reduction of **2** with zinc dust in refluxing ethanolic KOH[9] also yielded the same isomers but with the *endo*-monochloro isomer **4** being the major product. The isomers obtained from reduction in acetic acid were separated by column chromatography on silica gel using increasing ratios of ethyl acetate to benzene to elute the isomers 3-benzyl-6-*exo*-chloro-3-azabicyclo-[3.1.0]hexane (**3**) [(75% yield); PMR ($CDCl_3$), δ 1.70 (2 H, q, ^3J = 1.8 Hz), 2.35 (2 H, d of m, ^2J = 9 Hz), 3.07 (2 H, d, ^2J = 9 Hz), 3.31 (1 H, m), 3.55 (2 H, s), 7.27 (5 H, s); ir (film), 2790 (s, tertiary alkylamine), 1020 cm^{-1} (w, cyclopropyl ring deformation); uv (HCl salt) λ_{max} (methanol) 261 nm (ϵ 531); mass spectrum: *m/e* 207 (M$^+$); mp (HCl salt) 190–191°] and 3-benzyl-6-*endo*-chloro-3-azabicyclo[3.1.0]hexane (**4**) [(8.6% yield); PMR ($CDCl_3$) δ 1.79 (2 H, d of m, ^3J = 7 Hz), 2.80 (2 H, d, ^2J = 10 Hz), 3.03 (2 H, d of m, ^2J = 10 Hz), 3.40 (1 H, t, ^3J = 7 Hz), 3.66 (2 H, s), 7.31 (5 H, s); ir (film) 2790 (s, tertiary alkylamine), 1010 cm^{-1} (w, cyclopropyl ring deformation); uv (HCl salt) λ_{max} (methanol) 261 nm (ϵ 259); mass spectrum: *m/e* 207 (M$^+$); mp (HCl salt) 158–158.5°].



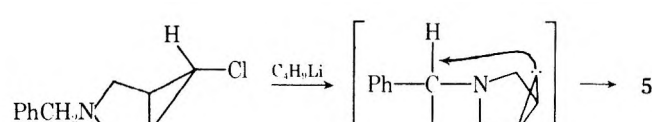
3 4

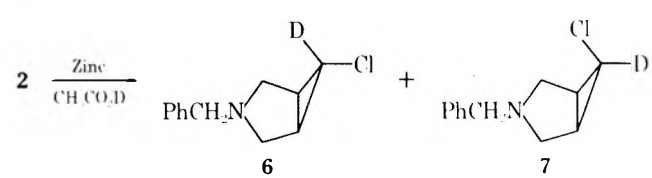
Addition of *n*-butyllithium solution (2 *M* in hexane) to a stirred solution of **3** in ether under nitrogen at 25° gave a product in 51% yield identified as 3-phenyl-4-azatricyclo[2.2.1.0^{2,6}]heptane (**5**) on the basis of its CMR, PMR, ir, and mass spectra: PMR ($CDCl_3$) δ 1.46 (3 H, m), 2.28 (2 H, d of d, ^3J = 9.5, 11 Hz, ^2J = 13 Hz), 2.70 (2 H, d of d, ^3J = 9.5, 11 Hz, ^2J = 14 Hz) 3.80 (1 H, s), 7.40 (5 H, m); ir (film) 1020 cm^{-1} (w, cyclopropyl ring deformation); uv (oxalate salt) λ_{max} (methanol) 261 nm (ϵ 396); mass spectrum *m/e* 171 (M$^+$); mp (oxalate salt) 155–156°. The 25.2-MHz ^{13}C proton decoupled spectrum of the oxalate salt of **5** in deuteriomethanol shows three carbons at 9.973, 10.708, and 2.160 ppm for the cyclopropyl carbons. The other ring carbons appear at 51.924, 58.489, and 71.56 ppm. The aromatic carbons give peaks at 129.892, 130,914, and 132.313 ppm. The single frequency off resonance (SFOR) spectrum of the salt shows each of the cyclopropyl carbons to give a doublet (coupled with one proton each), triplets for each of the pyrrolidine ring carbons with two protons, and a doublet for the bridging carbon which has only one proton. A multiplet absorption pattern appears for the aromatic carbons. To our knowledge, this is the first reported synthesis of the 4-azatricyclo[2.2.1.0^{2,6}]heptane ring system.



5

The endo isomer **4** failed to give **5** when treated with *n*-butyllithium in ether. Reaction of **2** with *n*-butyllithium in ether produced **5** in a low yield. Compound **5** would most probably be formed by an intramolecular C–H insertion via a carbene or carbenoid formed by reaction of butyllithium on **3**. To test this hypothesis, **2** was reduced with zinc and refluxing deuterioacetic acid to yield the two monochloro deuterated isomers **6** and **7**. These isomers were separated





6 7

by chromatography on silica gel to give 3-benzyl-6-*exo*-chloro-6-*d*-3-azabicyclo[3.1.0]hexane (**6**) (55% yield) [PMR ($CDCl_3$) δ 1.69 (2, H, m), 2.35 (2 H, d of m, ^2J = 9 Hz), 3.07 (2 H, d, ^2J = 9 Hz), 3.53 (2 H, s), 7.28 (5 H, s); ir (film) 2790 (s, tertiary alkylamine), 1020 cm^{-1} (cyclopropyl ring deformation); uv (HCl salt) λ_{max} (methanol) 261 nm (ϵ 267); mass spectrum *m/e* 208 (M^+); mp (HCl salt) 190–191°] and 3-benzyl-6-*endo*-chloro-6-*d*-3-azabicyclo[3.1.0]hexane (**7**) (~10% yield) [PMR ($CDCl_3$) δ 1.75 (2 H, s), 2.80 (2 H, d, ^2J = 10 Hz), 3.02 (2 H, d of m, ^2J = 10 Hz), 3.62 (2 H, s), 7.30 (5 H, s); ir (film) 2780 (s, tertiary alkylamine), 1020 cm^{-1} (m, cyclopropyl ring deformation); uv (HCl salt) λ_{max} (methanol) 261 nm (ϵ 474); mass spectrum: *m/e* 208 (M^+); mp (HCl salt) 157–158°].

Reaction of the *exo*-chloro deuterated isomer **6** with *n*-butyllithium in ether yielded **5** with no deuterium incorporation, indicating that the cyclopropyl proton at position 2 of the tricyclic structure came from insertion in a benzylic C–H bond.

Frazer-Reid has reported that treating 4-phenyl-8,8-dichloro-3,5-dioxobicyclo[5.1.0]hexane with *n*-butyllithium resulted in a tricyclic product formed by benzylic C–H intramolecular insertion. Reaction of butyllithium with *4-d*-4-phenyl-8,8-dichloro-3,5-dioxobicyclo[5.1.0]hexane in ether gave a tricyclic product containing deuterium.[10] These results supports our interpretation.

Acknowledgment. The authors appreciate the support of this research by the A. H. Robins Co., Richmond, Va.

Supplementary Material Available. Experimental procedures for preparation of substances **1–7** will appear following these pages in the microfilm edition of this volume of this 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 $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2419.

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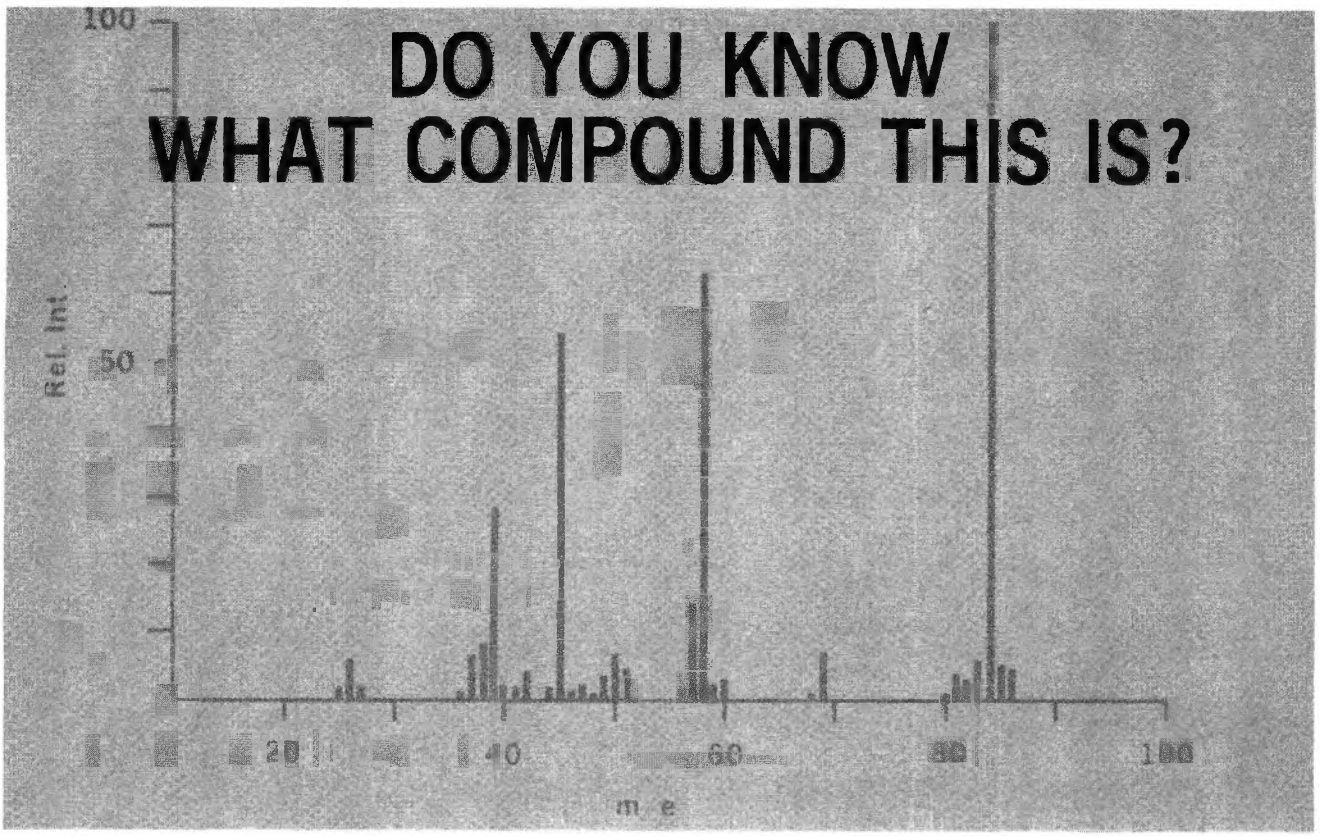

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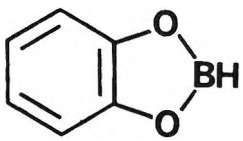
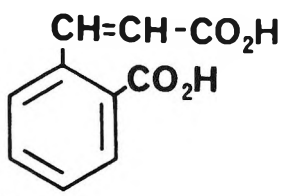
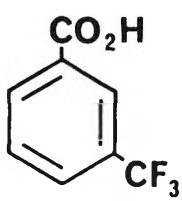
Synthetic Tools



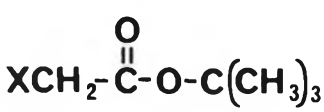
18,891-3 Catecholborane
For the preparation of synthetically useful alkylboronic acids. *J. Amer. Chem. Soc.*, **95**, 5786, 6456 (1973); *J. Org. Chem.*, **40**, 1834 (1975).
25g $17.00



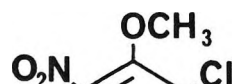
18,603-1
***o*-Carboxycinnamic acid**
10g $8.00



18,834-4
α,α,α-Trifluoro-*m*-toluic acid
10g $8.00 50g $26.00

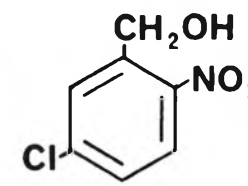


X = Cl
18,679-1 *tert*-Butyl chloroacetate
100g $9.00 500g $27.00
X = CN
18,693-7 *tert*-Butyl cyanoacetate
25g $7.35 100g $19.35
1Kg $125.00

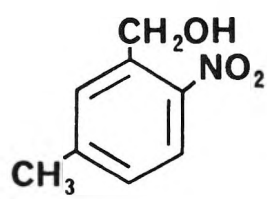


19,002-0 Sodium cyanoborodeuteride, 99 atom % D
Mild, selective reducing agent for the synthesis of deuterated compounds.
1g $27.00 5g 115.00

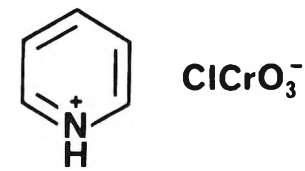
18,846-8
2-Chloro-6-nitroanisole
50g $9.00 250g $28.00



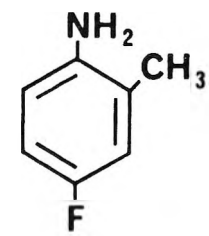
18,740-2
5-Chloro-2-nitrobenzyl alcohol
10g $7.00 50g $22.00



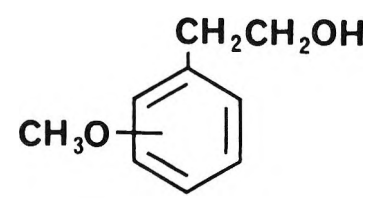
18,741-0
5-Methyl-2-nitrobenzyl alcohol
10g $5.50 50g $18.00



19,014-4
Pyridinium chlorochromate
Stable, versatile reagent for the oxidation of alcohols to aldehydes and ketones.
E.J. Corey and J.W. Suggs, *Tetrahedron Lett.*, in press.
100g $7.00 500g $24.00



18,924-3
4-Fluoro-2-methylaniline
5g $7.00 25g $20.00



18,792-5
***o*-Methoxyphenethyl alcohol**
5g $9.50 25g $32.50
18,793-3
***m*-Methoxyphenethyl alcohol**
5g $9.60 25g $32.00
15,418-0
***p*-Methoxyphenethyl alcohol**
10g $6.85 50g $18.75

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